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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 23-34, 2013
Atlanta, Georgia

Feb. 2014

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia

October 23-24, 2013

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday October 23			
8:00	**Welcome & Introductions**		Dr Thomas Frieden (Director, CDC) Dr Jonathan Temte (Chair, ACIP) Dr Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**Agency Updates** CDC, CMS, DoD, DVA FDA, HRSA, IHS, NVPO, NIH		
8:45	**Meningococcal Vaccine** • Introduction • Immunogenicity and safety of MenACWY-CRM • GRADE (grading of evidence) for MenACWY-CRM • Use of MenACWY-CRM for high-risk infants • Vaccines for Children	Information Discussion Vote VFC Vote	Dr Lorry Rubin (ACIP, WG Chair) Dr Peter Dull (Novartis Vaccines) Dr Elizabeth Briere (CDC/NCIRD) Ms Jessica MacNeil (CDC/NCIRD) Dr Jeanne Santoli (CDC/NCIRD)
10:15	*Break*		
10:45	**Child/Adolescent Immunization Schedule** • Introduction • Review of updates since 2013 • Child/Adolescent Immunization Schedule, 2014	Information Discussion Vote	Dr Renée Jenkins (ACIP, WG Chair) Dr Iyabode Beysolow (CDC/NCIRD)
11:30	**Adult Immunization Schedule** • Introduction • Adult Immunization Schedule, 2014	Information Discussion Vote	Dr Tamera Coyne-Beasley (ACIP, WG Chair) Dr Carolyn Bridges (CDC/NCIRD)
12:15	*Lunch*		
13:30	**Pneumococcal Conjugate Vaccine (PCV)** • Introduction • PCV13 herd effect • Reduced dose schedule: review of evidence • Cost-effectiveness of reduced dose schedule	Information Discussion	Dr Nancy Bennett (ACIP, WG Chair) Dr Matt Moore (CDC/NCIRD) Ms Tamara Pilishvili (CDC/NCIRD) Dr Charles Stoecker (Assistant Professor, Dept of Global Health Systems & Development, Tulane University School of Public Health, New Orleans, LA)
15:30	*Break*		
16:00	**Herpes Zoster Vaccine (HZV)** • Introduction • Long term persistence study and vaccine supply • Burden of HZ disease and effectiveness of HZV in older adults • Decision and cost-effectiveness of HZV in adults ≥50 years of age • WG considerations for use of HZV in adults 50-59 years of age	Information Discussion	Dr Jeff Duchin (ACIP, WG Chair) Dr Janie Parrino, Dr Eddy Bresnitz (Merck) Dr Craig Hales (CDC/NCIRD) Dr Ismael Ortega-Sanchez (CDC/NCIRD) Dr Craig Hales (CDC/NCIRD)
17:30	**Public Comment**		
17:45	**Adjourn**		

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	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Thursday October 24			
8:00	**Unfinished Business**		Dr Jonathan Temte (Chair, ACIP)
8:15	**Yellow Fever Vaccine** Plans to evaluate recommendations for booster doses of yellow fever vaccine	Information	Dr Joseph Bocchini (ACIP, WG Chair)
8:20	**Global Immunization Update** • Global health measures and Mid-Decade Goals • Decade of the Vaccine and the Global Vaccine Action Plan • SAGE/WHO Vaccine recommendations – 2010 to present • Current SAGE Working Groups and topics under consideration by SAGE	Information Discussion	Dr Jon Abramson (Chair, Dept of Pediatrics, Wake Forest School of Medicine, Winston-Salem, NC; Chair, WHO Strategic Advisory Committee of Experts on Immunization [SAGE])
9:05	**Human Papillomavirus (HPV) Vaccines** • Introduction • 2012 HPV vaccine coverage data • 9-valent HPV vaccine • Updated ACIP statement	Information Discussion	Dr Joseph Bocchini (ACIP, WG Chair) Ms Shannon Stokley (CDC/NCIRD) Dr Alain Luxembourg (Merck) Dr Lauri Markowitz (CDC/NCHHSTP)
10:00	**Vaccine Supply**	Information	Dr Jeanne Santoli (CDC/NCIRD)
10:15	*Break*		
10:30	**General Recommendations on Immunization** • Introduction • Vaccine administration – update on new routes • Clinical implications of nonstandard vaccination practices • Vaccination records	Information Discussion	Dr Jeff Duchin (ACIP, WG Chair) Dr Andrew Kroger (CDC/NCIRD) Mr Stuart Myerburg (CDC/NCIRD)
11:30	**Influenza** • Introduction • Update: influenza epidemiology • Vaccine coverage, 2012-2013 • Fluzone high-dose vaccine efficacy trial results	Information Discussion	Dr Ruth Karron (ACIP, WG Chair) Dr Lisa Grohskopf (CDC/NCIRD) Dr Jim Singleton (CDC/NCIRD) Dr David Greenburg (Sanofi Pasteur)
12:45	**Public Comment**		
13:00	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DOD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/CCID]
NCIRD	CDC National Center for Immunization & Respiratory Diseases [of CDC/CCID]
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases [of CDC/CCID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
TBD	to be determined
WG	Work Group

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Acronyms

AAFP	American Academy of Family Physicians
AAHS	Amorphous Aluminum Hydroxyphosphate Sulfate
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
ADLs	Activities of Daily Living
AE	Adverse Events
AFP	American Family Physicians
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
BRFSS	Behavioral Risk Factor Surveillance System
CAP	Community-Acquired Pneumonia
CAPITA	Community Acquired Pneumonia Immunization Trial in Adults
CDC	Centers for Disease Control and Prevention
CDSi	Clinical Decision Support for Immunization
CHIP	Children's Health Insurance Program
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practices Based on Evidence
DHS	Department of Homeland Security
DoD	Department of Defense
DOH-UK	Department of Health—United Kingdom
DoV	Decade of Vaccines
DSMB	Data Safety Monitoring Board
DT	Diphtheria-Tetanus Vaccine
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent Assay
EMEA	European Medicines Agency
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GAVI	Global Alliance for Vaccines and Immunisation
GBS	Guillain–Barré Syndrome
GIVS	Global Immunization Vision and Strategy
GMC	Geometric Mean Concentration
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
HAI	Hemagglutination Inhibition Assay
HBV	Hepatitis B

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HCP	Healthcare Personnel
HHS	(Department of) Health and Human Services
Hib	*Haemophilus influenzae B*
HICPAC	Hospital Infection Control Practices Advisory Committee
HMO	Health Maintenance Organization
HP2020	Healthy People 2020
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Human Serum Bactericidal Assay
HZV	Herpes Zoster Vaccine
IAC	Immunization Action Coalition
IC	Immunocompromising Conditions
IDSA	Infectious Disease Society of America
IHR	International Health Regulations
IHS	Indian Health Service
IIS	Immunization Information System
IISSB	Immunization Information Systems Support Branch
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
LTPS	Long-Term Persistence Study
MCV4	Meningococcal Conjugate Vaccine
MDG	Millennium Development Goal (WHO)
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
NACCHO	National Association of County and City Health Officials
NCBDDD	National Center for Birth Defects and Developmental Disabilities
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHFS	National H1N1 Flu Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIFS	National Internet Flu Survey
NIH	National Institutes of Health
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NITAG	National Immunization Technical Advisory Groups (WHO)
NIVW	National Influenza Vaccination Week
NMA	National Medical Association
NNV	Number Needed to Vaccinate
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
ONC	National Coordinator for Health Information Technology
OPV	Oral Polio Vaccine
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PHN	Post-Herpetic Neuralgia
PIDS	Pediatric Infectious Diseases Society
PKIDs	Parents of Kids with Infectious Diseases
PPSV23	Pneumococcal Polysaccharide Vaccine
PRAMS	Pregnancy Risk Assessment Monitoring System

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PT	Pertussis Toxin
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RCVs	Rubella-Containing Vaccines
RDD	Random Digit Dial
RIV	Recombinant Influenza Vaccine
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SBA	Serum Bactericidal Antibody
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
SIAs	Supplementary Immunization Activities
SJS	Stevens-Johnson Syndrome
SMFM	Society for Maternal-Fetal Medicine
SME	Subject Matter Expert
SPS	Shingles Prevention Study
STPS	Short-Term Persistence Study
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States
USPHS	US Public Health Service
USPSTF	US Preventive Services Task Force
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFA	Vaccines for Adults
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VLP	Virus-Like Particle
VRC	Vaccine Research Center (NIAID)
VSD	Vaccine Safety Datalink
VT	Vaccine-Type
VTEUs	Vaccine and Treatment Evaluation Units (NIH, NIAID, DMID)
VTrckS	Vaccine Tracking System
WHO	World Health Organization
ZEST	Zoster Efficacy and Safety Trial

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Welcome and Introductions

Welcome

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Pickering welcomed everyone to the October 2013 Advisory Committee on Immunization Practices (ACIP) meeting, pointing out that they were very fortunate to have Dr. Thomas Frieden provide the opening remarks.

Opening Remarks

Thomas Frieden, MD, MPH
Director, Centers for Disease Control and Prevention

Dr. Frieden welcomed everyone to the Centers for Disease Control and Prevention (CDC), especially the three new ACIP members: Dr. Allison Kempe, Ms. Cynthia Pellegrini, and Dr. Art Reingold. He also welcomed the international visitors from Japan and China, as well as those listening in on bridge lines and through other means.

He emphasized that one of the fundamental concepts of ACIP that is so important is one of the essential principles by which CDC operates—to base all decisions on the highest quality data, openly and objectively derived. That does not mean there will always be unanimity of opinions on what should be done, but it always means that the decision-making process, the data that go into that decision-making process, and the thinking that goes into the deliberations and decisions will be transparent. ACIP is a model of that. In order for progress to be made in health, collaboration is needed between the public and private sectors. There must be safe space for that to occur, and the ACIP is a safe space for that collaboration. The vaccine schedules represent a way that literally, as one country, everyone is congruent on vaccination. That does not mean that there will not be deviations from those schedules by some clinicians and some parents for some reason, but it does mean that there is a standard that has been openly and objectively derived.

Dr. Frieden stressed that CDC was delighted that the ACIP members and CDC staff were in attendance. The government shutdown was very frustrating, challenging, and anxiety-provoking. CDC was not able to keep all of its commitments to its partners in this country and around the world, maintain momentum on some of the programs being scaled up (e.g., HPV vaccination), or track diseases as intensively as in the past (e.g., influenza). He expressed gratitude to the Commissioned Corps Officers who completed some of the preparatory work for this meeting, as well as other tasks such as pipetting in the laboratory and feeding laboratory animals. Commissioned officers were not furloughed because they are part of the United States Public Health Service (USPHS).

It is known that vaccines are one of the great success stories of the past 100 years, that there have been enormous achievements, and that the return on investment has been phenomenal with about $10 in societal returns and about $3 in healthcare returns for every $1 spent on vaccines. It is also known that there is unfinished business in vaccination and that much more

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needs to be done. However, Dr. Frieden said that they also should take a moment to recognize a very special anniversary—the 20th anniversary of the Vaccines for Children (VFC) program. The VFC is truly one of the great success stories of public health in this country. It is easy sometimes to take this for granted, but it did not just happen. It happened because of a lot of hard work, advocacy, data, and involvement of groups outside and inside of the government. The VFC has virtually eliminated health disparities in vaccination rates among the nation's children. That is remarkable in and of itself, and it is remarkable as an example of what can be done to reduce health disparities. The VFC also resulted in children being vaccinated in their medical homes. This was a major problem before the VFC, which reinforced the medical home through another type of public-private partnership. This was good for children, parents, providers, and the community.

More progress can be made in many areas, but one in particular is human papillomavirus (HPV) vaccine. Dr. Frieden noted that he had cared for women who died from cervical cancer, and he thinks of them when considering the status of HPV vaccine. There has been some success. Recent data show that the infections addressed by HPV vaccine have been reduced by more than half since 2006. That is progress, but it is known that only about 1 in 3 girls are fully vaccinated in the US. Rwanda is at 85% or higher. If the US vaccination rate was that of Rwanda, there would be more than 50,000 fewer cases of cervical cancer among girls alive today 0 through 12 years of age. For every year this is delayed, 4400 more women will get cervical cancer despite Pap smear screening. The US needs to do much better. There is typically a scale-up when new vaccines are introduced of about 10% per year increase. The most recent year for which there are data, 2012, there was no increase in HPV vaccination rates. This is disappointing, and efforts must be stepped up to protect children. This is an anti-cancer vaccine, and that point needs to be made clearly.

Dr. Frieden thanked the ACIP members for being there and for their attention to detail on the materials, recognizing that they are all busy and have competing demands. He also expressed appreciation to everyone who contributed to this meeting. He concluded that it was time to remind everyone to get a flu shot, including healthcare workers, to protect their families, patients, and themselves.

Introductory Comments

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Jonathan Temte
Chair, ACIP

Dr. Pickering indicated that the proceedings of this meeting would be available to people not in attendance via the World Wide Web, and he 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: Felicia Betancourt, Natalie Greene, Reed Walton, Stephanie Thomas, and Chris Caraway. Dr. Pickering stressed that special thanks was due to these individuals because during the shutdown they could not complete their work, but returned to complete it in a yeoman's manner. He also especially thanked Dr. Jean Smith, who is a member of the Commissioned Corps, who was working with Dr. Schuchat to orchestrate the meeting. Without them, this meeting would not have been possible.

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Emphasizing that there would be a full agenda, Dr. Pickering noted that 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 during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within 90 days following this meeting. Due to the recent shutdown, the minutes from the June 2013 meeting had not been posted at the time of this meeting, but were to be posted soon. Members of the press interested in conducting interviews with ACIP members were instructed to contact Jamila Howard Jones or Jason McDonald for assistance in arranging interviews. Dr. Pickering welcomed the three new ACIP voting members for whom this was their first ACIP meeting, and turned the floor over to Dr. Temte for introduction of these new members.

Dr. Temte first congratulated Dr. Pickering for being the 2013 recipient of the Pediatric Infectious Diseases Society's (PIDS) Distinguished Service Award for outstanding contributions in the field of pediatric infectious diseases. Dr. Temte read the following, "Through all of his many endeavors, Dr. Pickering's passion and energy have improved the lives of children throughout the United States and around the world. Perhaps his greatest impact on global child health has occurred since 2005 when he was named as the ACIP's Executive Secretary. The ACIP determines all of the vaccine recommendations in the US, and Dr. Pickering has expertly guided this august organization to a position of global prominence through worldwide collaborations with counterparts in countries on every continent." Dr. Temte emphasized that the number of visitors who attend ACIP meetings from throughout the world is a testament to that as well. He then introduced the following new ACIP members:

Dr. Allison Kempe

Dr. Kempe is the Director of Primary Care Fellowship, University of Colorado School of Medicine; Director of Research, Division of General Academic Pediatrics; and Director of Children's Outcomes Research Program, The Children's Hospital of Denver. She has presented data at ACIP meetings several times in the past. She has extensive experience as a pediatric health service researcher and clinician. Coming from Denver and Denver Children's Hospital, she has received several research grants in the field of immunization services delivery and has been involved in designing and evaluating intervention to improve immunization coverage. She has published more than 30 original scientific manuscripts in this field and has established a vaccine policy collaborative initiative that provides rapid access to vaccine-related knowledge amongst primary care providers. She brings to ACIP the perspective of a practicing primary care pediatrician.

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Ms. Cynthia Pellegrini

Ms. Pellegrini is the Senior Vice President of Public Policy and Government Affairs for the March of Dimes Foundation in Washington, DC. As a historic note, the March of Dimes had its start 75 years ago when it was founded by Franklin Roosevelt as the National Foundation for Infantile Paralysis. Dr. Temte said they were hoping that during Ms. Pellegrini's tenure on ACIP, dramatic progress would be made toward the elimination of polio. Ms. Pellegrini is the ACIP consumer representative. From 2004 through 2011, she advanced the American Academy of Pediatrics (AAP) advocacy agenda on a number of issues, including disaster preparedness and response to immunization and environmental health. Since 2011, she has overseen the March of Dimes advocacy agenda at the state and federal levels. She has a longstanding reputation in the child advocacy community, and is a knowledgeable and unwavering advocate of pediatric health.

Dr. Art Reingold

Dr. Reingold is a Professor of Epidemiology in the School of Public Health, University of California at Berkeley. Many know Dr. Reingold from his ACIP presentations dealing with the Strategic Advisory Group of Experts (SAGE) in applications of Grading of Recommendation Assessment, Development and Evaluation (GRADE) through the World Health Organization (WHO). Dr. Temte noted that three years ago, ACIP unanimously adopted GRADE. Dr. Reingold has worked for over 30 years on prevention and control of infectious diseases at the national and global levels, especially in developing countries. He has a great deal of experience investigating vaccine preventable diseases. He is a past member of SAGE , where he has helped to develop the guidance on evidence-based recommendations throughout the world. He served as a liaison to ACIP's Evidence-Based Recommendations Working Group. Dr. Reingold brings a great deal of knowledge from his many past endeavors.

Ali Maow Maalin

Following introduction of the newly appointed ACIP members, Dr. Temte noted that Ali Maow Maalin was the last person in the world to contract smallpox. Following that, he spent his time working to eradicate polio in Somalia. He used his example of being a vaccine refuser for smallpox in talking to families and vaccine-hesitant parents to try to encourage the adoption and acceptance of polio vaccine in Somalia. Unfortunately, he died in July 2013 at age 59 from malaria.

In conclusion, Dr. Temte also extended special thanks to all of the dedicated CDC colleagues, who went to extraordinary efforts to allow this meeting to occur as scheduled despite the recent federal shutdown.

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Dr. Pickering then recognized the following international visitors who were in attendance at this ACIP meeting:

- Dr. Li Li, Director of the China CDC National Immunization Program. Dr. Li attended the last ACIP meeting and since then, he has acquired information about the US immunization program, especially regarding how the ACIP makes evidence-based vaccine recommendations. Dr. Li has observed the activities of several ACIP work groups, and will be at CDC for an additional 1.5 months. Dr. Pickering invited those who had not met Dr. Li to do so, noting that he is a wonderful gentleman and an accomplished scientist, and that CDC had thoroughly enjoyed him being there.

- Ms. Ya Li Wang, National Center for Adverse Drug Reactions Monitoring at the China Center for Drug Reevaluation in Beijing, China.

- Dr. Keli Li, Division of Adverse Events Following Immunization Surveillance of the National Immunization Program at China's Centers for Disease Control and Prevention, also in Beijing. Dr. Pickering invited everyone to interact with Ms. Wang and Dr. Keli Li to learn more about the systems in China.

- Longtime friend, Dr. Nobuhiko Okabe, Director General at Japan's Kawasaki City Institute for Public Health. Dr. Okabe is a former Director of the Infectious Disease Surveillance Center of the National Institute of Infectious Diseases.

- Ministry of Health representatives from member countries of the WHO Pan American Health Organization (PAHO) usually attend each ACIP meeting, but a group was unable to attend this meeting. CDC will host the next delegation at the February 2014 ACIP meeting.

With regard to information for future international visitors to ACIP meetings, due to changes in Department of Homeland Security (DHS) Policy, additional forms will be required for each meeting at the time an international guest registers. It is critical that international visitors complete and submit these forms as soon as possible following registration. Felicia Betancourt, Committee Management Specialist, will be able to help with any questions and concerns about the process. The next ACIP meeting will take place at CDC on Wednesday and Thursday, February 26-27, 2014. Registration for all meeting attendees is required and was open on the ACIP website during this meeting. The registration deadline for US citizens is Monday, February 10th. Registration for non-U.S. citizens will be cut off a week beforehand, on Monday, February 3rd.

Dr. Pickering offered the following notes regarding liaison representatives:

- Carol Hayes will be representing the American Nurses Association (ANA) while Katie Brewer is on maternity leave. Katie and her baby are doing very well.

- Unable to attend this meeting were the *ex officio* members from Department of Veterans Affairs (DVA) and Centers for Medicare and Medicaid Services (CMS), and liaison representatives from Association of State and Territorial Health Officials (ASTHO), Department of Health—United Kingdom (DOH-UK), Ministry of Health/Mexico, and Society for Healthcare Epidemiology of America (SHEA).

To avoid disruptions during the meeting, Dr. Pickering instructed those present to turn all cell phones off. He explained that topics presented during the ACIP meeting include open

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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. Time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before any votes. Those who planned to make public comments were instructed to visit the registration desk in the rear of the auditorium to have Felicia Betancourt record their name and provide information about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that 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 a member's expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those specific vaccines. However, they are prohibited from participating in 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 the vaccines of that company.

Applications for ACIP membership are due no later than November 15, 2013 for the 4-year term beginning July 2014. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

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

Nominations: http://www.cdc.gov/vaccines/acip/committee/req-nominate.html

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, reaffirmed, or retired. Links to these recommendations and schedules can be found on the ACIP website. A listing of recommendations that have been published since the June 2013 ACIP meeting follows:

ACIP Recommendations Published Since June 2013

Title	Publication Date	MMWR Reference
▪ Use of PCV-13 and PPSV-23 Vaccines Among Children Aged 6-18 Years with Immunocompromising Conditions	6/28/13	2013;62:521-524
▪ Updated Recommendations for use of VariZIG	7/19/2013	2013;62:574-576
▪ Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the ACIP – United States, 2013-2014	9/20/2013	2013;62(RR07):1-43

http://www.cdc.gov/vaccines/hcp/acip-recs/recs-by-date.html

Two pending documents not shown are *Haemophilus influenzae B* (Hib) and Japanese encephalitis (JE) vaccine for children beginning at 2 months through 16 years of age.

The following resource information was shared pertaining to ACIP:

Vaccine Safety:
www.cdc.gov/vaccinesafety/

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Immunization Schedules (2013):
http://www.cdc.gov/vaccines/recs/schedules/default.htm

Childhood Vaccine Scheduler (interactive):
https://www.vacscheduler.org

Adolescent vaccine scheduler (interactive):
http://www.cdc.gov/vaccines/recs/Scheduler/AdolescentScheduler.htm

Adult Vaccine Scheduler (interactive):
http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm

Vaccine Toolkit:
http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html

Immunization for Women (American College of Obstetricians and Gynecologists)
www.immunizationforwomen.org

Before officially beginning the meeting, Dr. Temte called the roll to determine whether any ACIP members had conflicts of interest. The following conflicts of interest were declared:

- Dr. Tamera Coyne-Beasley: Research support is allocated to the University of North Carolina by Merck Pharmaceuticals for clinical trials.
- The remainder of the ACIP members declared no conflicts.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat welcomed everyone, noting that the most common question she received during the shutdown was, “Are we going to have the ACIP meeting?” She said she felt like the ACIP meeting was the Rolling Stones concert and she was grateful that they did not have to cancel it. She reported that between July and September 2013, CDC issued six *Morbidity and Mortality Weekly Report (MMWR)* reports on coverage updates, including HPV, teens, kindergarteners, toddlers, and influenza coverage. There have been sustained high or increasing rates, with the notable exception of HPV. As Dr. Frieden indicated, that is CDC’s highest priority for urgent improvements in coverage.

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One fallout from the shutdown was the inability to have the tetanus, diphtheria toxoids and acellular pertussis vaccine (Tdap) in pregnancy session, so Dr. Schuchat provided a brief update. The statement on recommending Tdap in every pregnancy was published in February 2013, and an update was provided during the June 2013 ACIP meeting that sketched out the forward plans for this. CDC and the Food and Drug Administration (FDA) continue to monitor Vaccine Adverse Event Reporting System (VAERS) for reports, and the studies in the Vaccine Safety Data (VSD) link have begun. No data are available yet on coverage, though data through 2011 were presented during the June 2013 meeting. Those data showed that only 1.6% of pregnancies outside of California in the VSD sites had Tdap administration. In California, 29% of pregnancies had Tdap administered. CDC believes that coverage has improved and looks forward to updates on coverage data. Initial safety data from the VSD sites are expected by the summer of 2014 for the prespecified outcomes being assessed. The program is also developing a prospective clinical study of Tdap safety in pregnant women for the Clinical Immunization Safety Assessment (CISA) Collaboration.

Regarding federal support for immunization through the discretionary Section 317 program, like most programs during the era of budget pressures, CDC has to prioritize. Dr. Schuchat reminded everyone that CDC's three priorities for Section 317 funding include the following:

- ❑ Maintain the immunization infrastructure (e.g., the people and systems that support vaccine delivery, surveillance, and response to vaccine-preventable disease) and developing and maintaining the evidence base supporting immunization policy that ACIP reviews regularly

- ❑ Modernizing immunization systems and supporting innovative technology through the many IT initiatives underway, including interoperability between electronic health records (EHRs) and registries, completing the Vaccine Tracking System (VTrckS) rollout, et cetera

- ❑ Maintaining flexible funding for vaccine purchase to fill gaps, which primarily would include uninsured adults and public health response to emergencies or outbreaks

Recently, CDC implemented a change in the state vaccine ordering policy to no longer permit state or Children's Health Insurance Program (CHIP) ordering of vaccines that would rely on advancing credit from the 317 funding. Instead, states were required to have purchase orders before their orders could be placed through the VTrckS system for state or CHIP vaccine. This was implemented on October 1, 2013. Health departments did an enormous amount of work to prepare for October 1st, because there was little time for implementation. . This turned out to be "just in time" policy, because work had been done on this and there was a software update. The new system meant that the government shutdown and lapse in funding for 317 vaccines did not have to stop the ordering of state and CHIP vaccines. State and CHIP orders were processed for 800,000 doses of vaccine between October 1st and October 17th despite no dollars in the 317 vaccine fund. CDC is now working with ASTHO and the National Association of County and City Health Officials (NACCHO) on a working group to strengthen the collaboration around future program changes, and will be working forward on having more advanced notice before such changes.

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Centers for Medicare and Medicaid Services (CMS)

Dr. Hance was unable to attend; therefore, Dr. Temte read her CMS report into the record:

Medicare Flu Vaccine Data: CMS has worked with the Health Resources and Services Administration (HRSA) and the National Vaccine Program Office (NVPO) to post Medicare influenza vaccination information for those in fee-for-service on the NVPO website. The website is http://www.hhs.gov/nvpo/flu-vaccination-map and is updated weekly.

Coverage of Preventive Services for Adults Currently Enrolled in Medicaid: While the benefit package for adults who receive health care coverage under the Affordable Care Act (ACA) is required to include coverage of preventive services, including coverage of all ACIP recommended vaccinations, states continue to have the option to cover preventive services for adults currently enrolled in Medicaid. The Affordable Care Act addressed this by including a provision (section 4106) that provides an incentive to states which provide coverage of all ACIP recommended vaccines and their administration as well as the Grade A/S US Preventive Services Task Force (USPSTF) recommended services. To date, six states have submitted a request to CMS to cover these services and receive the incentive (California, Hawaii, Nevada, New Hampshire, New Jersey, and New York). CMS continues to work with all states to encourage coverage of preventive services.

Department of Defense (DoD)

Dr. Geibe indicated that while they had no new updates for this meeting, the DoD continues to align its service-specific vaccine policies with those of CDC and ACIP.

Department of Veteran's Affairs (DVA)

Dr. Kinsinger was unable to attend; therefore, Dr. Temte read her DVA report into the record:

The Veterans Administration (VA) and the DoD continue to work toward information exchange of clinical data between the two agencies' electronic health record systems.

The VA is working on certification of its electronic health records for Meaningful Use and has undertaken an effort to modify its underlying immunization file structure to address those needs.

The VA is also involved in several pilot projects that involve exchange of immunization information with retail pharmacies.

The VA has developed an influenza immunization mobile "app" that staff will be piloting this influenza season. The "app" is designed to provide an easy way to document administration of influenza vaccine in a mass vaccination scenario, such as a health fair. A few confirmed cases of influenza have been identified in VA facilities. A total of 867,493 doses of influenza vaccine have been recorded since August 1, 2013.

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Food and Drug Administration (FDA)

Dr. Sun reported that since the last ACIP meeting, the following noteworthy approvals had been made:

- FLULAVAL® quadrivalent influenza vaccine was approved for those over 3 years of age
- FLULAVAL® trivalent was approved for those 3 through 17 years of age
- Menveo® quadrivalent meningococcal vaccine was approved for children 2 month through 23 months of age
- So far this year, the strain change supplements for influenza vaccine include 4 quadrivalent vaccines and 4 trivalent vaccines

Health Resources and Services Administration (HRSA)

Dr. Caserta indicated that the proposed rulemaking by the Secretary to add seasonal influenza vaccine as opposed to trivalent should be published in the *Federal Register* shortly so that it will be covered under the program.

Indian Health Services (IHS)

Ms. Groom reported that the IHS is beginning to post its weekly influenza surveillance reports on its website. At this point, IHS had administered about 150,000 doses, which is about 15% of its patient population. HPV is clearly a high priority area, and the IHS is undertaking an effort to work with its sites on HPV vaccine, evaluate its data, and target some specific interventions in some sites in an effort to increase its rates.

National Institutes of Health (NIH)

Dr. Gorman reported that on September 3, 2013 in Bakersfield, California, CDC and NIH announced that they will launch a randomized clinical control trial (RCT) to better understand how to control coccidioidomycosis, or valley fever. The trial will involve about 1000 people diagnosed with community-acquired pneumonia (CAP), the most common presentation of valley fever. One half will be randomly chosen to receive a traditional antibiotic and a placebo, and the other half will receive an antibiotic plus fluconazole, an antifungal medicine usually used to treat valley fever. The patients will be tested immediately and then every two weeks to determine whether they have valley fever and which treatment proves to be most effective. Both Drs. Collins and Frieden, who were present at this announcement, said the trial will spread awareness about the disease and educate physicians, researchers, and patients about diagnosis and treatment. Within National Institute of Allergy and Infectious Diseases (NIAID), Dr. John Mascola has been named as Director of the Dale and Betty Bumpers Vaccine Research Center (VRC). He was Acting Director, and before that Director of the Core Virology Laboratory. His work demonstrated a protective role of antibody response in HIV infections. That work helped direct the discussion of the development of the HIV vaccines.

On September 16, 2013 NIAID held a Mini-Summit on Adenovirus Platforms for HIV Vaccines. The participants were greeted and given their charge by Dr. Fauci. A meta-analysis of previous studies using adenovirus platforms for HIV vaccines was discussed by Dr. Dean Follman. The questions of biologic plausibility for adenovirus increasing HIV acquisition risk and whether this potential risk applies equally to all other potential adenovirus vectors equally were discussed. There was a spirited discussion of these questions as well as future research pathways that could be taken to answer the questions raised. A written report of the meeting will be forthcoming.

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On August 8, 2013, an article was published in *ScienceOnline*® describing a malaria vaccine that was developed by the Sanaria Corporation and tested in the NIAID Clinical Center. The vaccine was found to be safe and effective and seemed to indicate that there is a dose-dependent immunologic threshold for development of malaria immunity, and that this immunity may be obtained by IV administration of attenuated, cryopreserved sporozoites [http://www.sciencemag.org/content/341/6152/1359.abstract].

With regard to the Division of Microbiology and Infectious Diseases (DMID), on September 18, 2013, the Vaccine and Treatment Evaluation Units (VTEUs) sites initiated mix and match studies for H7N9 vaccines with adjuvants. These trials will use influenza vaccine antigen from one manufacturer and administer this antigen either unadjuvanted, adjuvanted with MF59, or adjuvanted with AS03. There are two trials. One trial will test MF59 alone (NCT 01938742). The other trial will test mainly AS03, but will have MF59 components (NCT 01942265). The target enrollment for these two trials is 1700 subjects. At this time, approximately two-thirds of recruitment had been completed.

On September 26, 2013 a new round of VTEU awards were announced. There are now nine VTEU sites. They were awarded a 7 year contract and include the following:

- Baylor College of Medicine, Houston (PI: Wendy A. Keitel, MD)
- Cincinnati Children's Hospital Medical Center (PI: David I. Bernstein, MD, MA)
- Duke Medicine [new to VTEU program], Durham, North Carolina (PI: Emmanuel B. Walter, MD, MPH)
- Emory University, Atlanta (PI: Mark J. Mulligan, MD)
- Group Health Research Institute, Seattle (PI: Lisa A. Jackson, MD, MPH)
- Saint Louis University (PI: Robert B. Belshe, MD)
- University of Iowa, Iowa City (PI: Patricia L. Winokur, MD)
- University of Maryland, Baltimore (PI: Karen L. Kotloff, MD)
- Vanderbilt University, Nashville (PI: Kathryn M. Edwards, MD)

For several years and in several different vaccine and therapeutic areas, DMID has sponsored clinical trials that enroll pregnant women. While designing, implementing and conducting the data analysis of these studies, the DMID has identified multiple challenges specific to conducting research in this population. To address these challenges DMID continues to seek consultative input from experts in the fields of neonatal and perinatal medicine, pK, clinical trial investigators , regulatory issues, et cetera. During 2011 and 2012, DMID organized three consultative conferences to develop a template for protocol design of vaccines administered during pregnancy and harmonize assessment of adverse events emerging during these studies. The output is two related articles and an editorial recently published in the journal *Vaccine* and can be found through the following links:

http://www.sciencedirect.com/science/article/pii/S0264410X13009857
http://www.sciencedirect.com/science/article/pii/S0264410X13009742

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There is an ongoing HPV vaccine trial. This trial will examine the immunogenicity of the quadravalent vaccine series when not completed as per the label. The study hopes to enroll approximately 1400 girls, with the results of individuals not receiving the recommended series of vaccines in the recommended time with a "control" group of individuals who receive the vaccine as per the vaccine label (NCT01030562).

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that during its recent committee meeting, NVAC approved a revision to the *Standards for Adult Immunization Practices*. It has been 10 years since the earlier statement. The revised standards include recommendations for everyone, as well as an audience-based set of standards for vaccinating providers, providers who see patients but do not generally vaccinate, health departments, healthcare organizations, and others. NVAC also approved a report from the Global Immunization Working Group (GIWG) that focuses on six areas, including: 1) enhancing time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals 2) strengthening global immunization systems; 3) enhancing global capacity for vaccine safety monitoring and post-marketing surveillance; 4) improving global immunization research and development capacity; 5) strengthening capacity for vaccine decision-making; and 6) coordination of HHS global immunization efforts. NVAC has three other working groups, including the following:

- Maternal Immunization Working Group, with an initial goal to improve current implementation of recommendations for pregnant women, which will be followed by assessment of barriers to research and development with regard to development of new vaccines for pregnant women.

- Vaccine Acceptance/Hesitancy Working Group

- Human Papillomavirus (HPV) Working Group, which is actively working to address concerns to improve vaccination uptake.

National Vaccine Program Office (NVPO)

Dr. Gellin indicated that the *Standards for Adult Immunization Practices* would be published in *Public Health Reports* early in the spring. A summary table is currently being produced, which he encouraged everyone to review for an overview of the details. The CMS mapping tool for adult influenza immunization for CMS beneficiaries is on the NVPO home page as well as the HHS home page, which is currently receiving a lot of traffic. This tool allows zip code level information, particularly with regard to racial and ethnic disparities. At the end of September 2013, NVPO awarded RAND a contract to focus on developing an adult immunization strategy and adult immunization strategic plan. RAND helped with the National Vaccine Plan (NVP), so this layers on top of that. RAND will be collecting information about the direction that NVPO should be taking. The Institute of Medicine (IOM) has been developing a decision support tool on vaccine research and development priorities. IOM delivered a presentation to ACIP of the screen shots, which was part of their beta rollout. Dr. Gellin encouraged everyone to look at the IOM website called "Ranking Vaccines" to look at the live screens, and to provide feedback to NVPO.

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Meningococcal Vaccines

Introduction

Lorry Rubin, MD
Chair, Meningococcal Working Group
Advisory Committee on Immunization Practices

Dr. Rubin indicated that there are currently three meningococcal conjugate vaccines that are FDA-licensed for infants and toddlers, including the following:

- MenACWY-D (Menactra®, sanofi pasteur)
  - 2-dose series at 9 through 23 months
  - Licensed in September 2010

- HibMenCY-TT (MenHibrix®, GlaxoSmithKline)
  - 4-dose series at 2, 4, 6, and 12 through 15 months
  - Licensed in June 2012

- MenACWY-CRM (Menveo®, Novartis)
  - 4-dose series at 2, 4, 6, and 12 months
  - Licensed in August 2013

In terms of ACIP recommendations for infant meningococcal vaccination, during the October 2012 meeting, there was a recommendation for vaccination only of high-risk infants. The purpose of this session was to consider adding MenACWY-CRM to the list of available meningococcal vaccines for use in high-risk infants and included presentations on immunogenicity and safety of MenACWY-CRM, GRADE evaluation of MenACWY-CRM, and considerations of use of MenACWY-CRM in high-risk infants.

MenACWY-CRM provides protection against additional serogroups, and may be used for infants traveling to areas where meningococcal disease is hyperendemic or epidemic. This vaccine is given as four 0.5 mL doses intramuscularly at 2, 4, 6, and 12 months of age. It is immunogenic against serogroups A, C, W, and Y, but it does not offer protection against serogroup B. In general, the safety profile is similar to other childhood vaccines.

With regard to other activities of the Meningococcal Working Group (WG), in March 2013, a comprehensive ACIP meningococcal vaccine statement was published. The WG reviewed and updated the Hib vaccination recommendation, and there will be a recommendation report that was approved by this WG in February of 2013 that should be published in early 2014. The WG also is working on the approach to candidate serogroup B meningococcal vaccines.

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Immunogenicity and Safety of MenACWY-CRM

Peter Dull, MD
Head Meningitis & Sepsis Vaccines Clinical Franchise
Novartis Vaccines

Dr. Dull reported that Novartis Vaccines recently licensed a meningococcal B vaccine in Europe and Australia. Novartis Vaccines is working on the development of an A, B, C, W, Y vaccine, which is in clinical trials in the US and elsewhere. He also leads the clinical group for maternal immunization with a group B strep vaccine.

During this session, Dr. Dull reported on the incremental clinical data that have been generated for this vaccine since the last time he presented an overview to ACIP which included the following additional studies:

- MenACWY-CRM Phase 3 studies in infants
  - Immunogenicity at 7, 12, and 13 months for 2, 4, 6, and 12 month dosing regimen
  - Concomitant vaccination with routine infant vaccines
  - Safety
  - This is the study that is most prominently featured in the package insert associated with the recent US licensure

- MenACWY-CRM Phase 3 study in older infants
  - Immunogenicity of a 7-9, 12 month schedule in infants
  - Concomitant MMRV vaccination at 12 months
  - Safety

- MenACWY-CRM Phase 3b ongoing study of persistence after infant series

MenACWY-CRM (Menveo©) is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135. It is now approved for use in persons 2 months through 55 years of age. It has taken the last five or so years to change the indication from 2 years to 2 months of age. The formulation is comprised of 10 micrograms of the A component and 5 micrograms of each the C, W, and Y components. The formulation is a liquid lyophilized formulation, so it is a liquid C, W, Y, which is used to reconstitute a lyophilized A component. The vaccine is adjuvant- and preservative-free.

In terms of the scope of the clinical program, several key studies in infants 2 through 23 months of age provided data to support the licensure for Menveo® in infants. The Phase 2 (V59P5) study in infants from 2 months of age supported the dose and dose-regimen finding conducted in the United Kingdom (UK) and Canada. It also showed data with good immunogenicity early in the series after the second dose at 5 months of age. The Phase 3 (V59P14) study in infants from 2 months of age was conducted in the US and Latin America, and included concomitant use with Pediarix®. Pentacel®-based concomitant use was also assessed. Dr. Dull previously presented data on that study to ACIP in 2011, which showed that concomitant use was supported for the antigens contained in Pediarix® and Prevnar 7®. During this session, he reviewed three additional studies:

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- Phase 3b (V59P23) study of infants from 2 months of age, a 7700-subject safety study conducted at the US, Latin America, and Asia

- Phase 3 (V59_33) study in infants from 2 months of age, which provides the key immunogenicity data in a Pentacel®-based concomitant-use analysis

- Phase 3 (V59P21) study in older infants from 7 months of age, which is the 2-dose older-infant study.

In total, the MenACWY-CRM Phase 2/3 safety database studies include 9000 infants vaccinated with the 4-dose series and 2000 older infants vaccinated with the 2-dose series.

With regard to the Phase 3 results in infants from studies V59_33 and V59P23, this was a standard infant vaccination concomitant use study. One arm would have received MenACWY-CRM (Menveo®) with routine infant vaccines, while the other arm would have received routine vaccines alone. One of the challenges to this program was the lack of a licensed but non-recommended comparator in the infant space. Therefore, as opposed to conducting a placebo-controlled trial, after discussion with the FDA, all of these studies for the infant indication were run with open-label designs. The study objectives were to assess the adequacy of the immune response following a 4-dose series; and assess the safety and tolerability of MenACWY-CRM when given concomitantly with routine infant vaccines compared to routine vaccines alone [Clinicaltrials.gov Identifiers NCT01000311 (Study V59_33) and NCT00806195 (Study V59P23)].

In terms of the immunogenicity data from the V59_33 study, the results were very similar to the V59P14 study. There were good responses after the initial primary series to C, W, and Y with 94% to 98% of the children reaching the protective threshold for those serogroup. After the booster dose at 12 months of age, 90% plus across those 3 serogroups and 89% against serogroup A. A decline was observed prior to the booster dose more markedly with serogroup A, which also has been observed in other studies using human serum bactericidal assay (hSBA), but with good persistence in other serogroups. In the Pentacel®-based concomitant-use study, either the GSK or Merck hepatitis B (HBV) vaccine was used. There was a very similar immune response when MenACWY-CRM was given with routine vaccines and when routine vaccines were given alone.

For the four components of the pertussis vaccine, two different analyses were done, a seroresponse and a geometric mean concentration (GMC) ratio. FDA has an inclination toward the seroresponse endpoint more so than the GMC ratios. The point estimates of the GMCs in the concomitant-use data were actually higher when Menveo® was given with Pentacel® in this case. Non-inferiority was achieved in terms of the GMC ratio for all four of the pertussis antigens. In contrast, the seroresponse for 2 of the 4 antigens was just below the 95% confidence interval. The -10% was missed for both pertussis toxin (PT) and fimbriae (FIM). In the post-hoc analysis accounting for group and center effects, non-inferiority was achieved for PT, with a lower limit of 95%CI of -3.9%. FIM remained outside the limit with lower limit 95% CI of -10.2% [Nolan T, et al. Presented at the Infectious Diseases Society of America Annual Meeting; October 2012; San Diego, CA. Clinicaltrials.gov Identifier NCT01000311].

In terms of Prevnar 7®, as both Menveo® and Prevnar® contain the same CRM carrier protein, this is a topic of some interest. As mentioned earlier, study V59P14 assessed the post-third dose. In this study, non-inferiority was achieved for 13 of the 14 serotype analyses. Non-inferiority was achieved for all serotypes after the fourth dose. In study V59_33, non-inferiority was achieved for 5 of the 7 serotypes after the third dose. For 6B and 23F, non-inferiority was

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not achieved. This same post-hoc analysis was evaluated for center effect, and found that there was a strong center effect and non-inferiority was achieved after accounting for this effect. More importantly, for post-boost dose, a different endpoint was assessed. Because titers are quite high after the fourth dose, using a threshold level is felt to be less interesting than using a GMC ratio. Therefore, the typical FDA expectation is that a GMC ratio analysis is used to analyze whether the titers are meaningfully impacted by the concomitant use of a new vaccine. The lower limit of the 95% confidence interval is expected to be above 0.5 in that GMC ratio. After the boost, non-inferiority was achieved across each of the 7 serotypes in Prevnar 7®. This is similar to what was shown in Study V59P14 in the two different cohorts in which non-inferiority was achieved in 14 of 14 of the serotypes. There were 42 different analyses for Prevnar 7® post-primary and post-boost doses. Of those 42 analyses, 3 were not non-inferior. However, after the post-hoc analyses, 1 of the 42 was missed for non-inferiority. Importantly, after the boost dose, no non-inferiority analyses were missed in either of the studies analyzed.

Moving to reactogenicity, local injection site reactions were assessed for Menveo® or Prevnar®, which was the comparator used in the control group. Generally similar, if not lower, injection site reactions were solicited after Menveo® administration. This was not unexpected, given that it is an adjuvanted versus a non-adjuvanted vaccine. There were also similar rates in terms of the systemic reactions solicited within 7 days of vaccination with either MenACWY-CRM given concomitantly with routine vaccines, or with routine vaccines alone. Severe reactions were similar when Menveo® was added incrementally to routine vaccines.

Study V59P21 assessed late toddler or late infant vaccination, with the first dose administered between 7 and 9 months of age with a second dose administered at 12 months of age. The second dose was administered either alone or with measles, mumps, rubella, varicella (MMRV) vaccine administered concomitantly at 12 months. The study was begun in 2007 and was conducted when MMRV was more routinely given at the 12-month dose. The study objectives were to assess the immunogenicity of a 2-dose series of MenACWY-CRM; immune response to MMRV and MenACWY-CRM antigens when given concomitantly; and safety and tolerability as measured by local and systemic reactions. The same threshold for A, C, W, and Y needed to be met, as well as noninterference with the concomitant antigens. Blood was drawn at 8 to 10 months of age. There were lower responses to A, W, and Y, but good responses to the C component after a single dose at 7 to 9 months of age. After the booster dose, there were very high responses, meeting the pre-specified sufficiency criteria for the study. For the noninterference study analysis with the MMRV components, the lower limit of the 95% confidence interval was required to be above -0.5%. In each case, concomitant use was supported and non-inferiority was achieved for the MMRV vaccine.

From the earlier Phase 3 study, V59P14E1, children were followed through 3.5 years of age. More data will be collected on these children later this year when they are 5 years of age. A primary response was observed after the infant series, with declines most prominently observed in serogroup A. The best responses were observed for serogroups W and Y, with responses somewhere in between for serogroup C. At 40 months of age, between 34% and 76% of infants maintained C, W, and Y persistence of bactericidal antibodies at the ≥1:8 level.

In summary, MenACWY-CRM (Menveo®) is well-tolerated and immunogenic in over 7500 infants studied with a 4-dose series administered at 2, 4, 6, and 12 months. No unexpected safety signals of concern were observed. There is similar immunogenicity of all concomitant vaccine antigens when administered with MenACWY-CRM. MenACWY-CRM meets all non-inferiority across the 7 pneumococcal conjugate vaccine (PCV) serotypes at 13 months. Novartis is conducting an ongoing study with Prevnar 13®, for which data should be available in early 2014. MenACWY-CRM is also well-tolerated and immunogenic when administered as a

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2-dose series at 7 and 12 months. No interference with MMRV has been observed. Persistence of hSBA is evident at 40 months of age after the infant series, with further data at 60 months of age anticipated to be available in 2014.

Discussion Points

Dr. Warshawsky (NACI) inquired as to whether any head-to-head trials have been conducted with any other quadrivalent meningococcal vaccines to assess immunogencity.

Dr. Dull responded that during the licensure procedure, the licensure criteria were against Menactra® in the 11 through 55 and 2 through 10 year age groups. Non-inferiority was achieved for those analyses, and there was statistically higher immunogenicity against 3 of the 4 serogroups in that study versus Menactra® in the adolescent population.

Dr. Temte wondered whether any safety issues were observed in toddlers with the co-administration of MMRV.

Dr. Dull replied that these data are published, and that no increase was observed in the fever profile or change in the fever profile of MMRV. The study was underpowered to assess febrile seizures.

Dr. Duchin asked whether there were any data regarding pre-vaccination titers for 7- through 9-month old children in Study V59P21 for those data time points.

Dr. Dull responded that pre-vaccination could be inferred from the baseline infant data from the US population. Very low hSBA is observed, with no background increase seen without vaccination. That is, all titers were vaccine-induced.

GRADE Evidence for MenACWY-CRM

Elizabeth Briere, MD, MPH
LCDR, US Public Health Service
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Briere noted that on the third anniversary of GRADE, she would be presenting the third GRADE evaluation for meningococcal vaccines, specifically for MenACWY-CRM. The first step in the GRADE process is to formulate the study question. In light of the current ACIP recommendation for meningococcal vaccine for infants at increased-risk, the study question for this assessment was, “Should MenACWY-CRM be administered to 2, 4, 6, and 12 month old infants at increased risk for meningococcal disease?” This includes infants with persistent complement pathway deficiencies, infants with anatomic or functional asplenia, infants in communities with serogroup A, C, W, or Y disease outbreaks, and infants traveling to the Hajj or meningitis belt of Sub-Saharan Africa. In GRADE several key factors are evaluated when discussing considerations for vaccine use. First, the evidence is GRADEd to determine the balance between benefits and harms and the overall evidence type. The values and preferences of all involved (e.g., general population, patients, health care providers, and policy-makers) and the cost of vaccine also are considered.

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In terms of the outcomes GRADEd and the determination of evidence type for these outcomes, after determining the study question, the working group selected outcomes that they felt were important to answer this question. The quality of the evidence for these outcomes was then evaluated. First, the working group created a list of 5 outcomes to GRADE. Next, non-CDC members of the working group ranked the relative importance of the outcomes on a scale of 1-9 with 1-3 as not important; 4-6 as important, but not critical for answering the question; and 7-9 as critical for answering the question. Only evidence for critical and important outcomes are GRADEd. Regarding the rankings of the outcomes considered for infant meningococcal vaccines, only mild adverse events were ranked as not important.

The final outcomes that were graded included short-term and long-term efficacy to assess the benefits of vaccination and serious adverse events and interference to assess the harms of vaccination. In compiling evidence to GRADE for each of these outcomes, several inclusion criteria were used. US and non-US populations were used as long as the proposed US schedule of 2, 4, 6, and 12 months was used for MenACWY-CRM. The data were compiled for MenACWY-CRM by outcome and study design (e.g., RCT or observational study). A total of four studies met the inclusion criteria. One was published, two were presented at a conference, and one was unpublished. Only healthy infants were included in these studies. All of these studies were RCTs, but one study did not have a control group for the full series short-term efficacy outcome, so it was observational for this outcome. Doug Campos-Outcalt and Dr. Briere rated the evidence separately and compared results. Differences in the results were discussed with the working group until consensus was reached.

Due to the low incidence of meningococcal disease, pre-licensure clinical effectiveness studies are not feasible. Serum bactericidal antibody (SBA) titers are used as the immunologic correlate of protection. Multiple studies have shown that human SBA titers of 1:4 correlate with protection against meningococcal disease. While these studies were based on SBA activity against serogroup C disease, human SBA titers greater than 1:8 are accepted as correlates of protection for vaccine licensure for other serogroups. Indirect data adds to the confidence in SBA titers as correlates of protection. Effectiveness was demonstrated to correlate with SBA titers in the adolescent MenACWY-D in the US and the meningitis C conjugate vaccines in the UK [Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969 Jun 1;129(6):1307-26; Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from post-licensure surveillance in England. Clin Diagn Lab Immunol. 2003 Sep;10(5):780-6].

As presented by Dr. Dull, short-term efficacy was achieved for all serogroups after the infant 3-dose series and the full 4-dose series. Duration of protection 28 months post-fourth dose varied by serogroup. A higher percentage of patients had protective titers for serogroups W and Y than for serogroups A and C post-fourth dose. This waning immunity indicates that the vaccine is unlikely to provide protection long-term and that a booster dose would be necessary for children at high risk long-term.

In all studies that assessed serious adverse events, events were recorded from the time of vaccination through 6 months post-vaccination and were physician-verified. Among over 5000 infants studied, at least one serious adverse event was reported during the infant series for 3% of study participants and 2% of controls. At least one serious adverse event was reported one month after the infant series by 1% of both study participants and controls. At least one serious adverse event was reported 6 months after the full series by 2% of both participants and controls. Of the serious adverse events, 11 were considered possibly related to MenACWY-CRM by non-blinded investigators, including: acute encephalomyelitis, cellulitis, complex partial

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seizure, epilepsy, febrile seizure (3), fever, Kawasaki Disease (3). Deaths occurred among 10 subjects who received MenACWY-CRM and among 2 subjects in the control group. There was no clustering of any single one cause of death and no temporal clustering relative to receipt of vaccine. A 3:1 or 2:1 randomization was used in the studies. In one study, the control arm crossed over and received MenACWY-CRM at 12 months. At different time points in the study, there were between 7000 and 9000 total subjects who received MenACWY-CRM, and between 2000 and 4000 controls. Thus, the data were heavily weighted in person-time exposure to MenACWY-CRM recipients. However, none of these deaths were considered related to receipt of MenACWY-CRM.

Based on the three studies with data on interference with co-administered vaccines, antibody responses for diphtheria, tetanus, hepatitis B, and Hib antigens and all poliovirus, serotype met criteria for non-inferiority after co-administration with MenACWY-CRM. In two of the three studies, non-inferiority criteria to some pertussis antigens were not met. In one study, non-inferiority criteria were not met for pertussis toxin or FIM. However, after adjusting for center differences, non-inferiority criteria were met for pertussis toxin. In the second study, non-inferiority criteria were met for pertactin using GMC ratios, but not when using the secondary endpoint of seroresponse. In several studies, post-dose three, pneumococcal IgG antibody responses after PCV7 co-administration did not meet criteria for non-inferiority for serotypes 6B and 23F. However, after adjusting for center differences, non-inferiority criteria were met for these serotypes. Post-dose 4, all pneumococcal serotypes met non-inferiority criteria in all studies. Regarding the benefits and harms for an infant MenACWY-CRM series, the vaccine is safe and immunogenic in the short-term, although duration of protection two years post-vaccination varies by serogroup.

In GRADE, all of the available data for each outcome are evaluated on five criteria (e.g., risk of bias/methodological limitations, inconsistency, indirectness, imprecision) and other considerations (e.g., publication bias, strength of association, dose gradient), and a final evidence type is assigned. None of the studies for MenACWY-CRM were blinded. The working group felt that blinding was likely to introduce more bias for a more subjective outcome such as serious adverse events and less likely to introduce bias for an objective outcome such as efficacy or interference. Therefore, the evidence was downgraded for the serious adverse outcomes if there was single or no blinding, but efficacy outcomes were not downgraded. For risk of bias, the working group found serious limitations for the serious adverse events outcomes due to no blinding and large losses to follow-up or withdrawals. No serious limitations were found for inconsistency. Limitations were noted for indirectness for all outcomes because the data available were from healthy infants and no data on high-risk infants were available. The RCT for long-term efficacy 28 months post-dose 4 was downgraded for imprecision because the sample size was less than 300 and the lower limit of the confidence interval showed only a small difference in hSBA titers compared to the control group. There were no serious limitations for publication bias for any of the outcomes.

In summary, the evidence was downgraded for risk of bias for the serious adverse events outcome, for indirectness for all outcomes, and for imprecision for the long-term efficacy data. The evidence was not downgraded for any of the other outcomes. Therefore, the overall evidence type is 3.

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Values and preferences of the public and providers were part of the evidence considered during the June 2011 and October 2012 ACIP discussions on infant and toddler meningococcal recommendations. In June 2011, the ACIP voted to recommend routine vaccination of increased-risk toddlers 9 through 23 months of age with the only meningococcal vaccine licensed for this age group at the time, MenACWY-D. In October 2012, after licensure of the first infant meningococcal vaccine, HibMenCY, the ACIP voted to recommend vaccination of increased-risk infants 2 through 23 months of age. With these two votes, vaccination with meningococcal vaccine became the standard of care for high-risk infants. MenACWY-CRM provides an additional vaccine option for these infants. A cost-effectiveness analysis was not performed for the use of meningococcal vaccines in high-risk infants. However, based on the low estimated number of infants per year that are at risk for meningococcal disease and the cost of the available vaccine options for this age group, vaccinating infants with MenACWY-CRM has a low overall cost.

Therefore, in summary, the overall evidence type for the MenACWY-CRM data is a 3. The data support the safety and immunogenicity of the vaccine against Serogroup A, C, W, and Y. As vaccination of increased-risk infants is the current standard of care, MenACWY-CRM provides an additional vaccine option for these infants and has a lower overall cost. The GRADE evidence tables for MenACWY-D and HibMenCY vaccination in all infants were presented at past ACIP meetings and are posted on the ACIP GRADE website. The GRADE table presented during this session and evidence tables for the use of MenACWY-D and Hib-MenCY in high-risk infants also will be added to the GRADE website.

Discussion Points

Dr. Temte was somewhat troubled by the number of deaths in the study group versus the control group, and requested further explanation. That number of deaths in a relatively small cohort of healthy children was amazing to him. Cardiac arrest, cardiopulmonary failure, lung infections, and so on are not typical outcomes in healthy infants. He also inquired as to whether there was similar recruitment between the control and study groups.

Dr. Dull responded that a majority of subjects were enrolled in the US, but probably about 7 or 8 of those deaths were in Latin America or in Taiwan. Infant mortality is an important consideration in those populations. The same randomization ratio was applied throughout. In attempting to understand this, consideration was given to a number of questions, including: Is there a temporal association? Is there a set of syndromes? Is it all respiratory deaths? Are some autoimmune? Novartis and FDA assessed this, and no concerning pattern was observed. Overall, there was a 3:1 randomization in person-time years and 5:1 deaths. That type of split is not unlikely in terms of outcomes.

Use of MenACWY-CRM for High-Risk Infants

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. MacNeil reviewed the proposed recommendations for use of MenACWY-CRM in infants at increased risk for meningococcal disease. On August 1, 2013, FDA approved an expanded indication for MenACWY-CRM as a 4-dose primary series in infants with doses at 2, 4, 6, and 12 months of age. This vaccine had previously been approved for children and adults aged 2 through 55 years. MenACWY-CRM, or Menveo®, is the third meningococcal vaccine licensed for use in infants. Menactra® is licensed as a 2-dose series at 9 and 12 months. MenHibrix®, a

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bivalent serogroup C and Y meningococcal vaccination, is licensed as a 4-dose series at 2, 4, 6, and 12 to 15 months of age. MenACWY-CRM® is the first quadrivalent meningococcal vaccine licensed for use in children 2 through 8 months of age.

ACIP currently recommends vaccination of infants aged 2 through 23 months at increased risk for meningococcal disease. There is no recommendation for routine vaccination of all infants, although infants less than one year of age have higher rates of disease. This decision was based on the current epidemiology of meningococcal disease in infants, including the high proportion of serogroup B disease and the highest rates prior to 6 months of life. Meningococcal disease is currently at historic lows in the US. Therefore, a routine infant recommendation would prevent a low proportion and low absolute number of cases in this age group.

Very few infants and young children are considered at increased risk for meningococcal disease. Infants at increased risk include those with recognized complement component deficiencies; functional or anatomic asplenia, including those with sickle cell disease; infants who are in a defined risk group for a community or institutional outbreak; or infants traveling to an area where meningococcal disease is hyperendemic or epidemic. The total number of infants at increased risk for meningococcal disease is likely somewhere between 2000 and 5000 per year out of a birth cohort of 4 million infants.

The incidence of meningococcal disease continues to decline in the US. In 2012, 551 cases were reported among persons of all ages. Of those cases, 113 were reported among children less than 5 years of age. In terms of the average annual number of cases of meningococcal disease caused by each of the four major serogroups for children less than 5 years of age during 2010 to 2012, 50% of disease in this age group occurred in children 0 to 8 months of age. Overall, 64% of disease in children less than 5 years was caused by serogroup B.

Vaccination with three doses of MenACWY-CRM results in a protective immune response for all serogroups, although a lower response is seen for serogroup A. Following a full 4-dose series, over 89% of infants achieved protective antibody titers to all four serogroups. MenACWY-CRM is also immunogenic as a 2-dose series at 7 through 12 months of age. Two years after a complete 4-dose series, antibody levels wane, especially for serogroups A and C, indicating that the vaccine is unlikely to provide protection until the 11-year-old dose and may require a booster to maintain protection. When the 4-dose infant series was administered concomitantly with routine childhood vaccines, no interference was observed for diphtheria, tetanus, hepatitis B, polio, or Hib antigens. With a 2-dose series in older infants, no interference was observed with the MMRV antigens when MenACWY-CRM was administered concomitantly at 12 months of age.

In several studies, seroresponse to the pneumococcal serotypes 6B and 23F was lower when PCV7 was co-administered with MenACWY-CRM. Post-dose 3, serotypes 6B and 23F did not meet statistical criteria for non-inferiority. However, no interference was seen for the other five PCV7 vaccine serotypes. Post-dose 4, non-inferiority criteria were met for all serotypes, including serotypes 6B and 23F. No data are available on the co-administration of MenACWY-CRM and PCV13. These interference data were shared with both the meningococcal and pneumococcal working groups. The consensus was that MenACWY-CRM may be administered with PCV13, including in asplenic children, because the immune response was sufficient post-dose 4; whereas, for Menactra®, interference was observed with the final dose at 12 months of age.

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MenACWY-CRM appears to be well-tolerated and safe, with reported adverse events similar between infants receiving MenACWY-CRM with routine childhood vaccines and control infants receiving routine childhood vaccines alone. Of the serious adverse events, 11 were considered possibly related to the vaccine, which means vaccine receipt and adverse events were reasonably related in time. But the adverse event could be explained by causes other than the vaccine. No deaths were attributed to the vaccine.

With the licensure of MenACWY-CRM, infants at increased risk for meningococcal disease now have a third vaccine option in addition to Menactra® and MenHibrix®. Based on the immunogenicity, safety, and interference data for all three vaccines, there is no preference for any of the licensed vaccine formulations for use in infants at increased risk for meningococcal disease except for two situations. First, MenHibrix® does not provide protection against serogroups A and W, so it is not recommended for use in infants traveling to the meningits belt or Hajj where protection against serogroups A and W is required. Second, Menactra® is not recommended for infants 9 through 23 months of age with functional or anatomic asplenia in order to avoid potential interference with the fourth dose of PCV13. Guidance for use of MenACWY-CRM in infants at increased risk will be integrated with the existing guidance for MenHibrix® and Menactra®.

The following table summarizes the three vaccine options for infants and toddlers at increased risk for meningococcal disease, with MenACWY-CRM being the only quadrivalent vaccine licensed for use in infants 2 through 8 months of age:

Meningococcal Vaccines for Children Aged 2 through 23 Months at Increased Risk

Vaccine	Primary Vaccination	Booster Doses	Indicated for:	Not indicated for:
MenACWY-D (Menactra)	• 9, 12 months	• 3 yrs after 1⁰ series, then every 5 years	• Complement deficiencies • Outbreaks • Travel	• Asplenia
HibMenCY-TT (MenHibrix)	• 2, 4, 6, and 12-15 months	• 3 yrs after 1⁰ series, then every 5 years (using MenACWY-D or –CRM)	• Complement deficiencies • Asplenia • Outbreaks	• Travel • Booster dose
MenACWY-CRM (Menveo)	• 2, 4, 6, and 12 months	• 3 yrs after 1⁰ series, then every 5 years	• Complement deficiencies • Asplenia • Outbreaks • Travel	

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The following table highlights the recommendations and indications for use of meningococcal vaccine in infants and children 2 through 23 months of age at increased risk for meningococcal disease:

Vaccines for Children – Recommended Vaccination Schedule and Intervals

Age Group	Vaccine	Routine Recommendations	Dosing Schedule
2 mos - 10 years	MCV4-Crm (Menveo, Novartis)	High-risk only[1]	**Primary:** • Age 2 through 6 months: 4 doses at 2, 4, 6, and 12 months • Age 7 through 23 months: 2 doses should be given with the second dose given in the second year of life • Age 2 through 10 years: 1 or 2 doses **Booster (for persons who remain at risk[1]):** • 1st booster 3 years after primary series for children who received primary series prior to age <7 years, then every 5 years • Every 5 years for children who received primary series after 7th birthday
	MCV4-D (Menactra, Sanofi)	High-risk only[1]	**Primary:** • Age 9 through 23 months: 2 dose series with 12 weeks between doses • Age 2 through 10 years: 1 or 2 doses **Booster (for persons who remain at risk[1]):** • 1st booster 3 years after primary series for children who received primary series prior to age <7 years, then every 5 years • Every 5 years for children who received primary series after 7th birthday
	HibMenCY-TT (MenHibrix, GSK)	High-risk only[1]	**Primary:** • Age 2 through 23 months: 4 dose series with doses at 2, 4, 6, and 12-15 months **Booster (for persons who remain at risk[1]):** • Use MCV4-D or MCV4-Crm (see above)

These recommendations are part of a larger table of recommendations which are included in the VFC resolution for children 18 years of age and younger. The portion of the VFC table to be updated based on the vote during this session is highlighted in yellow above. In order to integrate the proposed recommendation into the current high-risk infant meningococcal recommendations, the following language will be included:

- ❑ Infants 2 through 23 months of age at increased risk* for meningococcal disease should be vaccinated with an age- and formulation-appropriate meningococcal conjugate vaccine.

- ❑ MenACWY-CRM is an additional option for vaccinating infants 2 through 23 months of age at increased risk for meningococcal disease.

  *Infants at increased risk for meningococcal disease include those with recognized persistent complement component deficiencies, those with functional or anatomic asplenia (including sickle cell disease), healthy infants who are part of the risk group for a meningococcal disease outbreak for which vaccination is recommended, and infants traveling to or residing in areas with hyperendemic or epidemic meningococcal disease.

Language that will be included in the policy note as guidance for use includes the following:

- ❑ Those who remain at increased risk for meningococcal disease should receive a booster dose three years after the primary series and additional boosters every five years thereafter.

- ❑ If MenACWY-CRM is used to achieve protection against serogroups A and W meningococcal disease, a quadrivalent vaccine should be used to complete the series.

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The proposed recommendations to be voted on during this session read as follows:

- MenACWY-CRM can be used for protection against serogroups A, C, W, and Y in increased risk infants aged 2 through 23 months
  - Infants aged 2 through 8 months who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic are recommended to receive MenACWY-CRM prior to travel to provide protection against meningococcal serogroups A and W
  - MenACWY-CRM may be co-administered with PCV13, including in asplenic children

Discussion Points

Regarding the recommendations for travel and meningococcal A responses, Dr. Karron inquired as to whether there were any data to show how this compared to the MenACWY-D formula with respect to meningococcal A. There are data immediately after vaccination and at 40 months, but it was unclear whether there were any data at intermediate time points? Her concern was waning immunity to meningococcal A in travelers.

Ms. MacNeil responded that this is the only vaccine for infants 2 through 8 months of age that contains serogroup A, so that is the only vaccine that is recommended for this age group.

Dr. Dull added that there are no comparative data, but it has been compared to Menactra® in older populations and later time points were assessed in those 11 through 18 years of age. There is comparable immunogenicity at later time points for the meningococcal A component comparing Menactra® versus Menveo®, but there are no comparisons for infants.

Dr. Karron said she understood in the 2 through 8 month age group, but wondered whether there was an alternative for older infants 8 through 23 months of age, about the response and durability to meningococcal A in MenACWY-D versus MenACWY-CRM, and whether there are any MenACWY-D data that could be informative.

Dr. Dull replied that the older age cohort has not been followed out, although they may be able to infer something from the data derived in older-aged populations as to how they might compare in the younger-aged populations—imperfectly.

Dr. Cohn added that in general in comparing Menactra® and Menveo®, the serogroup A responses do appear to be somewhat improved for Menactra® over Menveo®. Fortunately, with the use of the MenAfriVac® in the Meningitis Belt, the risk for serogroup A disease among infants who travel is becoming considerably smaller. In fact, the risk for serogroup A in travelers has never been as well-established. There has never actually been a case of serogroup A meningococcal disease in a traveler to the Meningitis Belt. While it is a recommendation, the working group feels that the immune response for infants in the 2 through 8 month age range is sufficient since there are no other options. The differences between Menactra® and Menveo® in the older age groups are not sufficient to prefer Menactra® over Menveo®.

Dr. Harriman noted that although not presented during this session, cost-effectiveness data have been presented previously. To her knowledge, those evaluations did not include any indirect benefits of the vaccine in the sense of the herd immunity benefit due to decreased carriage. Data from the UK and elsewhere have shown dramatic impacts of herd immunity (protection). She wondered whether the working group could conduct that type of cost evaluation. As far as she could tell, 35 countries outside of the Meningitis Belt have a routine

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recommendation for meningococcal vaccines. Of those, 28 countries have an infant or toddler dose schedule. Usually, there are one to three doses total with monovalent serogroup C vaccine. Given that infant and toddler vaccines are licensed in the US, she asked whether the working group would be willing to consider alternate schedules for meningococcal vaccines. For example, a very common schedule in other countries is one dose at age 12 to 14 months and a booster dose in mid-adolescence. Canada could probably offer information about that. If there is not going to be a routine recommendation for all healthy infants, she harkened back to an editorial written 10 years ago by Paul Offit and Georges Peter in the *New England Journal of Medicine*. At that time, there was no routine recommendation for any meningococcal vaccines. Obviously, there is a difference between public health policy and individual patient care. But in that editorial, the authors stress that if there was not going to be routine use of these vaccines, policies and practices should be established to inform parents of infants and toddlers about the existence and potential benefits of the vaccine. She wondered whether there were plans to make sure that parents and providers are aware of this vaccine, because if a vaccine is not recommended by ACIP, providers often think perhaps there is some reason they should not be giving it. Having read all of the papers, she thought there was pretty strong evidence of a herd effect, which does change the cost-effectiveness evaluation.

Dr. Cohn indicated that the herd immunity observed in the UK has not been observed with quadrivalent vaccines in the US. The US has not been able to show a reduction in carriage in the same way that they showed a reduction in carriage with meningococcal C vaccines, and the immunogenicity was substantially greater. The program that was introduced in the UK was very different from the program introduced in the US as well, so the actual impact on the programs are hard to compare. Even considering carriage data alone, the working group did not feel that there were sufficient data for these vaccines to incorporate herd immunity into meningococcal vaccine effectiveness studies. Consideration has been given to this in terms of sensitivity analyses, and it did not reduce cost-effectiveness substantially in the same way that it did in the UK with the program that they implemented.

Dr. Schuchat added that much of the effort leading up to evaluation of meningococcal conjugate vaccines in ages younger than 11 was based on the epidemiology of the disease in the US rather than the vaccine performance, because many of the countries that have routine recommendations have much higher rates of C disease than the US. There has been a very surprising and interesting decline in endemic meningococcal disease in the US, so there is much less disease to prevent or even to document a herd effect. The other issue the committee dealt with in the past few years was the surprising and somewhat disappointing waning of protection of the 11-year-old adolescent dose that led to a second dose in teenage years. ACIP continues to assess the epidemiology and performance of vaccines, but much of the decision-making during the past couple of years that supported not recommending a routine infant or toddler schedule was due to the very low burden of disease in the US. Conversely, the US has routine vaccination for diseases that other countries that have been using toddler doses of meningococcal vaccine for years have not yet introduced.

Dr. Brady (AAP) noted that while they were recommending the vaccine in children at high-risk for meningococcal disease, the studies were all conducted in healthy children. He wondered whether any studies were planned that would make them feel comfortable that similar immune responses are being achieved in immunocompromised children. He expressed concern that as has been found in other immune-deficient populations who are older, additional doses need to be given in order to make sure adequate antibody levels are achieved.

Ms. MacNeil responded that as far as she was aware, there are no studies planned in children with these high-risk conditions, but they would be recommended to receive booster doses if they

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have complement deficiency or asplenia at three years after the primary series and then every five years thereafter in order to maintain protection. Their primary series would result in adequate levels to provide protection.

Regarding the second bullet point in the recommendation, Dr. Grogg (AOA) noted that the last sentence stated, “prior to travel, to provide protection against meningococcal serogroups A and W.” He suggested ending it at the end of “to travel,” because it made it look as though it does not protect against the other two serogroups at all.

Ms. MacNeil replied that the suggested change could be made. The goal was to highlight the fact that A and W are the true risk to travelers.

Dr. Pickering noted that while there has only been one case of serogroup A in the US in the last 10 years, travel is still of concern with respect to mass gatherings. The data show that subsequent to the post-7 to 9-month dose, there is about 50% protection that decreases to approximately 25%. The decay curve for the older groups is down to 10% percent at 40 months. There is only one vaccine licensed in this age group for travel, but perhaps there should be a qualifier that it is not a perfect vaccine.

Dr. Cohn responded that this could certainly be discussed more in the background section of the document. There are recommendations in the infant statement for Menactra® that both doses be received prior to travel, and that they can be given as close as 8 weeks apart instead of waiting until 12 weeks. In this case, the second dose would be in the second year of life. Language could be added about trying to receive the vaccine closest to travel, which may protect infants during the period of travel. Infants who are living in the Meningitis Belt, for example, would be in a different situation because they would require longer-term protection. But at least for traveling infants, that may be of benefit.

Dr. Baker pointed out that while she did not disagree with Drs. Karron or Pickering, this imperfect vaccine is the only one there is and they do not counsel parents about other imperfect vaccines, including influenza vaccine. She also said that Dr. Harriman’s suggestion would be great in a perfect world, but the pediatrician or family practitioner has limited time to talk about routine vaccines. Educating parents about a very low-prevalence/incidence disease would not be practical in terms of making sure uptake of routinely recommended vaccines occurs.

Dr. Karron suggested including guidance language that this vaccine is protective for the short-term, but may be inadequate protection against meningococcal A for infants who are going to reside in certain countries.

Regarding the GRADEing of the evidence, Dr. Reingold said he was fully aware of the need to bridge from immunogenicity studies to make inferences about efficacy or effectiveness. However, he wondered whether it was wise to discuss efficacy in the GRADE tables when, in fact, immunogenicity data is all there are available . Regarding the question of recommendations for travelers and what is known about the dynamics of the immune response following immunization and how quickly the antibody levels rise, he expressed concern that many people who are traveling rush to get their shots right before they leave. While they did not want people to obtain vaccines too far in advance, he was not sure they should be vaccinated right before they leave either. Thus, he wondered how precise the recommendations are for travelers regarding the timing of doses.

Dr. Cohn responded that no recommendations are made with regard to timing for doses. There may be language saying two weeks prior to travel, at least in the older age groups. The only

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specific recommendation is that the two doses may be given within a shorter period of time in order to acquire the second dose prior to travel in the infant-toddler age group.

Dr. Clark indicated that there are requirements for the Hajj for getting a Visa to document vaccination. For Africa, it is much looser. But as was said before, there are not documented cases in travelers to Africa.

Dr. Kempe noted the potential for confusion about the issue of Menactra® co-administration with PCV13 and whether there needs to be a clarification about whether it is okay to crossover and use Menveo® in that instance.

Dr. Cohn replied that these recommendations will be integrated with the recommendations for Menactra® and HibMenCY, and it will be made clear that Menactra® is not recommended until after 2 years of age, but Menveo® may be used in children with asplenia through age 2 years and beyond. After age 2 years, the recommendations are that Menactra® should be given one month after the last PCV13 dose in case a final dose has not been received prior to age 2 years. The hope is to integrate the language. A Notice to Readers will be distributed for comment prior to publication.

Dr. Loehr reminded everyone that this is a very rare situation, probably less than 1 in 1000 children. As a practicing family physician, he said he would have to look this up every single time and read the book because it would not be something he would have in his memory at all.

Public Comment

Dr. Walt Faggett
Speaker for the House of Delegates
National Medical Association and
Assistant Professor of Community and Family Medicine
Howard University College of Medicine

Thank you very much. Dr. Walt Faggett, National Medical Association (NMA). Again, I want to, at this point, ask that—well, there's a real concern about the use of the term "routine vaccination of high-risk infants." I'm sure that was part of the confusion for some of the misrepresentation in the letter that was sent to the ACIP from NMA. In fact, our staff contractor did not really understand the implication of saying "routine immunization." So, I think this is something we need to look at. We're talking about immunizing high-risk infants, and to say "routine immunization" to the non-clinician, I think, could be a question. NMA fully supports immunizing high-risk infants and children. And again, as an organization, we fully subscribe to an evidence-based approach. At this time, I do want to retract the letter that was sent. We really, urgently, want to retract that letter. As a pediatrician and former NMA liaison to the ACIP back in the day, our President, Dr. Lenoir, and our chairman of the board, Dr. George Saunders, sent me here specifically to assure that the ACIP knows that we, the NMA, support our representative, who is Dr. Pat Williams. She brought to our attention the inaccuracies reflected in the letter. Indeed, we don't have disparities. I think Dr. Cohn's paper that you have before you fully shows decreasing disparities. We in the NMA hope that we are part of the solution in that, so we really apologize for any misrepresentation that we're trying to put something conflicting in the record. But, we do subscribe to an evidence-based approach in developing clinical guidelines. So, at this time, we want to emphasize that we support the recommendation as presented here now. We're specifically supporting immunization of high-risk children, not as incorrectly stated in that letter which we are asking to be retracted in which we talk about routine immunization. I see that as a misunderstanding; people didn't understand the difference. So again, we look forward

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in the NMA to continuing to work with CDC in closing the gap. It was so exciting to hear Dr. Frieden's comments, and we fully subscribe, and will have all of our resources available to you to assist as we move forward. Thank you.

John Becker
Lesbian, Gay, Bisexual, Transgender (LGBT) Activist

Good morning. I'm an independent LGBT activist and an advocate for our community, and I'm here on my own just as a concerned citizen. I represent gay, lesbian, bisexual, and transgender Americans who are concerned about the growing threat of bacterial meningitis in our community. There's been an outbreak of meningitis in the gay communities of several major American cities in recent years, with several deaths in New York City alone and other deaths reported in California and Utah. We believe the best way to ensure that bacterial meningitis does not kill any more innocent people is to expand the vaccination program in the United States as widely as possible. We are asking ACIP to expand its recommendation of the bacterial meningitis vaccine to include children and infants as young as 6 months old. Expanding the use of this vaccine would help protect the hundreds of thousands of same-sex couples in the United States with children. The current Census Bureau estimates are that there are at least 115,000 same-sex couples in this country that are raising children. Expanding the vaccine recommendation would also increase herd immunity to protect people with compromised immune systems. In our community, that's especially important because of the heightened incidence of people infected with HIV and AIDS. I recently launched a campaign calling on the CDC and ACIP to help protect the lives of LGBT Americans by expanding the vaccine recommendations for bacterial meningitis. So far, this campaign has received more than 14,000 signatures, and we've just begun. We should probably meet the 15,000 threshold today. We will continue to push for the vaccine program to be expanded, because we believe strongly that it offers the best chance to ensure that this deadly disease never again threatens our community. We in the gay community, unfortunately, know too well how quickly an outbreak can turn into an epidemic. We're incredibly fortunate to have a safe and effective vaccine available, and it's essential, in my view, that we expand its use far and wide to prevent this disease from spreading. Thank you very much.

Dr. Temte requested that the record show the petition was distributed to ACIP members and would be placed into the minutes of this meeting. The petition read as follows:

To: CDC Advisory Committee on Immunization Practices

I am writing today to ask the Center for Disease Control's Advisory Committee on Immunization Practices to add the bacterial meningitis vaccine to the list of recommended vaccines for infants and children.

Bacterial meningitis is an incredibly dangerous disease that has affected the lesbian, gay, bisexual and transgender community since 2001. In New York City, 22 men have been infected with the disease, and seven have died. Other deaths have been reported in gay communities in California and Utah.

Thankfully, a bacterial meningitis vaccine is available that is safe and effective. The LGBT community knows this firsthand - officials in New York City and other cities with large gay populations began a vaccination program after a surge in new cases in the fall and winter of 2012. At least 16,000 people received the bacterial meningitis vaccine in New York City alone, through a campaign conducted at gay bars, public events, and through web-based marketing.

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Because of this aggressive approach to vaccination, no new cases of this deadly disease have been reported in NYC since February of 2013 - the longest the city has gone without a new case in more than a year.

The current CDC recommendations for the bacterial meningitis vaccine leave one critical group dangerously unprotected: infants and children. This is particularly alarming given the fact that the infection rate for invasive meningococcal disease is the highest for children under the age of one year.

Vaccinating babies and small children against bacterial meningitis will make children and families safer, including the more than 115,000 same-sex households with children in the United States. It will increase herd immunity by helping to prevent the spread of the disease, particularly to those with compromised immune systems, including people with HIV and AIDS. In short, it will protect children and save lives.

The LGBT community has seen the devastating impact bacterial meningitis can have, and we know all too well how health crises can spread and become epidemics. The best approach to fighting bacterial meningitis is to ensure that the vaccine is made available to everyone.

I urge you to do just that - please recommend the bacterial meningitis vaccine for babies and small children.

Christopher Boone
Meningitis Angels

I'm Chris Boone with Meningitis Angels. I have no conflicts. This is my wife, Heather, and my son Ethan. I'm not a public speaker. I'm, probably going to get emotional. I'm sorry. On June 15, 2008, my healthy 7-month-old little boy started running a fever. Thirty hours from running that fever, his heart stopped. He had meningococcemia. Thirteen days later, they amputated all four extremities. Sometime after that, his nose fell off his face. After 65 days of being in the hospital and five operations, he was sent home. His little body was destroyed. He's had a surgery every summer to reconstruct his face, and I think it would be irresponsible not to vaccinate children from meningococcal disease. Thank you.

Frankie Milley
Founder / National Director
Meningitis Angels

I am Frankie Milley. I'm the National Director of Meningitis Angels, and I'm the mother of an only child who died from meningococcal disease at the age of 18—totally healthy. I just wanted you to meet Jeremiah Mitchell, who is 10 years old now. Jeremiah's first-grade class in Oologah, Oklahoma had an outbreak. Six children in that class, within 48 hours, contracted meningococcal disease. Two of them died, and you see Jeremiah. Jeremiah has had massive face construction. The damage to his body is massive, but I'm proud to tell you he has a 12th-grade reading and language skill. I went to all of the ACIP meetings a couple of summers ago, and time after time, I heard, "It's not cost-effective. The incidence rate is not high enough." But yet, every parent who was there who was against vaccines voted, when the vote came down, to vaccinate infants against this disease—even those parents who were against it. You know, we educate parents in this country who are anti-vaccine. We spend a lot of money and a lot of time doing that, but we're not educating parents on a disease that can do this to a baby or kill my son in 14 hours—my perfectly healthy son who didn't even have a cavity in his mouth, but had blood coming from every orifice of his body in 14 hours. We worry about cost-effectiveness. Is this

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cost-effective? Is Ethan cost-effective? The hundreds of children within our network are all not at high risk. I say to you one baby, one child, one teen is too many, especially when it comes to being yours. You know, I'm standing here today, and I want to tell you, I have the utmost respect, and admiration, and gratitude to these people right here because they dedicate their lives to this—to making sure our kids are vaccinated. I'm really disappointed, though, that we're only looking at this for high-risk. What is high risk? You look at statistics. I look at real little people, real little faces. I listen to parents every day of my life who watch their kids have seizures so bad they have to have parts of their brain dissected; who, every time they take them to the doctor, they get revisions on amputations; who develop kidney disease; who develop joint disease; who, once they reach puberty, they develop emotional problems and anger issues. We've seen suicide within our families, and high divorce rates. My God, please, this should be a routine—at least permissive—recommendation for all of our infants. Give us all that chance. Let our parents be educated. Let our healthcare providers be educated. Give us that. I'm real disappointed that this is only for high-risk. I think they're all high risk and they're all worth being protected. Thank you.

Vote: Recommendation for Use of HibMenCY in High-Risk Infants

Dr. Duchin made a motion to accept the proposed language, with the addition of language in the commentary section of the recommendation that would expand upon consideration for timing of vaccine for travelers who wish to be protected against meningitis serogroup A. Dr. Campos-Outcalt seconded the motion. Dr. Coyne-Beasley added that she would like ACIP to consider in the future making this a permissive recommendation if the data support doing so.

The motion carried with 13 affirmative votes, 1 negative vote, and 1 abstention. The disposition of the vote was as follows:

13 Favored: Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harrison, Karron, Kempe, Jenkins, Reingold, Rubin, Temte, and Vazquez
1 Opposed: Harriman
1 Abstained: Pellegrini

Vaccines for Children

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

Dr. Santoli indicated that the purpose of the VFC resolution was to update the resolution to include use of a meningococcal vaccine recently licensed in a new age group, and to simplify the language within the recommended vaccination schedule and intervals section. The eligible groups for the vaccine remain unchanged and include the following:

- Children aged 2 months through 10 years who are at increased risk for meningococcal disease, including
  - children who have complement deficiencies (e.g., C5-C9, properdin, factor H, or factor D);
  - travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic;
  - children who are part of an outbreak of a vaccine-preventable serogroup.
  - Children who have anatomic or functional asplenia

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- All children aged 11 through 18 years

The recommended schedule follows:

Recommended Schedule, Intervals (1)

Age Group	Vaccine	Routine Recommendations	Dosing Schedule
2 mos – 10 years	MCV4-Crm (Menveo, Novartis)	High-risk only[¶]	**Primary:** • Age 2 through 6 months: 4 doses at 2, 4, 6, and 12 months • Age 7 through 23 months: 2 doses should be given with the second dose given in the second year of life • Age 2 through 10 years: 1 or 2 doses **Booster (for persons who remain at risk[¶]):** • 1st booster 3 years after primary series for children who received primary series prior to age <7 years, then every 5 years • Every 5 years for children who received primary series after 7th birthday
	MCV4-D (Menactra, Sanofi)	High-risk only*	**Primary:** • Age 9 through 23 months: 2 dose series with 12 weeks between doses • Age 2 through 10 years: 1 or 2 doses **Booster (for persons who remain at risk[¶]):** • 1st booster 3 years after primary series for children who received primary series prior to age <7 years, then every 5 years • Every 5 years for children who received primary series after 7th birthday
	HibMenCY-TT (MenHibrix, GSK)	High-risk only[§]	**Primary:** • Age 2 through 23 months: 4 dose series with doses at 2, 4, 6, and 12-15 months **Booster (for persons who remain at risk[¶]):** • Use MCV4-D or MCV4-Crm (see above)

Recommended Schedule, Intervals (2)

Age Group	Vaccine	Routine Recommendations	Dosing Schedule
11-18 years	MCV4 (Menveo or Menactra)	Children aged 11 through 18 years	**Adolescents:** • Primary dose at age 11-12 years with booster dose at age 16 years • A booster dose is not recommended if the first dose is given on or after the child's 16th birthday **Adolescents with complement component deficiency, or functional or anatomic asplenia; HIV infection: (if another indication for vaccination exists):** • 2 doses, 8-12 weeks apart **Booster for adolescents who remain at increased risk (complement component deficiency, functional or anatomic asplenia, traveling or part of a meningococcal outbreak more than 5 years after the prior dose):** • 1st booster 5 years after primary • Additional boosters every 5 years

The first three tablenotes address the groups of high-risk children and discuss how those groups are defined:

Table Notes:

- [¶] For children with complement component deficiency, functional or anatomic asplenia, part of a community or organizational outbreak, or traveling internationally to a region with hyperendemic or endemic meningococcal disease.
- *For children with complement component deficiency, functional or anatomic asplenia, part of a community or organizational outbreak, or traveling internationally to a region with hyperendemic or endemic meningococcal disease. For infants receiving the vaccine prior to travel, the two doses may be administered as early as 8 weeks apart. Infants with functional or anatomic asplenia should wait until 2 years of age to prevent immune interference with PCV13.
- [§] For children with complement component deficiency, functional or anatomic asplenia, part of a community or organizational outbreak, Hib-MenCY-TT is not recommended for use in children who are traveling international to a region with hyperendemic or endemic meningococcal disease. MCV4 should be used as booster doses for children who are given a primary series with Hib-MenCY-TT.
- Note: Use of brand names is not meant to preclude the use of other meningococcal vaccines where appropriate.

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No changes were recommended for dosage or contraindications and precautions, which remain as follows:

Recommended dosage

- Refer to product package inserts.

Contraindications and Precautions

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

As always, the following statement would be included regarding updates based on published documents:

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

Discussion Points

Dr. Loehr (AAFP) noted that HIV was shown in the high-risk group in the proposed VFC resolution, which differed from the definition of high-risk groups defined in some of the previous presentations.

Dr. Santoli responded that that language was included in terms of how to use the vaccination rather than being in the front.

Dr. Cohn added that HIV was not included in the actual language in the written resolution. That was clarified a couple of years ago. The recommendation is if a child with HIV has another indication, that they should receive two doses. She suggested checking the published language.

Dr. Santoli indicated that she would double-check the language, and could remove it from the section of the resolution she showed, if that was the request, and would keep it as listed in the table.

Dr. Rubin suggested that it be deleted from the proposed resolution, because he did not think they wanted to indicate that all HIV-infected children should receive meningococcal conjugate vaccine unless they have another high-risk condition. He thought it was fine to leave it in the table, because children who do receive the vaccine should get a 2-dose regimen.

Dr. Grogg (AOA) noted that it appeared that travelers would be covered by VFC in this case, although typically travel immunizations are not covered.

Dr. Santoli clarified that the language included in the current recommendation was not supposed to change, and that Dr. Grogg was correct.

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VFC Vote

Dr. Bennett made a motion to accept the proposed VFC language. Dr. Bocchini seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

13 Favored:	Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Kempe, Jenkins, Reingold, Rubin, Temte, and Vazquez
0 Opposed:	N/A
1 Abstained:	Pellegrini

Child/Adolescent Immunization Schedule 2014

Introduction

Dr. Renée Jenkins, Chair
Child/Adolescent Immunization Working Group
Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention

Dr. Jenkins explained that the reason this topic was being presented was for ACIP approval of the proposed schedule prior to publication in *MMWR* in January 2014. Recommendations in this schedule are not only approved by the ACIP , but also by the AAP, the American Academy of Family Practice (AAFP), and the American College of Obstetricians and Gynecologists (ACOG). The schedule is published in their respective society professional journals. These groups approve the proposed schedules prior to the January 2014 publication as well. Though everyone was stunned by the government shutdown and thought that it would not be possible to meet the January 2014 publication deadline, it appeared that because of the amazing Commissioned Corps members who were still working, meeting the deadline would be possible after all. Dr. Jenkins reminded everyone that new vaccine policy is not established in the proposed schedule. Instead, the annual schedule reflects only the recommendations already approved by ACIP.

Child/Adolescent Immunization Schedule, 2014

Dr. Iyabode Beysolow
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Beysolow noted that as in previous years, the Child/Adolescent Immunization Schedule Working Group began the year by reviewing the schedule that was published in February 2013 in the *MMWR*. Over the course of the year, multiple working group calls were convened, with the goal of improving the clarity and readability of the footnotes and the catch-up table. In the interest of time, she discussed only those vaccines with significant changes. ACIP members were provided with the full set of footnotes, as well as updated figures in a document dated 10/22/13. The only change proposed to Figure 1, the Routine Schedule for Persons 0 through 18 years of age, was the starting age for MCV4-CRM down to 2 months from 2 years of age. In terms of Figure 2, the Catch-up Immunization Schedule, edits were proposed to the Tdap,

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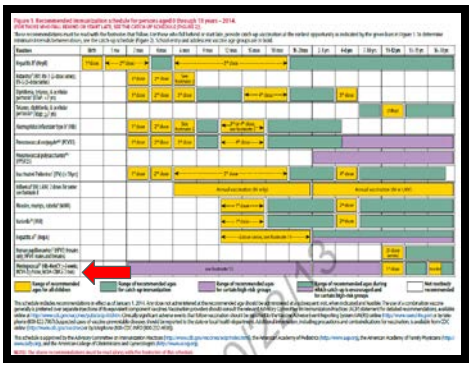
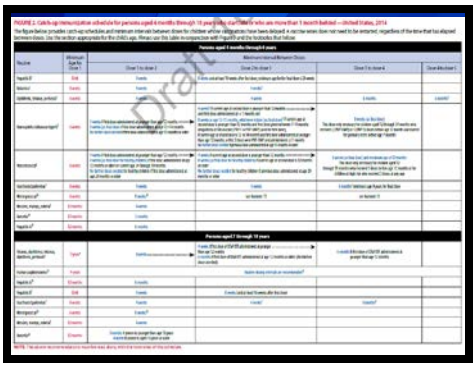
pneumococcal, and meningococcal rows, Hib conjugate was added, and arrows were introduced to help guide the provider along in the schedule where appropriate:





In terms of the footnotes, only minor changes were made for hepatitis B vaccine to clarify the timing of hepatitis B immunoglobulin for a subset of infants born to HepB surface antigen positive mothers. In an attempt to make it easy for the busy provider, the working group proposed that generic names and trade names be referenced in the title of each vaccine's footnotes. The trade name alone could be used in the body of the footnotes.

Under the catch-up vaccination section of Tdap vaccines, the footnotes were enhanced to include further information on vaccination of persons 7 years of age and older with a single lifetime dose of Tdap vaccine, except for pregnant adolescents, and also language was included from the 2006 recommendations on inadvertent administration of DTaP vaccine in persons 7 years of age and older. To assist providers, language was added to the Tdap row of the catch-up schedule to clarify that as the provider follows the table, there are references to DTaP or DT vaccine in certain places, so the words DTaP/DT were inserted.

For the Hib vaccine footnotes, clarification was provided for routine doses, both for the primary series and booster doses, mainly for consistency in language across the vaccine footnotes. Similarly, language was clarified for Hib vaccine catch-up. This is all consistent with the published ACIP recommendations.

In February 2013, ACIP voted to accept the following updates to the soon to be published Hib vaccine ACIP recommendation statement:

Vaccination of persons with high-risk conditions:

- Children aged 12 through 59 months who are at increased risk for Hib disease including those with: *anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, early component complement deficiency, or chemotherapy recipients*, who have received either no doses or only one dose of Hib vaccine before 12 months of age should receive two additional doses of Hib vaccine 8 weeks apart; children who received two or more doses of Hib vaccine before 12 months of age should receive one additional dose.

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- ❑ Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.

- ❑ For patients <60 months of age undergoing chemotherapy or radiation treatment who received Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.

The language regarding vaccination of high risk groups was inserted into the footnotes for Hib vaccines. The Hib tables were voted on by ACIP in February 2013, so the attempt was to match the schedule to the language presented in February. This refers to vaccination of children 12 through 59 months of age at increased risk of disease who are incompletely vaccinated with Hib vaccine, including patients with asplenia and HIV infection. The footnotes also include Hib vaccine recommendations for recipients of hematopoietic stem cell transplant and persons who have undergone chemotherapy or radiation treatment. The footnotes also address vaccination of unimmunized persons anticipating elective splenectomy, and unimmunized persons 5 years of age and older who are at increased risk. To help clarify the Hib catch-up table even further, additions were made to the two columns, Dose 2 to Dose 3, and Dose 3 to Dose 4, to help clarify the timing of the dose of Hib vaccine based on the patient's age at the time and their prior history of Hib vaccination.

With regard to pneumococcal vaccine, clarification was made that PCV13 vaccine was being referred to in the routine and catch-up sections for all children, primarily because all of the pneumococcal vaccines were placed in one footnote:

6. Pneumococcal Vaccines (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)

   Routine vaccination with PCV13
   - Administer a 4-dose series of PCV13 at ages 2, 4, and 6 months, and, at age 12 through 15 months.
   - For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

   Catch-up vaccination with PCV13:
   - Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - For other catch-up issues, see Figure 2.

The entire section on vaccination of persons with high risk conditions with PCV13 and PPSV23 was rewritten to provide clarity on which patients are to receive both vaccines, not only based on age and risk factor, but also regarding when these doses should be administered. This information is directly from the ACIP pneumococcal vaccine recommendations that are published in the 2010 *MMWR* edition.

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Vaccination of persons with high-risk conditions with PCV13 and PPSV23 (Minimum age: 2 years):

- All recommended PCV13 doses should be administered prior to 23-valent Pneumococcal Polysaccharide Vaccine (PPSV23) if possible.
- For children aged 24 through 71 months with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection, chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:

    i. Administer 1 dose of PCV13 if 3 doses of PCV (PCV7 and/or PCV13) were received previously.
    ii. Administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
    iii. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 schedule were received previously. (from 2010 recs, table 11).
    iv. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
    v. For children previously unvaccinated with PPSV23, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.

- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiences; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma

    i. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
    ii. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
    iii. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.

An attempt was made to separate all of the different risk groups by age, so as shown, the bullet referencing children 24 through 71 months of age with high risk conditions defines them and indicates how many doses of PCV13 or PPSV23 they would need. For children 6 through 18 years of age, two separate sets of recommendations are included as shown. The first set is for the persons in this age group at highest risk for disease, specifically those immunosuppressed secondary to either disease or treatment. The second set are those children 6 through 18 years of age with other conditions that put them at risk, but who are not at as high a risk as the first group in this age range. Revaccination recommendations for those persons who should receive a second dose of PPSV23 are also addressed. Similar to the Hib vaccine catch-up section, language was added for pneumococcal vaccine to specify who should receive additional doses based on the child's current age.

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For influenza vaccines, because the schedule will span two influenza seasons, providers are referred to the respective ACIP vaccine recommendations for that season for guidance on dosing for children 6 months through 8 years of age:

Routine vaccination:

- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) those with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) those who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV see MMWR 2013; 62 (No. RR-7):1-43, available at http://www.cdc.gov/mmwr/pdf/rr/rr6207.pdf.
- Administer 1 dose to persons aged 9 years and older.

For children aged 6 months through 8 years:

- For the 2013–14 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. For additional guidance, follow dosing guidelines in the 2013 ACIP influenza vaccine recommendations, see MMWR 2013; 62 (No. RR-7):1-43, available at http://www.cdc.gov/mmwr/pdf/rr/rr6207.pdf.
- For the 2014–15 season, follow dosing guidelines in the 2014 ACIP influenza vaccine recommendations.

Hepatitis A footnotes were also updated to include the list of persons at high risk for HepA disease, as delineated in the ACIP HepA vaccine recommendation statement:

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

Special populations:

- Administer 2 doses of Hep A vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of Infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory setting; persons with clotting-factor disorders; persons with chronic liver disease.

Over the course of the last year, numerous questions have been received from providers regarding inclusion of the minimum intervals between doses for HPV vaccine, so this information was included in the bullets as shown here for HPV vaccine:

12. Human papillomavirus (HPV) vaccines. (HPV4 [Gardasil] and HPV2 [Cervarix]). (Minimum age: 9 years)

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Routine vaccination:

- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11-12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 12 weeks after the second dose AND at least 24 weeks after the 1st dose.

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

As heard in the previous presentation, MenACYW-CRM was licensed down to age 2 months by the FDA in August 2013. ACIP has now voted to recommend this vaccine for certain persons 2 months and older at high risk. Because of the varying vaccine options now available to providers, the working group felt that it would be best to separate this information based on risk factor, as there are different recommendations based not only on age of the patient, but also risk factor and which vaccine could be used for that particular patient. The following footnote language represents the attempt to do so based on the current recommendations:

13. Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo]).

Routine vaccination:

- Administer a single dose of Menactra or Menveo vaccine at age 11–12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo, with at least 8 weeks between doses.
- For children aged 2 months through 10 years with high-risk conditions, see below.

Vaccination of persons with high-risk conditions and of other persons at increased risk of disease.

Children with anatomic or functional asplenia (including sickle cell disease):

i. For children younger than 19 months of age, administer a 4-dose infant series of MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.
ii. For children aged 19 through 23 months who have not completed a series of MenHibrix or Menveo, administer 2 primary doses of Menveo at least 3 months apart.
iii. For children aged 24 months and older who have not received a complete series of MenHibrix or Menveo or Menactra, administer 2 primary doses of either Menactra or Menveo. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.

Children with persistent complement component deficiency:

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i. For children younger than 19 months of age, administer a 4-dose infant series of either MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.

ii. For children 7 through 23 months with persistent complement component deficiency who have not initiated vaccination, 2 options exist depending on age and vaccine brand:
a. For children who initiate vaccination at 7 months through 23 months of age, using Menveo, a two dose series should be administered with the second dose in the second year of life and at least 3 months after the first dose.
b. For children who initiate vaccination at 9 months through 23 months of age , using Menactra, a two dose series of Menactra should be administered at least 3 months apart.

iii. For children aged 24 months and older, who have not received a complete series of MenHibrix, Menveo or Menactra, administer 2 primary doses of either Menactra or Menveo.

For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or to the Hajj, administer an age appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj. See MMWR 2013 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.
For children at risk during a community outbreak attributable to a vaccine serogroup administer or complete an age and formulation-appropriate series of MenHibrix, Menactra or Menveo.

- For booster doses among persons with high-risk conditions refer to MMWR 2013 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

Catch-up recommendations in persons with high risk conditions are addressed as follows:

Catch-up recommendations in persons with high-risk conditions:

- If MenHibrix is administered, all 4 doses should be administered to achieve protection against Meningococcal disease.
- If the first dose of MenHibrix is given at or after 12 months of life, 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
- For other catch-up recommendations in these persons, refer to MMWR 2013 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.
- For complete information on use of meningococcal vaccines, including issues related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

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Dr. Beysolow indicated that the working group would make revisions as necessary based on feedback received during this session, and based on clearance through CDC. The document will then be submitted to *MMWR* for editing, and the final edited copy will be presented to pertinent organizations in early January 2014. As Dr. Jenkins mentioned, the hope is to proceed with publication at the end of January of 2014. She also reminded everyone that CDC now offers a service called Content Syndication. Inevitably, despite best efforts, errors may be caught at a later time or updates to the schedules may be needed after publication. When schedules are updated, organizations using the Content Syndication feature will receive immediate schedule updates on their sites. This decreases everyone's time and removes the consuming process of checking the CDC website for any updates.

Discussion Points

Dr. Kempe suggested making a change to pneumococcal vaccine footnote 4 to better define what is meant by "including asthma if treated with high-dose oral corticosteroid therapy" in terms of whether this refers to chronic therapy. Many children receive intermittent high-dose corticosteroid therapy, so this is likely to be confusing.

Also regarding pneumococcal vaccine footnote 4, Dr. Sawyer recalled that cigarette smoking was restricted to adults 19 and above. He requested clarification regarding whether alcoholism, chronic liver disease, and cigarette smoking were now included for children.

Dr. Beysolow responded that with a recent publication in June 2013, those indications were listed for 6- through 18-year olds as well [Update after October meeting from Pneumococcal vaccine subject matter experts. The June 2013 publication contained an error and cigarette smoking is not an indication for PPSV23 in persons under 19 years of age].

Dr. Temte thought that raised a larger point that sometimes the childhood schedule overlaps with the adult schedule, and he made a plea for consistency. For example, under pneumococcal for asplenics or sickle cell, it might be worthwhile to provide guidance as to what happens after they turn 19 if they have already had two PPSV23s. Similarly, the hepatitis A footnotes include "persons who work with HAV-infected primates." Not too many children are going to be in that situation.

Dr. Beysolow replied that she would take this suggestion back to the working group, noting that this had been an area of discussion.

Regarding the hepatitis B footnotes, Dr. Lett suggested using the word "recommended" to ensure that people feel comfortable that it is safe to administer four doses.

Dr. Beysolow responded that it was pointed out to the working group that there were some instances when that fourth dose would not have to be given. The language was changed to "permitted" versus "recommended" because it is not recommended in all instances.

Also referring to the hepatitis B footnotes, Dr. Bocchini pointed out that the third bullet indicates "the minimum interval between dose 1 and 2 is 4 weeks, and between dose 2 and 3 is 8 weeks." If that was followed, potentially the third dose would be given 12 weeks after the first. But the next sentence states "the final third or fourth dose in the series should be administered no earlier than 24 weeks and at least 16 weeks after the first dose." That is somewhat confusing and gives some different data. The catch-up schedule says it nicely in a single sentence or phrase, which is, "dose 2 to dose 3 at 8 weeks, and at least 16 weeks after first dose. The

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minimum age for final dose is 24 weeks." He suggested replacing the footnoted language with the language in the catch-up schedule.

Dr. Pickering inquired as to whether AAFP and AAP had signed on to Content Syndication.

Dr. Beysolow indicated that she would check with the web developers, noting that Content Syndication was offered to both at the end of 2012.

Dr. Loehr pointed out that pneumococcal footnote 3, "If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23," differed from the recommendation for adults. He wondered whether there were any data for either of those recommendations.
Dr. Beysolow clarified that the recommendations do differ. This was discussed extensively during the pneumococcal deliberations a year or two ago.

Dr. Middleman (SAHM) reiterated what Dr. Sawyer mentioned about the footnote and changes in the table regarding smoking in this age group. She was not aware of evidence presented about smoking in this age group. This potentially could include a large number of adolescents who smoke cigarettes and would then be obligated to the polysaccharide vaccine, which is known to have greater issues of hyper-responsiveness and potentially may have effects in terms of response later. She suggested that this be a future point of discussion in terms of including it in the table [After the October ACIP meeting, the Subject Matter Experts confirmed that the June 2013 ACIP publication had an error and that Cigarette smoking is not an indication for PPSV23 in persons under 19 years of age].

Regarding the footnotes for the Tdap recommendations, Dr. Michael Decker (sanofi pasteur) expressed concern about the line stating, "Repeat doses of Tdap are not recommended except for the pregnant adolescent during every pregnancy." He thought the intent was to reflect the ACIP vote based on the pharmacoeconomics suggesting that a repeat booster of Tdap was not warranted as a universal recommendation. However, he was concerned that the phrasing would be interpreted by the user community as meaning that it is bad to give another dose of Tdap. There are plenty of situations where it is clearly good to give another dose of Tdap (e.g., an outbreak in a school, a cocooning effort around a newborn, or something else). He suggested that a better reflection of the totality of ACIP's desires would be to include a sentence reading something to the effect of, "Repeat doses of Tdap are not routinely recommended, except for pregnant adolescents . . . but may be considered based on local circumstances or provider or parental preference." This would leave the door open for people to use their judgment rather than having it be interpreted as "bad things happen if you give another dose of Tdap."

Dr. Beysolow responded that as mentioned earlier, the schedules can only reflect the actual ACIP recommendations. The ACIP recommendations are for a single dose of Tdap per lifetime for everyone except for pregnant women.

Dr. Temte added that Dr. Decker's comments could be taken back to the Pertussis Working Group.

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Dr. Rubin pointed out that the language in the meningococcal footnote stating, "If MenHibrix is administered, all 4 doses should be administered to achieve protection against Hib disease," was in the context of catch-up. For a 9-month old who has not gotten Hib vaccine, a 4-dose schedule would not be appropriate for protection against Hib. He suggested perhaps deleting that line to read "to complete the series" rather than the number of doses, because there is a nuance regarding the number of doses depending upon age and whether it is given before or after 12 months of age.

Dr. Pickering suggested clarifying the pneumococcal recommendations to reflect that they do not apply to those who smoke e-cigarettes.

Vote: 2014 Child/Adolescent Immunization Schedule

Dr. Bocchini made a motion to accept the proposed recommendations with the changes that were suggested by the ACIP membership, to be modified as appropriate by the working group. Dr. Vazquéz seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored:	Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Kempe, Jenkins, Pellegrini, Reingold, Rubin, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

Adult Immunization Schedule 2014

Introduction

Dr. Tamera Coyne-Beasley, Chair
Adult Immunization Working Group
Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention

Dr. Coyne-Beasley reminded everyone that, like the child/adolescent immunization schedule, ACIP updates the adult immunization schedule annually to reflect and summarize existing ACIP policy versus addressing new policy. This effort is done through a series of monthly meetings of the working group and consultation with vaccine subject matter experts. There are many nuances and very specific issues that often have to be addressed. The schedule will be updated and approved with any policy changes made up through the October 2013 ACIP meeting if published in *MMWR* prior to publication of the adult schedule, which is anticipated to be early in 2014. The working group also works collaboratively with many colleague organizations, including the American College of Physicians (ACP), AAFP, ACOG, and the American College of Nurse Midwives (ACNM), which also approve the adult schedule.

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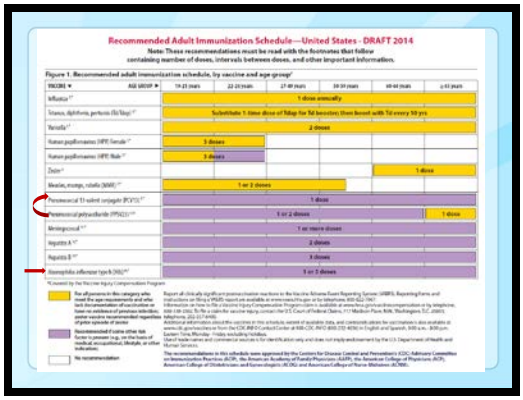
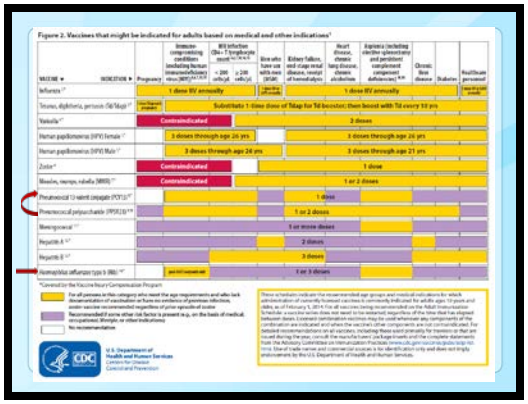
Adult Immunization Schedule, 2014

Dr. Carolyn B. Bridges, CDC Lead
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Bridges reported that updates to Figures 1 (by age group) and 2 (by health conditions) were to move the PPSV23 bar below the bar for PCV13 and to add a bar for Hib vaccine:





Consistent with the language already voted on by ACIP, for the immunocompromising conditions column, the only group for whom Hib vaccine is recommended is comprised of patients who are post-stem cell transplant. The decision was made not to include a separate column, given that the space on the figure is limited.

The proposed updates to the footnotes included the following:

- Influenza Vaccine
  - Information on the recombinant influenza vaccine (RIV) and the use of RIV and inactivated influenza vaccine (IIV) among egg-allergic patients was added
- Td/Tdap Vaccine
  - Harmonizes language with pediatric schedule
  - Include information on Td boosters in the footnote – the language was inadvertently removed from footnote in prior schedules, but was continuously included on the figure
- Varicella Vaccine
  - Clarifies that immunocompromised adults born in the US before 1980 may not be immune to varicella
- HPV Vaccine
  - Language harmonized with pediatric schedule regarding intervals between 1st and 2nd, 2nd and 3rd and 1st and 3rd doses.
  - Removed bullet on healthcare personnel (HCP) and vaccination, similar to Zoster footnote
- Zoster vaccine

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- Simplified by removing statement about healthcare personnel not a specific indication for vaccination

- PCV13 and PPSV23
  - PCV13 footnote and row on the figures was placed ahead of the PPSV23 vaccine so that providers seeing patients who had indications for both vaccines will have information about the recommendation to administer PCV13 before PPSV23

- Meningococcal vaccine
  - Clarified which persons needed 1 versus more than one dose of MCV4 or MPSV4 and
  - Clarified that persons with HIV are not routinely recommended for MCV4, but clarifies that 2 doses of MCV4 should be given among HIV-infected persons who are vaccinated

- Hib vaccine
  - Updated language added per the recently ACIP approved updated Hib recommendations
  - The updated Hib recommendations are pending publication in the *MMWR*

With regard to the contraindications table, RIV information was added, information was updated on influenza vaccine use among persons with egg allergy, and Hib vaccine was added.

In terms of next steps, the adult schedule will be revised based on the ACIP meeting. It will then be submitted for CDC clearance, including re-review by vaccine specific subject matter experts (SMEs) and review by professional medical organizations (AAFP, ACP, ACOG, ACNM) on October 28, 2013. The schedule will be submitted to *MMWR* on December 2, 2013. Publication in the *Annals of Internal Medicine* and *MMWR* is anticipated in early February 2013, along with publication of the 2011 National Health Interview Survey (NHIS) estimates of non-influenza vaccine coverage in adults.

Discussion Points

Dr. Temte wondered whether the varicella footnote might be confusing because it discusses the evidence of immunity, except if immunocompromised, and at the same time it is contraindicated to vaccinate. He worried that this may set up an internal conflict for people trying to use this for guidance, and indicated that any clarity would be appreciated.

Dr. Bridges replied that there was discussion about writing this footnote a couple of ways, one of which was to say nothing about immunocompromised persons in the second footnote and to have evidence of immunity to varicella in adults among whom vaccination is being considered. They could certainly return to that language if it was clearer.

Dr. Riley (ACOG) commented that on Figure 2 there was a white box for pregnancy under PCV13 and Hib. Recognizing that Figure 2 did not reflect anything new, and that they could not add anything new, she requested that during a future meeting there be a specific conversation about the safety of inactivated vaccines for pregnant women. When there is a white box, there is an assumption that it is unsafe. There is something specifically written about not using HPV vaccine during pregnancy, so having a white bar there makes sense. Nothing is written about PCV or Hib; however, the data do not show that these are unsafe. Clarity for all of the inactivated vaccines suggested for use in pregnancy would be beneficial.

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Dr. Temte suggested submitting this to the Pneumococcal and Hib Working Groups for consideration.

Dr. Duchin inquired as to whether it would be useful to make the white box "No Recommendation / Not Contraindicated."

Dr. Riley (ACOG) responded that the problem with that would be that there is a specific recommendation to delay HPV vaccination until after pregnancy. Her understanding was that for someone at high risk, PCV could be given during pregnancy.

Dr. Loehr (AAFP) noted that there were 6 white boxes, 2 of which were "Not Applicable" because they are male/female discordant, 1 of which was "Not Recommended" and the other 3 could be "Not Recommended / Not Contraindicated." So, there could be different answers for different white boxes.

Dr. Schuchat said she thought that the schedule was challenging, and that they wanted to be everything for everyone. However, once the list was on the left, there was a desire to figure out what to do in particularly populations. Another way to think about the schedule is for a practitioner caring for a person in one of the columns to consider what ACIP recommends that they give. While there is a desire to be comprehensive, inclusive, and comment on everything on the left, the reality is that there are a couple of vaccines that are important for pregnant women to receive because they are pregnant. There are many vaccines people with diabetes are recommended to receive. The number of adults in the US who really need a Hib vaccine is miniscule, but there are many pregnant women. Therefore, she would like to ensure that pregnant women receive the key vaccines they need to have. Perhaps some thought should be given to what practitioners actually need. Ideally on the internet there could be a schedule for each group, given the limited space on the overall adult schedule.

Ms. Pellegrini inquired as to whether it was possible that they were getting hung up on the phrase "No Recommendation," because it sounded like ACIP meant something very specific by that. It did not necessarily mean that there is no guidance about what to do in those cases. She suggested refining the wording somewhat to indicate that providers should go to the footnote for additional guidance.

Ms. Hayes (ANA/ACNM) indicated that her experience was clinically that when vaccinating pregnant women, she did not even look at the schedule. She refers to the lengthy section that addresses each vaccine and why it is or is not recommended, or why it is contraindicated. She said she thought the red boxes were the only ones that really matter.

Dr. Jenkins noted that it sounded like there was additional information about these vaccines, which would not fit on the schedule. She suggested highlighting that there is additional information.

Dr. Temte indicated that when he used to be involved in obstetrics, he did not pay attention at all to ACIP. He paid attention to the flow sheet from ACOG for his guidance during pregnancy. He made a plea for the guidance used not only by ACOG's members, but also by family physicians to be proactive.

Dr. Riley (ACOG) responded that ACOG works from the ACIP adult schedule and does not create its own information. She said the issue was not so much that she was worried about the boxes, but she thought for general practitioners who do look at the schedule, clarity would be

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helpful. She thought it would be helpful for ACIP to comprehensively assess all of the inactivated vaccines that should now be given to pregnant women, with clear safety data, to alleviate the assumption that if there are no data, it is unsafe.

Dr. Lett (CSTE) recognized that clinicians seeing pregnant women in their practices need readily available guides, and it would be great if everything was in the schedule. However, CDC has a great guide for pregnant and breastfeeding women that she gives out regularly. It has a wonderful description of which vaccines have been studied, which ones have not, and their FDA ratings. There is an accompanying chart that can be put on the wall that has the colors and more detailed guidance.

Dr. Pickering noted that the liaisons on ACIP who are members in the organizations that receive the content information would likely be willing to help. He suggested considering the inclusion of electronic links in the footnotes. Once the mobile apps are available, a link could be included for evidence of immunity and other information rather than listing everything. He suggested reviewing the schedules to determine whether next year, appropriate links could be added.

Dr. Fryhofer (AMA/ACP) agreed that the schedule being encouraged during pregnancy is important, and that the contraindications are clear. The two yellow bars on the adult schedule, influenza and Tdap, are what they are trying to encourage during pregnancy. The other vaccines will require deeper insight. An OB/GYN is probably going to get an internist to help. Another point about making everything just web-based, she finds it very useful to have information in the exam room in a paper form that she can show patients. She requested that the paper format not be eliminated, because it is really helpful.

Dr. Loehr (AAFP) inquired as to whether it would address the concerns if inside the white box small words could be included to state “Not Applicable,” “Safe,” et cetera.
Dr. Bridges noted that during one of the working group calls when they were discussing the boxes for pregnancy, one suggestion was that potentially it might be helpful to have a separate session during a future ACIP meeting to review the safety data on inactivated vaccines and pregnancy.

Dr. Temte said he thought it would be premature to include anything in the boxes at this point, and that they should remain as they are at this time. The point was made that the major targets were influenza and Tdap vaccines during pregnancy, and avoiding anything that carries a higher likelihood of risk. In terms of dealing with some of the nuances and the boxes in question, those are people who are at high risk for other things to begin with. It then becomes a weighing of whether a person should be getting one of those vaccines because of other contraindications, and they are pregnant, and depends upon discussion between a physician and the patient. He did not believe there was sufficient evidence one way or another to offer much guidance, especially without having further discussion.

Dr. Bridges noted that the HPV footnote includes language stating, “If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the 3-dose series should be delayed until completion of pregnancy.”

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Vote: 2014 Adult Immunization Schedule

Dr. Bennett made a motion to accept the proposed recommendations. Dr. Karron seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Kempe, Jenkins, Pellegrini, Reingold, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Pneumococcal Vaccines

Introduction

Nancy M. Bennett, MD, MS
Pneumococcal Vaccines Working Group Chair
Advisory Committee on Immunization Practices

Dr. Bennett opened the session outlining the Pneumococcal Vaccines Working Group's terms of reference:

- Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines
- Review current recommendations considering up-to-date evidence, including epidemiologic studies conducted post-licensure, and assess strength of the evidence
- Revise or update recommendations for pneumococcal vaccine use, as needed

The focus of this session was on 13-valent pneumococcal conjugate vaccine (PCV13), and the routine infant immunization schedule for PCV13.

PCVs have had quite an impact on the epidemiology of pneumococcal disease over recent years. In February 2010, the FDA licensed Prevnar® (PCV13), a new conjugate vaccine for the prevention of pneumococcal disease in young children that replaced PCV7. By October 2010, recommendations had been made for the use of this new vaccine. In December 2011, PCV13 was licensed for adults 50 years of age and older. During the February 2012 meeting, ACIP deferred routine recommendations for adults pending the results of the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA) and to observe the indirect effects of immunizing children with PCV13. In June 2012, ACIP made recommendations for use of PCV13 in adults with immunocompromising conditions (IC). In January 2013, PCV13 was licensed for children 6 through 17 years of age. In February 2013, ACIP made recommendations for children 6 through 18 years of age with IC, thus harmonizing the adult and childhood recommendations.

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This is a different era. Pneumococcal conjugate vaccines have been used for 12 years on a 4-dose schedule at 2, 4, 6, and between 12 through 15 months of age. The use of PCV7 led to reductions in otitis media in children and invasive pneumococcal disease (IPD) and pneumonia in children and adults. Increasing evidence is emerging that supports a 3-dose PCV schedule. There have been several RCTs evaluating the efficacy and immunogenicity of a 3-dose schedule, and observational studies have evaluated the impact of 3-dose PCV programs. At least 34 high or upper-middle income countries have introduced PCV13 or PCV10 with 3 doses. Some of those countries have switched from a 4-dose to a 3-dose schedule.

The objective for this session was to offer information only. No specific recommendations were presented. ACIP members were asked to review the evidence and discuss considerations for including a 3-dose PCV13 schedule for infants, with the following specific questions in mind to give direction to the working group:

- ❑ Is the evidence adequate to consider including a 3-dose PCV13 schedule for infants?
- ❑ If not, what additional data or information would be required?

Presentations for this session included an update on PCV13 direct and indirect effects and vaccine effectiveness; a review of the evidence for reduced dose schedules of PCV13 for children; and a discussion on the cost-effectiveness of PCV13-reduced dose schedules.

PCV13 Herd Effect

Matthew R. Moore, MD, MPH
Captain, USPHS
Medical Epidemiologist

Dr. Moore began by saying that he was really excited to be able to provide an update on the impact of PCV13 use in the US. As Dr. Bennett noted, PCV13 was licensed in the US in February 2010. That licensure was based primarily on non-inferior immunogenicity against serotypes common to both PCV13 and PCV7. There were no randomized controlled trials with clinical endpoints as a condition for licensure. ACIP recommended PCV13 in February 2010 for all infants at 2, 4, 6, and between 12 through 15 months of age. Infants who started their schedule with PCV7 were recommended to complete the schedule with PCV13. “Serotype catch-up” was implemented for children who were already fully vaccinated with PCV7. All children less than 5 years of age were able to receive a single dose of PCV13 for additional protection. By the end of 2012, the National Immunization Survey (NIS) showed that coverage among 19 through 35 month-olds was about 92% with 3 or more doses and about 82% with 4 doses [http://www.cdc.gov/vaccines/stats-surv/nis/data/tables_2012.htm#overall].

In this context, it was important to think through the various ways to assess the impacts of the vaccine on IPD. CDC monitors IPD using active, population-based surveillance in 10 areas in the US as part of its Active Bacterial Core Surveillance (ABCs) program. CDC evaluated cumulative counts of IPD, undertook some modeling exercises that were presented briefly during a previous ACIP meeting, and has been conducting a case-control study of vaccine effectiveness (VE) among children 2 through 59 months of age who were eligible to receive the vaccine.

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The cumulative number of cases of IPD among children under the age of 5 was assessed for those serotypes uniquely affected by the 13-valent vaccine but not affected by the 7-valent. This was referred to as PCV5 because the 6B antigen in the 7-valent vaccine has demonstrated substantial cross-protection against 6A serotype that is also in the 13-valent vaccine. PCV5 represents the 5 serotypes that are uniquely affected by the 13-valent vaccine, and CDC wanted to assess the incremental benefit over and above what was already known about the 7-valent vaccine. Pneumococcal disease is very seasonal. Disease increases fairly quickly over the winter months and flattens out over the summer months. In 2010, disease flattened out again whereas in previous years, it increased substantially. This was the first indication that PCV13 was having an impact on these particular serotypes. This became much more dramatic in 2011, and continued in 2012 and through the first quarter of 2013. This suggested that direct impact of the vaccine on IPD in children was being observed.

Because of the experience with PCV7, CDC was also interested in knowing whether the vaccine was interrupting transmission from children to adults. In adults 65 years of age and older, the seasonality of pneumococcal pneumonia is the same. Disease accumulates fairly rapidly over the wintertime, flattens out during the summer, and begins again in the late fall and early winter. There was some evidence of impact in 2011, but it was very obvious in 2012 that rates of disease were declining. This pattern continued into 2013. It is very exciting that the vaccine is working as expected at a population level.

CDC decided to try to estimate exactly how much disease has been prevented in terms of reductions in incidence and number of cases prevented using data from ABCs. First, the actual cases observed during each month until vaccine introduction were determined. A time series model was then developed that attempted to mimic that. The 5 serotypes that are uniquely affected by PCV13 were increasing in incidence before vaccine introduction. Continuing the time series model out past the period of vaccine introduction, a dramatic drop-off was observed, indicating that the number of cases caused by those additional serotypes had declined dramatically compared to what would have been expected in the absence of vaccine. This was estimated to be an 88% reduction in invasive disease caused by these serotypes in this population during the second year after vaccine introduction. The same modeling was done for adults 65 years of age and older, which resulted in approximately a 47% reduction of disease among adults after vaccine introduction. Repeating this exercise in a variety of age groups shows statistically significant reductions in vaccine-type IPD in all age groups within the first 2 years after PCV13 introduction—quite a dramatic indirect effect of vaccination, as illustrated in the following table:

Age group, years	Percent Decrease in Rate (95%IE)	
	2010-11	2011-12
<5	67 (62, 70)	88 (86, 89)
5-17	35 (22, 45)	59 (48, 66)
18-49	33 (26, 38)	65 (60, 68)
50-64	24 (18, 28)	54 (51, 58)
≥65	23 (13, 31)	47 (39, 53)

Also noteworthy is that reductions in the second year were uniformly larger than those observed in the first year. Thus, there is improvement with each year of vaccination. CDC is working to

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update these data in order to include data from July 2012 through June 2013, and hopes to be able to share those data during a future ACIP meeting.

Also important to consider were how many cases of disease and how many deaths have been prevented as a result of vaccine introduction. CDC used the data based on 10 areas throughout the country and projected those to the rest of the country based on what is known about the age and race distribution of the country. It is believed that over 25,000 cases have been prevented since vaccine introduction. Not surprisingly, a large number of them are in children under the age of 5 who should be receiving the vaccine. Substantial prevention has also been observed in those who primarily are not recommended to receive this vaccine at all. Very few children die of IPD. Most of the deaths that occur are in adults. Therefore, it was not surprising that the vast majority of deaths prevented were in adults. These are very promising results showing that a lot of disease is being prevented.

CDC is also interested in knowing how well the vaccine is working at the individual level. Dr. Moore shared preliminary results through May 2013 from a case-control study of PCV13 effectiveness. In this study, cases of invasive pneumococcal disease are identified through CDC's routine surveillance among children 2 through 59 months of age residing in the 10 ABCs areas. For the purpose of this study, catchment was expanded to include New York City, Los Angeles County, and Utah. An attempt is made to enroll four controls for every case matched on age and zip code. As of May 2013, 765 cases had been enrolled. Of these, 224 (29%) had PCV13-type IPD and 209 (93%) were caused by serotypes 19A, 7F, and 3. That suggests that the majority of IPD is caused by those three serotypes. Also enrolled at this time were 2274 controls, or about 3 controls per case. Receipt of at least 1 dose of PCV13 was compared from June through November 2010 to December 2012 through May 2013, which showed that coverage with at least 1 dose had increased from 37%. Thus, uptake appears to be very good. The following table reflects what is being observed in terms of the different outcomes being assessed:

Outcome	VE ≥1 dose, %	95% CI
All IPD	65	52-75
PCV13-type IPD	89	79-95
Serotypes 19A, 7F, 3 (as a group)	89	79-95
Serotypes 19A, 7F (as a group)	93	82-97

Very little disease is caused by serotypes 1, 5, or 6A that are in PCV7. Most of the results are being driven by serotypes 19A, 7F, and 3. Compared to 19A and 7F, there is relatively little serotype 3, so 19A and 7F were assessed without 3 to show very good effectiveness of 93%.

In summary, 89% effectiveness has been observed with at least 1 dose PCV13 versus PCV13-type IPD. An 88% reduction has been observed in PCV5-type IPD among children, and a 47% reduction in PCV5-type IPD has been observed among adults 65 years of age and older. Over 20,000 cases of IPD and 2,000 deaths have been prevented based on CDC's estimates. Thus, PCV13 appears to be highly effective at preventing IPD among children who receive the vaccine. Substantial indirect effects are evident within the first 3 years of vaccine introduction.

Discussion Points

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Dr. Duchin inquired as to whether any studies had been conducted to assess individual cases of the emergence of strains that either underwent capsular transformation or capsular switching with non-vaccine serotypes emerging with the basic chains of a 3 or 19A strain.

Dr. Moore replied that there is a broad issue of serotype replacement and whether increases are being observed in disease caused by serotypes not included in the vaccine, and thus far replacement has not been observed. Surveillance will monitor for that. The issue of capsular switching whereby a particular serotype like a 19A loses the genetic material for a 19A capsule and takes on genetic material for a different serotype like a 35B or 11A can occur. Capsular switching phenomenon was observed post PCV7 introduction, but it played a relatively minor role in the overall serotype replacement story. It seemed that what was happening with serotype replacement was that those serotypes that were common before vaccine introduction were the ones that were most likely to become replacement serotypes. Although capsular switching occurred, it was comparatively an uncommon event.

Dr. Vazquéz asked whether Dr. Moore could comment on specific types of IPD. With PCV7, there seemed to be an upsurge of empyema in a majority of invasive cases, and she wondered whether anything was known about the number of cases of empyema since routine use of PCV13.

Dr. Moore responded that while empyema had not been evaluated specifically in the PCV13 era yet, CDC's data did not show a substantial increase during the PCV7 era. He did not know whether that was perhaps related to something different about the local epidemiology in places where that was observed. For example, in Utah serotype 1 increased after PCV7 introduction and was associated with empyema. Interestingly, empyema associated with serotype 1began to decline in Utah before PVC13 was introduced. Dr. Moore indicated that CDC could report on assessment of empyema in the PCV13 era at a future meeting.

Dr. Harrison asked Dr. Moore to comment on remaining disease burden due to PCV13 serotypes in adults.

Dr. Moore replied that in terms of the proportion of remaining invasive disease caused by PVC13 serotypes in adults, there were less than 100 cases of the additional serotypes in adults 65 years of age and older in 2013. Using 2012 as a marker, there were about 175. Using an approximation that this is roughly 10% of the US population, that could be multiplied by a factor of 10. In terms of the proportion of all disease, while Dr. Moore had not looked recently, he was able to say that before PCV13 introduction, the PCV13 serotypes caused about 45% of disease in adults. A 50% reduction has already been observed, which suggests the 20% range.

Dr. Jenkins inquired as to how much uptake of the vaccine this represented in adults, given the challenges in getting a percentage of the population vaccinated.

Dr. Moore responded that PCV13 was licensed for adults in 2011, and the subsequent ACIP recommendations were only for immunocompromised adults, which is a small proportion of the total. At this time, CDC did not know how much uptake there was in adults. They would expect that the data reflected primarily indirect effects of vaccinated children, because uptake was so high in children. A considerable part of this effect occurred before PCV13 was even licensed for adults, let alone being recommended for just the population of immunocompromised adults.

Dr. Bocchini wondered whether among the children who developed invasive disease there were enough data to assess epidemiologic risk factors.

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Dr. Moore replied that a risk factor study is embedded in the vaccine effectiveness study, so CDC will be assessing risk factors. Historically within the ABCs, it has been a relatively small proportion, on the order of about 10%, of all of the cases among children who have underlying conditions. Thus, 90% of disease is in healthy children.

Dr. Bocchini asked whether CDC would also assess child care center attendance, socioeconomic groups, et cetera, which are important to consider in terms of defining who is and is not at high risk.

Dr. Moore indicated that CDC's routine surveillance does not capture those data, but the case-control study is capturing information on day child care attendance, underlying conditions, administration of other vaccines, and socioeconomic status (SES).

Dr. Sun (FDA) asked whether Dr. Moore had data on the pediatric rates of cases in terms of how many received 3 versus 4 doses.

Dr. Moore replied that from the case-control study, one of the greatest challenges has been very clear about which children received the 7-valent and which received the 13-valent due to the transition period during which both were available. CDC is working hard to acquire information on 1 versus 2 versus 3 versus 4 doses. Not enough of that information was finalized to do the analysis and present the results during this meeting, but it is an important part of the ultimate analyses that will be done for the case-control study.

Dr. Whitley-Williams (NMA) asked whether the same impact had been observed when the data were broken down by race or ethnicity, particularly in the adult population given the low immunization rates, and in Native American and Eskimo populations, particularly where certain serotypes are a major issue.

Dr. Moore responded that this has not been done yet for PCV13 as the focus had been on everything as an aggregate. Based on the experience with the 7-valent vaccine, there were substantial disparities in IPD between African Americans and Whites. PCV7 essentially eliminated the disparity in the disease caused by the vaccine serotypes, but did not eliminate the disparities caused by the other serotypes. There is still some remaining disparity there for children and adults. He did not have the data available for Native American/Alaska Native (AI/AN) populations, but indicated that he could present them during a future meeting. This has been a major issue, and CDC has been hearing from its colleagues that they are seeing similar effects of the vaccine in those populations.

Ms. Groom (IHS) indicated that IHS is interested in any information the working group might have or could assess regarding the specific impact of reducing the series for the AI/AN population because of the higher background rates pre- and post-vaccine that continues to be observed in certain geographic regions. Dr. Moore responded that the working group would be happy to work with IHS on this issue.

Dr. Temte noted that a manuscript was in preparation assessing all-cause respiratory infections in a very large primary care population. With the Christmas holiday, there is a substantial drop-off that increases afterward.

Reduced Dose Schedule: Review of Evidence

Tamara Pilishvili, MPH
Respiratory Diseases Branch

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National Center for Immunization & Respiratory Diseases

Dr. Pilishvili reviewed the evidence supporting the use of a 3-dose PCV schedule for infants, with a focus on the evidence that was reviewed by the working group during the preceding few months. In terms of the working group's rationale for discussing this topic, the evidence supporting the use of 3-dose PCV schedules has been emerging. A 3-dose PCV13 schedule is approved by the European Medicines Agency (EMEA). Recently, WHO published a position statement recognizing a 3-dose schedule as an acceptable alternative to a 4-dose schedule [Wkly Epidemiol Rec, 2012]. At least 34 countries (21 high- and 13 upper-middle income) have introduced PCV13 or PCV10 with 3 doses or have switched from a 4- to 3-dose schedule. Use of 7-valent pneumococcal conjugate vaccine (PCV7) in the US has led to dramatic reductions in disease burden. Large reductions have been observed in invasive pneumococcal disease and pneumonia in children and adults, and reductions in otitis media in children. PCV7 serotypes have virtually been eliminated from all age groups as causes of disease. Disease due to PCV13 serotypes not in PCV7 has also been rapidly declining. The US now has a mature PCV program, which means that there have been high coverage and stable rates for many years, and there is high acceptability of this vaccine in this country. This raises the question, "Can a 3-dose PCV13 schedule be included into a routine schedule for infants?"

Many factors need to be considered when deciding whether a policy change is warranted. First and foremost, consideration must be given to whether the available evidence supports the change. The working group has also considered other factors. While other considerations were not discussed in detail during this session, the working group welcomed committee feedback on the specific issues that should be considered related to each of these considerations (e.g., safety, programmatic considerations, communication challenges, economic considerations, policy/statute considerations).

In reviewing the available evidence for the 3-dose PCV infant schedules, the working group focused on studies which evaluated schedules with 2 doses in the primary series followed by a booster in the second year of life (2+1) or a schedule with 3 doses in the primary series with no booster in the second year of life (3+0). The working group reviewed evidence from RCTs evaluating efficacy of PCV schedules, post-licensure effectiveness studies (e.g., case control or indirect cohort analysis), ecologic studies evaluating impact of PCV introduction on a population level, and breakthrough cases. Dr. Pilishvili highlighted key studies and presented conclusions for the outcomes of IPD, pneumonia, acute otitis media (AOM), nasopharyngeal colonization, and immunogenicity studies; as well as the indirect effects of 3–dose schedules.

There were 5 RCTs evaluating vaccine efficacy against vaccine-type IPD including the following Finland (Palmu 2013), Gambia (Cutts 2005), South Africa (Klugman 2003), USA (Black 2000), and USA (O'Brien 2003). The study in Finland, the most recent one, evaluated the efficacy of a 10-valent conjugate vaccine (PCV10) for a 2+1 schedule and a 3+1 schedule (3 primary series followed by a booster, which is the schedule used in Finland). The study was not powered to make direct comparisons between the two schedules; however, the efficacies were similar at 92% for 2+1 and 100% for 3+1. Two of the trials, one in South Africa and one in Gambia, evaluated 9-valent conjugate vaccine (PCV9) using a 3+0 schedule. The South Africa study reported 83% efficacy, while the Gambia trial reported 71% efficacy. As a comparison, two trials in the US using PCV7 on a 3+1 schedule, one in the general population of US infants and one in the Navajo population, reported efficacy of 94% and 83% respectively.

The six observational studies evaluating effectiveness against vaccine-type IPD included studies from Canada (Deceuninck 2010), USA (Whitney 2006), Spain (Barricarte 2007), USA

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(de Serres 2008), USA (Mahon 2006), and Germany (Ruckinger 2010). These were comprised of 3 case-control studies and 3 studies using the indirect cohort method, which evaluated the effectiveness of various schedules of PCV7. Effectiveness following 2 infant doses ranged from 70% to 99% in 5 of the studies. The effectiveness of 2+1, 3+0, and 3+1 were very similar and ranged from 77% to 100%. None of these studies were designed to make direct comparisons between the schedules.

Surveillance studies conducted in 7 countries (e.g., UK, Norway, Denmark, Canada, England/Wales, Australia, US, Germany) describing the impact of national PCV introduction on vaccine-type-IPD among young children were reviewed. The impact is measured as the percent reduction in vaccine-type (VT) IPD rates post-vaccine introduction among young children. Although surveillance methods varied and each study only reported the impact of one particular PCV dosing schedule, some general comparisons between schedules can be made across this group of studies. One similarity observed among nearly all studies was a significant impact of PCV introduction on VT-IPD over time in populations routinely using 2+1, 3+0, and 3+1 schedules as soon as 1 to 2 years post-vaccine introduction, with reductions ranging from 65% to almost 100%. In general, more pronounced reductions were seen at more than 3 years compared to less than 3 years post-PCV introduction.

To summarize the findings for IPD, RCTs and observational studies demonstrate that both schedules (3+0 and 2+1) are highly effective against IPD. There are no studies directly comparing 3-dose schedules to 4-dose schedules.

Regarding studies evaluating effect of PCV schedules on pneumonia, results of a systematic review of RCTs published from 1994 through 2011 documenting the efficacy of PCV dosing schedules on clinical and radiologically-confirmed pneumonia were reviewed. Of these, 3 studies evaluated the efficacy of 3+0 schedule, and 2 of the these showed efficacy against clinical or radiologically-confirmed pneumonia. The clinical trial in the Philippines (Lucero, et al) showed impact of 11-valent vaccine (PCV11, sanofi pasteur) on radiologically-confirmed pneumonia, but not clinical pneumonia. Three clinical studies evaluated the efficacy of a 3+1 schedule against pneumonia. All clinical trials showed evidence of PCV benefit on clinical and radiologically-confirmed pneumonia; however, one German study had a CI overlapping null. This was a non-randomized, single-blinded clinical trial, which limits interpretation of their findings.

Four observational studies evaluated the effectiveness of a 2+1 PCV schedule on pneumonia. In the study from Italy (Ansaldi et al 2008), significant reductions in hospitalization rates for all-cause and pneumococcal pneumonia based on discharge diagnosis were observed in subjects born after widespread uptake of the vaccine. The percent reductions ranged from 15.2% for all-cause pneumonia to 70.5% for pneumococcal pneumonia. The study by Esposito et al (2007) was a retrospective cohort study evaluating the impact of PCV7 on radiologically-confirmed pneumonia. Parents participating in the study could choose whether to have their children vaccinated, and providers and parents were not blinded to the intervention. The effectiveness reported in this study was somewhat higher (65%) compared to other observational studies and clinical trials.

Quebec introduced PCV7 first for high risk children in 2002, and then in 2004 for all children on a 2+1 schedule. Hospital discharge records were analyzed using monthly frequencies in the diagnosis of pneumonia. Overall, hospitalizations for all-cause pneumonia decreased steadily during the period from April 2004 to March 2006. Beginning in the spring of 2004, after a routine PCV7 program started for all children on a 2+1 schedule, there was a sudden decrease in the frequency of lobar pneumonia that continued to the end of the study period irrespective of

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the season, while the frequency of unspecified pneumonia tended to increase [de Wals, 2008]. A study from Poland presents the number of hospitalized pneumonia cases per 1,000 children in the two years preceding vaccination (2004 and 2005) and two subsequent years (2007 and 2008). After implementation of the vaccination program, significant reductions were reported in the incidence rates in post-vaccine years for children in the first year of life (65%) and those 2 through 4 years of age (23%) [Patrzalek, 2010]. In Australia, where a 3+0 PCV7 program began in January 2005 for the general population of children, analysis of monthly hospitalization rates for all-cause pneumonia showed a statistically significant decrease in rates in the period following vaccine introduction. After adjusting for background trends and seasonal cycle, a reduction of 38% was observed for all-cause pneumonia among children aged less than 2 years [Jardine, PIDJ 2010].

One observational study directly compared the impact of 2 versus 3 primary PCV doses against clinical pneumonia incidence in a general pediatric population for a 2002 birth cohort. This was a propensity-score-matched case-cohort study conducted in the US that evaluated the rate of hospitalizations and ambulatory visits for pneumonia. The study found that children who received 3 doses in the primary series had fewer ambulatory visits and hospitalizations up to the point of receipt of a booster dose (9.5 admissions per 1,000 children) than those who only received 2 primary doses (17.3 admissions per 1,000 children), resulting in a rate difference of 7.8 cases per 1,000 children (95% CI: 0.8, 14.8). This difference disappeared after the booster dose was administered. The investigators repeated the analysis for the 2003 birth cohort, and this difference between 2 and 3 primary doses was seen for children born in the 2002 birth cohort, but not for children born in 2003. The authors hypothesized that by 2003, 3 years after introduction of PCV7, herd effects had lessened the difference in risk between the two groups [Pelton et al. 2009].

To summarize findings for pneumonia outcome, schedules with 3 PCV doses (2+1 and 3+0) prevent pneumonia. One observational study showed that 3-dose primary series are better than 2-dose primary series before booster dose against pneumonia. No differences were observed post-booster or for later birth cohorts. Schedules with 4-doses maybe more beneficial early post-introduction.

There are no randomized controlled trials evaluating efficacy of 3-dose schedules against otitis media. Results of three observations studies evaluating effectiveness of 2+1 schedules were reviewed from Italy (Ansladi 2008), Italy (Esposito 2007), and Canada (DeWals 2009). The effectiveness estimates ranged from 13% to 36%. Monthly incidence of AOM in children born in 2002 who received 2 or 3 doses in the primary PCV7 series was compared using propensity score matching using data from the insurance claims database. The study assessed AOM rates after completion of the primary series and before the booster dose, and after the booster dose until four years of age. Results showed that pre-booster dose incidence rates were 0.38 per person for children receiving 2-doses primary series and 0.35 per person for those receiving 3-dose series, but these rates were not statistically different. Post-booster incidence rates were also very similar and there was no statistically significant difference between the groups [Stoecker et al Vaccine 2012].

To summarize findings for AOM, there are no clinical efficacy data for 2+1 or 3+0 schedules. Data from observational studies show a reduction in AOM following PCV7 introduction on a 2+1 schedule. No significant difference was observed in AOM incidence for 2+1 versus 3+1 before or after booster.

There is a large body of evidence from immunogenicity studies on various 3-dose schedules. Dr. Pilishvili presented the results of meta-analysis and systematic review of immunogenicity

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studies comparing schedules with a 2- or 3-dose primary series, with and without a booster. GMCs and proportion of subjects over 0.35 mcg/mL, which is the reference point post 3-dose primary series developed for invasive disease outcome, were analyzed in most of the immunogenicity studies that were part of the meta-analysis and systematic review. The studies showed that the proportion of subjects over 0.35 mcg/mL was high for both schedules with 3- and 2-dose primary series. Schedules with 3-dose primary series produced higher antibody response than the 2-dose schedule for some serotypes. In the second year of life (pre-booster and post-booster dose), little to no difference was observed between those with 3-dose and 2-dose primary series, and there was a small but significant difference for serotypes 6B and 23F [Scott P et al Vaccine 2011, Rückinger et al Vaccine 2011, Knoll et al PIDJ 2013 In press]. Recently published results of a randomized clinical trial of PCV13 reported immunogenicity for 4 different schedules. In this trial, 400 infants were randomly assigned to receive PCV13 at either ages 2, 4, and 6 months; at ages 2 and 4 months; at ages 3 and 5 months; or at ages 2, 3, and 4 months; with a booster dose at age 11.5 months. Antibody GMCs against PCV13-serotypes 1 month after the booster dose and 1 month after the primary series were compared between schedules.

Focusing on the comparisons relevant for the US schedule (2,4,6 months or 2 and 4 month primary series), the 3-dose primary series schedule had higher antibody concentrations compared to 2-dose primary for 11 serotypes, although for most serotypes, the percentage of subjects with GMCs above the 0.35 mcg/ml level was high in both groups. Post-booster dose, the 3-dose primary series schedule had higher antibody concentrations compared to the 2-dose primary schedule for serotypes 6B, 18C, and 23F. In a way, this study confirmed the findings of the large meta-analysis. However, the difference before the post-primary series was observed for a larger number of serotypes in this study compared to the meta-analysis. For the 2-dose primary series, the antibody levels were lower compared to other studies for some serotypes. However, this is a very recent study and the working group has not had a chance to discuss it and a different laboratory method was used—a bead assay instead of an enzyme-linked immunosorbent assay (ELISA). The working group has not fully reviewed the results to understand whether that contributes to some of the differences observed.

To summarize the findings of immunogenicity studies, both 3+0 and 2+1 schedules induce good antibody response. After the primary series, GMCs maybe higher for schedules with 3-dose primary series compared to 2-dose primary series, but the difference is no longer apparent in the second year of life before the booster dose. After the booster dose, the differences between the schedules are only seen for 2 serotypes for most of the studies in the meta-analysis or for 3 serotypes in the recently published immunogenicity trial. It is important to point out that the immunogenicity studies reviewed by the working group were conducted outside of the national immunization programs. In these settings, no underlying herd effects have been observed in the population. In addition, the GMC cutoff of 0.35 ug/mL applied to the results of these studies should be interpreted with caution because it is an aggregate cutoff that was developed for all serotypes and is not well-established for individual serotypes. In addition, this was a reference point for antibody levels post-primary series, and its significance for endpoints other than invasive disease is not well-established.

In terms of the evidence for PCV effects on nasopharyngeal carriage, 2 clinical trials (Fiji and Gambia) had direct comparisons of schedules with 2 or 3 primary series. A study by Russel et al in 2010 compared carriage of vaccine-type strains (VT) at different time intervals following the administration of 0, 1, 2, or 3 doses of PCV7 and showed that the percentage of VT carriage was lower overall for schedules with 3-dose primary series. However, in a study by Ota et al in 2010, infants were assigned randomly to receive 1, 2 or 3 doses of PCV7 between 2 and 4 months of age, plus PPV at 10 months of age. The results showed that at 11 months, the 3-

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dose group showed a borderline significant reduction in vaccine-type carriage compared to the 2-dose group (10.0% v. 16.7%, p=0.056). No statistical differences were seen at 5 and 15 months. Two clinical trials (Israel and Netherlands) had direct comparisons of schedules with 2 or 3 primary series and the effect of a booster dose. A study by Dagan et al in 2012 showed that pre-booster (7 through 12 months of age), carriage rates for all PCV7 types were non-significantly lower in the 3+1 group as compared to the 2+1 group (22.6% vs. 28.4%, p=0.089). Differences were significant for types 6A and 6B, and there were no statistical differences post-booster. A study from Netherlands by Van Gils et al in 2009 assessed the effects of a 2-dose and a 2+1-dose schedule of PCV7 on vaccine serotype pneumococcal carriage in children and showed a significantly lower prevalence of PCV7-type carriage at 18 months in the 2+1 group (16%) than the 2+0 group (24%, p=0.01). No statistical difference was found at 12 or 24 months.

In a systematic literature review of PCV carriage studies published from 1994 through 2011, no direct comparisons were made between schedules, but vaccine type carriage rates were compared between vaccinated and unvaccinated. Ten clinical trials evaluated differences between vaccinated and controls for 2 or 3 dose primary series before booster dose. A total of 23 arms were examined. All arms of a 2-dose primary series found reductions in VT carriage prevalence among PCV recipients compared with controls. All but one arm with 3-dose primary regimens observed reductions in VT carriage, and most of these were statistically significant. Thirteen clinical trials assessed VT carriage with samples taken after the first year of life. Among the 29 arms reported in these studies, 28 showed reduction in VT compared with control subjects. The differences between schedules are difficult to discern from this analysis when making comparisons across the studies [Fleming-Dutra PIDJ 2013 In press].

To summarize nasopharyngeal colonization, all schedules with a 3-dose primary series had lower vaccine type carriage rates than schedules with a 2-dose primary series during 1 through 7 months following the series before the booster dose, but no differences were observed at 12 months of age before the booster after the booster dose.

In summary of the results of the entire evidence review, clinical efficacy of 3-dose schedules has been evaluated for all outcomes except acute otitis media. Observational and controlled trials are available comparing 3-dose schedules directly to a 4-dose schedule for pneumonia, immunogenicity, and carriage outcomes. One PCV10 trial evaluated efficacy of both 2+1 and 3+1 against IPD, but was not powered to make direct comparisons of schedules. In terms of differences observed between 3-dose and 4-dose schedules by outcome, studies with invasive disease outcome show that both 3-dose schedules and 4-dose schedules are effective but comparisons are made across studies. For the pneumonia outcome, the differences between 3- and 4-dose schedules may be observed early post vaccine introduction. No differences are noted for acute otitis media, but studies evaluating 3-dose schedules are limited. For immunogenicity and carriage studies, the differences between schedules with 3- and 2-dose primary series are noted following the primary series but following the booster dose, differences are observed only for some serotypes.

It is important to interpret the results of the evidence review in the context of the US PCV13 program. Differences in antibody response between schedules may lead to differences in carriage and, potentially, in disease rates. However, studies conducted outside of the national immunization program showed no herd effects. The serotypes in question are very rare in the US and are, therefore, less likely to cause disease. Rates of PCV13 type IPD are extremely low among children 6 through 11 months of age. Direct and indirect effects of 3-dose PCV programs at the population level are similar to the ones observed in the US. In terms of the results of a systematic review of PCV dosing schedules published from 1994 through 2011 to

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evaluate indirect effects of PCV on IPD among older children and young adults, programs with both 3-dose schedules (2+1, 3+0) demonstrated large reductions in incidence among young adult groups. Reductions in VT-IPD were observed as early as one year after introduction. In general, reductions for all schedules were larger ≥3 years after introduction compared to reductions seen within 3 years of introduction. Indirect effects of 3-dose programs are similar to the ones observed in the US.

In the editorial published by Grijalva and colleagues, an analysis was done to compare indirect effects of PCV7 programs on hospitalized IPD in the US and England and Wales where a 2+1 PCV7 schedule is used. Incidence rates were compared 4 years post-PCV7 introduction to rates in pre-vaccine years. Absolute rate differences for PCV7-type incidence were strikingly similar between two countries [Grijalva et al. Lancet 2011]. Regarding the results of the nasopharyngeal carriage study evaluating early impact of PCV13 on carriage of PCV13 types, nasopharyngeal carriage was evaluated among children 6 through 59 months of age and compared during five sequential 6-month study periods during 2010 through 2012. PCV13 serotypes declined from 29% to 8.7% (P<0.0001). Serotype 19A declined from 25.8% to 4.4% (P<0.0001). It is important to point out that from PCV7 serotypes, only type 19F was isolated during any study period. Vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 18C, or 23F were not isolated during any study period. Serotypes 6B, 18C, 23F, for which differences were noted in immunogenicity studies between schedules, have not been isolated during any study period [Desai et al. PIDJ 2013 In press].

The risk of invasive pneumococcal disease among children less than 2 years of age is also low. Overall rates are 14.6 /100,000 and PCV13 type rates are about 2 cases per 100,000. The working group wanted to determine, given the window of time during which the differences in antibody responses following the primary series were observed, what the risk of disease is among children 6 through 11 months of age. More than 1/3 of PCV13 type cases in this age group occur before 2 months of age, and only one PCV13-type case was reported in 2012-2013 among children 6 through 11 months of age [Active Bacterial Core surveillance, unpublished].

The working group also reviewed PCV13 coverage data from the NIS to understand the proportion of children receiving only 3-doses currently, and which 3-dose schedules they receive. According to 2012 NIS data, 92% of children surveyed receive 3 or more PCV doses and 82% receive 4 or more doses. This means that approximately 10% of children who received 3 doses do not receive a 4th dose. In terms of age distribution for the timing of the 3rd dose among children receiving a total of 3 doses, 22.5% of children who received a total of 3 doses received a 3rd dose at age 6 months and, therefore, were vaccinated on a 3+0 schedule. Similarly, 43% of children who received a total of 3-doses received the 3rd dose at 13 months or after and, therefore, were vaccinated on a 2+1 schedule. Given that only a small percentage of children overall received a total of 3 doses, these data cannot provide input on what the preferred 3-dose schedule would look like, but the data signify that children are receiving 3-dose schedules and the 3rd dose may be administered anywhere between 6 months of age to 13 months or later [Courtesy of Black C. and Qian Li. CDC unpublished].

The working group also reviewed vaccine failure and breakthrough infections reported to the ABC surveillance system in order to evaluate whether any particular incomplete PCV schedules were associated with breakthrough infections. Of 817 children less than 5 years with IPD during April 2010 through July 2013, 715 had serotyping data available, 443 had a vaccination history, and 238 had received at least 1 PCV13 dose. Of the IPD cases who received at least one PCV13 dose, 41 cases were caused by PCV13 serotypes, and were classified as breakthrough cases. The vaccination status of breakthrough cases was examined by serotype and PCV13 schedule. Only 4 serotypes were associated with breakthrough infections. The majority of

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breakthrough cases (74%) were caused by type 19A, followed by type 3 (22%), and one case of 7F. Only one PCV7 serotype, 19F, was associated with a breakthrough infection. The majority of breakthrough cases were vaccinated using schedules other than 3+1, 3+0, or 2+1. The majority of those in the "other" category received only one PCV13 dose.

In summary, 3-dose PCV schedules are effective against IPD, pneumonia, and otitis media. Immunogenicity and carriage studies show that 3+1 schedule may be better than 2+1 before booster. No differences were observed post-booster for most serotypes. Strong direct and indirect (herd) effects were observed in countries using 3-dose PCV schedules. Differences between schedules may not be meaningful due to PCV7 serotypes rarely causing disease in children and adults, PCV13 serotype disease rapidly declining, and similar herd effects so no changes should be expected at the population level.

Though not discussed in detail during this session as noted earlier, the working group did raise other points. In terms of policy/statute issues, a 3-dose schedule is not approved by FDA and, therefore, this would be an off-label recommendation. In addition, it is important to ensure that the wording of a potential recommendation allows for ACA coverage for insurance reimbursement of the 4th dose. The cost-effectiveness analysis preceded working group discussions, so only one 3-dose schedule was considered and no consideration was given to the fact that the vaccine price may be adjusted. It is important to ensure that the language of recommendations allows for no cost-sharing if providers choose to give a 4th dose. There are also programmatic considerations, which will vary and will be specific to a specific policy option.

The working group concluded that including a 3-dose PCV13 schedule for routine use among infants would not adversely impact the individual protection against invasive pneumococcal disease, pneumonia, otitis media, or herd effects. An acceptable schedule in the setting of a mature immunization program and strong herd effects may not need to be the same as that chosen at the time of licensure. A 3-dose PCV13 schedule for infants is likely appropriate to maintain already observed benefits from 13 years of PCV use in the US.

Given that there is much more work to be done, the working group invited input from ACIP, AAP, and AAFP to help identify gaps in data and information. The working group would like to further review data by timing of dose. The GRADE process will be required to evaluate appropriate 3-dose schedules, considering effectiveness and safety data. Following these steps, more specific policy options could be presented during a future ACIP meeting.

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In conclusion, Dr. Pilishvili posed the following questions for discussion:

- ❑ Is the available evidence adequate to consider including a 3-dose PCV13 schedule?

- ❑ If not, what are the gaps in information?
  - ➢ Supporting evidence/data
  - ➢ Provider/practice level issues
  - ➢ Public health program level issues
  - ➢ Parent considerations

- ❑ Does the committee have concerns about potentially including a 3-dose PCV13 schedule for routine use among infants?

Discussion Points

Dr. Harrison requested that Dr. Pilishvili comment on the antibody persistence for a 2+1 versus 3+0, and said he was thinking back to the UK experience with the meningococcal C vaccines where a 3+0 had very good antibody response and protection for one year that basically fell off to virtually no protection.

Dr. Pilishvili responded that antibody levels following both the 2-dose primary series and 3-dose primary series do decrease. However, there is a boosting effect with the 2+1 schedule. With a 3+0, there is no booster, so it would not be appropriate to compare antibody levels 2+1 post-booster to a 3+0 around the same age with no booster. In a setting of circulating serotypes, natural boosting may occur following 3+0 schedule, and, therefore, we do not know what the differences between schedules mean in terms of clinical protection. The studies that were evaluated were conducted in a setting of no herd effects, so no differences were observed. In a setting where the strains are not circulating, this may not be observed.

Dr. Karron asked whether the working group was surprised by the data regarding the fact that only 22% of 6 through 7 month olds had received the 3rd dose, and whether they had any insight into the reason for that percentage and whether it meant anything in the consideration of 3-dose regimens.

Dr. Pilishvili clarified that the number presented was not 22% of children who received a 3rd dose at 6-7 months of age. It was 22% of children who had received a total of 3 doses, which was already 10% of those who were surveyed. These children received the 3rd dose at 6 months of age and did not receive a booster, or 3+0. This is a small fraction of the population (22% of 10%).

Dr. Campos-Outcalt clarified that of the children who received only 3 doses, 22% received their 3rd dose during the timeframe between 6 to 7 months of age. The 414 children received 3 doses by that age and never got another dose, but that does not indicate what percentage of children had 3 doses by that age.

Dr. Kempe thought it would be very helpful to see those data for 4 doses, because if moving to a 3-dose schedule, the other decision is whether to use a 3+0 or 2+1 schedule. She said she had even worse concerns about the fall off at dose 1.

Dr. Jenkins asked how old the children were when the survey was conducted.

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Dr. Pilishvili replied that the survey is conducted annually among children 19 to 35 months of age.

Other than cost, it was unclear to Dr. Campos-Outcalt why this was being considered. The schedule is set, everybody is used to using it, and there is good effectiveness of the schedule as currently used. Therefore, he wondered why consideration was being given to altering the schedule other than due to cost and potential adverse reactions with PCV13 and influenza vaccine administered together. Having said that, he emphasized that he thought it was worth considering, but the quality of the studies presented was unclear to him. He would not be willing to change a working schedule without knowing the quality of the studies upon which the evidence was based.

Dr. Pilishvili responded that although they would be presenting cost data during this session, cost was not one of the considerations of the working group regarding a 3- versus 4-dose schedule. The working group realizes that that cost-effectiveness analysis is based on the assumption that the price of the vaccine would not be adjusted. The main rationale for the working group to approach this topic was the evidence began emerging from multiple locations in the world showing that 3-dose schedules work. It was simply a matter of the working group doing its job to consider all of the available evidence to determine whether it warranted a change in the dosing regimen in the US as well. The working group will consider the quality of evidence in detail when the GRADE process and framework are applied. In addition, the working group will consider the safety of Prevnar® co-administration with other childhood vaccines.

Dr. Temte inquired as to whether there were populations for which there was compelling evidence to continue with a 4-dose schedule, and how well high risk groups could be identified if there was a move to a routine 3-dose schedule. He said that while he did not necessarily expect an answer at this time, this needed to be considered.

Dr. Warshawsky (NACI) reported that Canada has been using the 2+1 schedule for PCV13. It is a permissive recommendation by NACI, which means that they federally set the recommendations, but each province can choose what they decide to do. Of the 13 provinces, 11 have decided to move to the 2+1 schedule. Two small territories have decided to continue with the 3+1 schedule. These are communities with a predominance of First Nations Aboriginal communities, and they are quite small. In implementing that, NACI chose 2, 4, and 12 months. One reason was to make sure that the booster was given at 12 months, given that there have been failures with other conjugated vaccines when just the 3 doses are given without the booster. For Canada that caused a problem in terms of crowding the schedule at 12 months, because Canada also gives conjugate meningococcal vaccine and MMR at 12 months. That was an implementation difficulty, but this has been overcome by encouraging people to give 3 doses at one visit. Exceptions are made for high risk groups, so those in the high risk meningococcal groups receive the 3+1 regimen. Consideration was given to the incremental cost of the 4th dose in terms of how much disease is prevented and how much that costs. One of the reasons the 2+1 schedule was very attractive was because it is quite effective, and the incremental cost of the 1 or 2 cases that might not be prevented with the cost of the extra dose is quite large.

Ms. Pellegrini pointed out that if they could consult them, the 0 through 12 month olds would vote wholeheartedly for a 3-dose schedule regardless of whether it was 2+1 or 3+0, and that their parents probably would as well.

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Dr. Sun (FDA) shared the FDA's following prepared statement on this topic, "The FDA appreciates the opportunity to provide input into this discussion of a PCV13 reduced dosing schedule in healthy children. FDA and CDC staff have been working together on this issue since February 2012. FDA has considered the available evidence, as well as the regulatory implications. We understand that the ACIP is now evaluating the evidence supporting a possible recommendation for a reduced dose schedule for PCV13 in healthy children. We have concerns that this could result in a discrepancy between the ACIP recommendation and FDA approved vaccine labeling. With regard to a 2+1 or reduced dose schedule, we agree that the observational data, primarily with PCV7, provide some evidence that the reduced dose schedule is effective against invasive disease. Nevertheless, FDA notes several concerns with the removal of one of the doses of PCV13 from the vaccine series. No studies for PCV13 have compared the effectiveness of the 2+1 with the 3+1 schedule we have right now for prevention of invasive disease. The only published head-to-head randomized controlled trial comparing the 2+1 and 3+1 schedules reported higher antibody levels for most serotypes between the third and fourth dose of the current US 3+1 schedule. Also, with regard to otitis media, the other indication for which PCV13 is approved, no data are available that compare the effectiveness of different dosing schedules of PCV13. In the absence of specific safety or efficacy concerns regarding the licensed product, FDA does not have the authority to compel the manufacturer to conduct studies of PCV13 comparing a 2+1 schedule to the licensed schedule, or to submit safety and efficacy data in support of a label change. The licensed vaccine has been shown to be safe and effective with a 3+1 schedule. When evaluating a labeling change, FDA reviews the data submitted by the manufacturer. If the manufacturer could demonstrate adequately the effectiveness of the abbreviated dosing schedule, then FDA could not approve a labeling change. FDA raises these issues because Prevnar13® is a universally recommended childhood vaccine. FDA believes that a discrepancy or ambiguity between an ACIP recommendation and the labeling for the vaccine regarding the dose schedule could lead to confusion among parents, healthcare providers, insurers, and the manufacturer."

Dr. Loehr (AAFP) posed a scenario in which Vaccine X initially requires 4 doses, but in 5 years it is determined that only 2 doses are needed, and he asked what evidence ACIP would need to recommend a 2-dose schedule. He complimented the working group for raising this issue, because if there is evidence that 4 doses are not required, this should be addressed. He thought they were creating a conversation to determine what evidence ACIP would need to state that 3 doses are just as good.

Dr. Harriman also applauded the working group for taking on this issue. ACIP should always be considering these issues as new evidence emerges about existing recommendations and existing vaccines on the schedule.

Dr. Moore (AIM) said that from an immunization program standpoint, AIM agrees that this is an important conversation to have. However, it is also important to ensure that booster dose coverage remains as high as it needs to be to maintain the level of protection expected. It is already a struggle to get children in for a booster dose after their first birthday, and that is often the dose that is missed. If one of the infant series is dropped, it could impact the safety net that has been created and result in children only receiving 2 doses in a 3-dose schedule if they do not receive the booster dose.

Dr. Sawyer (PIDS) suggested that the younger doses at 2 and 4 months also be assessed, particularly the 4 month dose, to determine how many children are delayed in getting the 4-month dose. In a 2+1 schedule, those children may only get a 1+1 schedule. It is probably not a large number, but this should be assessed.

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Ms. Groom (IHS) pointed out that this is one of the reasons IHS would like the working group to assess that issue. If the American Indian population was considered a special population in certain geographic regions for a 4-dose series, the IHS can implement that but is not the only provider who sees American Indians and Alaska Natives. The definition of who really is at risk becomes much more complex with two different recommendations.

Dr. Duchin inquired as to whether any data are available on the types of systems that the other studies are describing when evaluating alternate schedules, and the success or failure in different environments in different countries in terms of how their infrastructure compares with the US infrastructure with respect to completion of doses at various ages, or whether research could be done or research is available on the US's likelihood of success in getting people immunized with a 2+1 schedule. Dr. Pilishvili responded that she did not have this information, but could look into obtaining it.

Dr. Kimberlin (AAP) said that for him, slides 7 and 8 from Dr. Pilishvili's presentation seemed to be the most informative looking at vaccine effectiveness against IPD. It appeared to him that generally speaking, the 3+1 schedule looked better than the 3+0 or 2+1 schedule. The US has had great success with the program, and he personally wondered why they would "rock the boat" now.

Dr. Pilishvili cautioned that when comparing the schedules across the studies, one needs to consider that the populations in these studies are very are different. The 3+0 schedules were conducted in Africa, and the 2+1 study was conducted in Finland.

Dr. Hosbach (sanofi pasteur) disclosed that he represented a vaccine manufacturer, but that they do not make a pneumococcal conjugate vaccine. He thought a lot of good studies were presented, but what was missing was evidence of the unexpected benefit of the immunization of this population in the US and this schedule of the herd effect relative to what is occurring in the elderly population. What also came to mind was what occurred with Hib during a Hib shortage. The US had to go to a 3+0 schedule temporarily, and when unimmunized populations were exposed to the underlying circulating organism, there were a couple of deaths and disease occurred. He expressed concern about the acceptance of, or confidence in, immunization when changing to a 3+0. When the Hib schedule was changed to 2+1, in the booster doses, a reduction was observed in the immunization rates. That could continue and expose more vulnerable populations again, whether it be due to herd effects for other populations or populations that are unimmunized. Those populations tend to be increasing currently.

With regard to herd effects, Dr. Pilishvili pointed out that there is vast evidence from countries that are using 3-dose schedules that do demonstrate effect. What she showed was just a snapshot that was part of the systematic review that was done, so the table excluded some of the older age groups because of the focus of the paper. Herd effects have definitely been shown in younger adult age groups. It is also important to take into account the number of years post-vaccine introduction and compare it to the same time period in the US. The study that included the elderly and compared the herd effects across two different populations using two different schedules also showed that the herd effect in the elderly was very similar compared to the programs that use the 3-dose schedule.

It seemed to Dr. Jenkins that this was an important conversation from a public trust point of view. She thinks the public is really concerned about the number of immunizations that the US gives to children, and whether they are all really necessary. It is important to carefully assess the science of this and the longer-term effect, especially in terms of the decreasing prevalence of some of these diseases now, ACIP needs to make assessments to determine whether the

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schedules need to be changed down. ACIP is aggressive about changing a schedule up, but also needs to consider whether to ratchet schedules down.

Dr. Jodar (Pfizer) thanked ACIP for contributing to this discussion, which Pfizer thinks is a very important debate. It is important to emphasize that in the context of the US, Pfizer believes that the clinically proven approved FDA 4-dose schedule is the optimal schedule for the prevention of pneumococcal disease. Since 2000 when PCV7 was introduced, extraordinary results have been shown in reductions of invasive and non-invasive disease in vaccinated and non-vaccinated individuals. Dr. Moore showed beautiful, encouraging results with a 3+1 schedule after three years of the introduction of PCV13. He also applauded the job that the working group did on the collection of the evidence available. However, Pfizer believes that the current evidence does not support a reduction at this stage of a reduction to a 3-dose schedule because of three considerations. The first regarded the quality of evidence. Clearly, there are not randomized studies with PCV7 or PCV13 that compare a 3+1, versus a 2+1, or a 3-dose and 4-dose schedule, especially for non-bacteremic pneumonia and also for acute otitis media. Also, there is no comparison in terms of impact of the effect between a 3-dose and a 4-dose schedule simultaneously. In terms of the magnitude of the effect of a 4-dose schedule versus a 3-dose schedule, he did not think there was enough evidence to demonstrate that they are equivalent, especially in countries with disparities in compliance rates. The discussion about compliance rates has been raised, and it has been argued increasing compliance rates might mitigate the potential of negative effects that reduction to a 3-dose schedule may have. It is also true that about 20% of children do not receive the 4-dose schedule. It is simply not known what the impact might be in those children. Those disparities are further emphasized in terms of ethnicity, socioeconomic conditions, or whether the provider is public or private. It is important to understand that it is not known whether dose effect can be sustained moving to a 3-dose schedule. Dr. Jodar concurred with the FDA statement. It is important to remember that PCV13 was licensed in a 4-dose schedule at 2, 4, 6, and 12 to 15 months, and that was based on the evaluation of the 4-dose series immunological responses. It is highly unlikely that under the current licensing criteria that a 3-dose schedule will be licensed. In view of the spectacular results that have been observed, Pfizer still considers the 4-dose schedule to be the optimal schedule in the context of the US, but is committed to continuing the scientific dialogue and to contribute in any way possible to generate the evidence to establish the best immunizations programs in the US and the rest of the world.

Dr. Gorman (NIH) inquired as to whether, when the EMEA approved a 3-dose schedule, the package submitted by the sponsor supported that recommendation.

Dr. Jodar (Pfizer) responded that this statement had to be qualified. For individual protection, the approved schedule in the EMEA is 3+1. However, in the context of a national immunization program, an alternative schedule of 2+1 can be considered by countries.

Dr. Gorman (NIH) requested that Dr. Jodar answer the same question for the 34 countries that have introduced PCV13 or PCV10 on a 3-dose schedule in terms of whether the packet was a 3+1 but there was an acceptable alternative of a 3-dose schedule.

Dr. Jodar (Pfizer) responded that the packet in every country was always a 3+1 schedule for individual protection. Many other countries have decided that a 2+1 schedule, based on the immunogenicity data and in the context of national immunization programs, is acceptable.

Dr. Whitney (SME) clarified that the packet submitted included data showing 2+1 immunogenicity.

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Dr. Warshawsky (NACI) suggested that it would be interesting to assess the cost per case averted for a meningococcal strategy versus the cost per case averted for the 4th dose in the pneumococcal strategy.

Cost-Effectiveness of Reduced Dose Schedules

Dr. Charles Stoecker
Assistant Professor
Department of Global Health Systems & Development
Tulane University School of Public Health and Tropical Medicine

Dr. Stoecker presented the economic analysis of reduced dose schedules, which reflected the results of a work published earlier in the year. The objective of this analysis was to evaluate the cost-effectiveness of switching the PCV13 schedule from a 3+1 to a 2+1 schedule, modeling the removal of the dose at 6 months and comparing potential program cost savings with potential increases in disease, medical costs, and nonmedical costs [Stoecker, Charles, Lee M. Hampton, Ruth Link-Gelles, Mark L. Messonnier, Fangjun Zhou, and Matthew R. Moore. "Cost-effectiveness of using 2 vs 3 primary doses of 13-valent pneumococcal conjugate vaccine." Pediatrics 132.2 (2013): e324-e332].

The model was a cohort model following the 2010 US birth cohort. Events were tracked annually, except in the first year of life, which was tracked separately in two 6 month periods of those between 0 through 6 months of age and 6 to 12 months of age. Events occurred within the first 10 years of life, and the consequences of those events were tracked against life expectancy. The model was conducted from the societal perspective, with costs in 2011 dollars, a discount rate of 3%, and a new steady state (e.g., long-term effects of switching to a 2+1 schedule). This was a decision model, which has two arms of IPD or non-invasive disease. For IPD, the outcomes were meningitis, pneumonia, bacteremia without focus, and other syndromes. For meningitis, all cases result in hospitalization which can subsequently lead to fatality, mental retardation, deafness, or potentially no sequelae. For pneumonia and the other three IPD outcomes in the model, the cases can result in hospitalization and fatality or no hospitalization and fatality. The non-invasive disease arm considered otitis media, which can lead to tympanostomy tube placement or a case of acute otitis media, or non-invasive all-cause pneumonia, which can result in hospitalization and fatality or potentially no hospitalization.

The model included the following 6 key assumptions:

1) Both schedules have similar direct effects against IPD
2) Both schedules have identical herd effects
3) Both schedules have identical replacement disease
4) 2+1 provides zero direct protection against otitis media and all-cause pneumonia between 6-11 months
5) 2+1 provides same direct protection against otitis media and all-cause pneumonia as 3+1 after the booster dose
6) No price response from vaccine manufacturer

The following table reflects the baseline disease rates used in the model for those in the first five years of life. The first line is those between 0 through just under 0.5 years of age, and the second line is those between those 0.5 years of age to just under 1 year of age. Though the model goes through age 10, only the first five are shown in the above table for brevity:

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Pre-PCV7 Baseline Rates (per 100k population)

Age (yrs)	Acute Otitis Media[1]	Tymp. Tube Placement[1]	Outpatient Pneumonia[1]	Inpatient Pneumonia[1]	IPD[2]
0-<0.5	32,264	121	4,500	649	34.3
0.5-<1	92,086	477	4,500	649	41.6
1-<2	124,350	4,680	9,000	1,297	32.6
2-<3	80,475	2,370	6,500	418	15.9
3-<4	36,600	1,130	4,000	418	10.1
4-<5	36,600	1,020	4,000	418	9.5

[1] Non-IPD rates for children younger than 5 are adapted from Ray et al 2009. Incidence rates in the first year of life are broken into 6-month categories by the proportions reported in Ray et al 2006.
[2] IPD incidence rates are averages from 2006–2008 Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011).

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The following table reflects the assumed percent reductions in pneumococcal disease by syndrome, age, and schedule. These represent the composite of both direct and indirect effects. The differences between the two schedules are highlighted in red. The second to last column shows the total of reductions of 2+1, and the last column has the total reductions for 3+1. The 6.7 highlighted for those between 0.5 and 1 year of age is the indirect effect, since no direct effect is assumed of the 2+1 schedule against otitis media. The 14.6 assumed for the 2+1 schedule is after the direct effect is added in:

Assumed Percent Reduction in Pneumococcal Disease by Syndrome, Age, and Schedule

Disease	Ages (yrs)	2+1	3+1
Acute Otitis Media[1,2]	0-<0.5, 1+	14.6	14.6
	0.5-<1	6.7	14.6
Tympanostomy Tube Placement[1,2]	0-<0.5, 1+	25.1	25.1
	0.5-<1	11.5	25.1
Outpatient Pneumonia[1,3]	0-<0.5, 1+	6.3	6.3
	0.5-<1	0	6.3
Inpatient Pneumonia[1,3]	0-<0.5, 1+	13.8	13.8
	0.5-<1	7.5	13.8
Invasive Pneumococcal Disease (Vaccine Serotypes)[4]	0-<1	96	96
	1+	98	100

[1] Adapted from Ray et al 2009.
[2] Adapted from Fireman et al 2003.
[3] Adapted from Pelton et al 2010.
[4] Adapted from Whitney et al 2006.

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Vaccine costs and related parameters assumed include a public vaccine price[1] of $97, private vaccine price[1] of $121, public share[2] of 65%, wastage[3] of 5%, and vaccine administration[4] of $15 [[1] CDC vaccine price list 2011; [2] CDC Biologics Surveillance Data (unpublished), 2010; [3]Ching 2007, [4] Zhou et al 2005. The assumptions related to disease costs are shown in the following table:

Disease Costs

Item	Medical	Non-Medical
Inpatient Pneumonia, age 0-5 yrs[1]	$7,763	$371
Inpatient Pneumonia, age 5+ yrs[1,2]	$5,329	$749
Outpatient Pneumonia[1]	$248	$371
Acute Otitis Media[1]	$59	$147
Tympanostomy Tube Placement[1]	$2,556	$367
IPD, Meningitis, age 0-5 yrs[1]	$18,189	$2,603
IPD, other, age 0-5 yrs[1,2]	$3,471	$497
IPD, age 5+ yrs[1,2]	$13,591	$749
Deafness[3]	$34,230	$110,240
Disability[3]	$182,700	$123,107

[1] Ray et al 2009.
[2] Non-medical costs from hospital stay length from ABCs data 2001 and lost wages from Widdowson et al 2007.
[3] MMWR 53(3) 2004 and MMWR 55(32) 2006.

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Quality-adjusted life year (QALY) lost per episode of disease were used to compare mortality outcomes with non-fatal outcomes, and included the following weights: Acute Otitis Media 0.005; Tympanostomy Tube Placement 0.005; Inpatient Pneumonia 0.006; Outpatient Pneumonia 0.004; IPD, Meningitis 0.0232; IPD, other 0.0079; Deafness 0.73; and Disability

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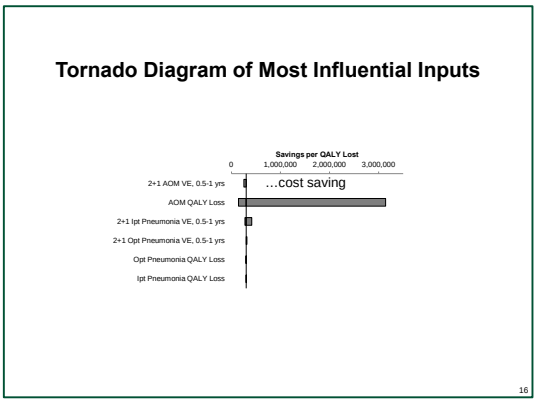
0.68. To put this in context, 0.005 is about 1.8 days of life [QALY decrements assembled by Rubin et al 2010].

Regarding the results, this represented a very simple model in which it was assumed that a 2+1 and 3+1 schedule have identical effects on all syndromes. There were no additional cases of IPD, hospitalized, pneumonia, or any of the other outcomes. Also considered were the total cost savings. For the base case, it was assumed that there were some differences between the two schedules. Under these assumptions, there were an additional 44 cases of IPD, which represented an 8% increase over about 550 cases of IPD in those 0 through 10 years of age. There were 1452 extra cases of hospitalizes pneumonia and 261,000 extra cases of otitis media. The total costs savings were lower at $421 million because there were potential increases in medical and non-medical costs due to the additional cases of pneumococcal syndromes. The key numbers for the cost-effectiveness analysis were a savings/QALY lost $300,000 and a savings/life-year lost of $6,014,000. This showed that non-fatal cases are really driving the cost-effectiveness results in this model.

The following diagram shows the most important influential inputs in this model, going from the most important at the top to the least important at the bottom. There are hundreds of inputs in this model, and this diagram could go on for a few more feet. The top line is the effectiveness of the 2+1 schedule against acute otitis media in the 0.5 to 1 year old age group, and the base case is shown in the black line ($300,000 saved/QALY lost), which can range somewhat to the left of that, so fewer dollars saved/QALY lost, all the way over to cost saving, which is undefined for this graph:



The second most important parameter in this model is the QALY assigned to acute otitis media. Under the ranges assumed for the model, that could range anywhere from about $150,000/QALY saved to over $3 million save/QALY lost. The other top 6 important inputs into the model are all on non-invasive disease and are much less important than those assumptions around otitis media.

All of this motivated the investigators about which parameters to look at for the sensitivity analysis. They turned first to assess other functions around the otitis media parameters. The assumption was made that the otitis media QALY loss is worth 0.110 years or about 4 days as opposed to the 1.8 days assumed in the base case. The cases in the model remained unchanged at 261,324, but the cost-effectiveness ratio changed from $300,000 to $143,000 saved/QALY lost. Thus, if increased weight is placed on otitis media parameter, zero dollars per QALY lost are saved because more QALYs are lost. Assuming that the two schedules were identical in effectiveness against otitis media, there were zero additional cases and a savings/per QALY loss of about $4 million.

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Also assessed was the sensitivity of the model to assumptions against other syndromes that were much less important in terms of cost-effectiveness. There were identical effects against IPD. Instead of the 44 additional cases of IPD, zero cases were observed and the savings/QALY lost increased to $305,000. This shows that IPD is not driving results in the model. In terms of how important the assumptions surrounding inpatient pneumonia were to the model, instead of 1453 additional cases of hospitalized pneumonia, there were zero additional cases. $323,000 was saved/QALY lost. Again, this does not differ much from the base case of $300,000. Assuming that the two schedules have identical impacts against outpatient pneumonia, instead of 10,000 cases there were zero and there was very little change in the $300,000/QALY saved.

An experiment was also done to imagine what would happen if PVC13 coverage could be increased. This model included coverage for the primary series and coverage for the booster dose. Coverage denotes coverage with complete recommended schedule, so for the model a coverage rate of 83.3% was used for the 3+1 schedule. The same people receiving only the 2+1 resulted in the base case. An increase in coverage for a 2+1 schedule to 86% would result in a cost savings/life-years lost. Two things were done here, the number of doses assigned were decreased and coverage was increased. If coverage could be increased by about 3%, more deaths would be prevented. Increasing coverage for the full schedule by about 10% would completely negate any potential loss of QALY.

There are several important limitations for this study to note. The 2+1 and 3+1 comparative effectiveness is based on observation studies. There is some RCT evidence that effectiveness is similar for invasive disease. There is no RCT evidence of PCV13 efficacy. Estimates in the model are adjusted from PCV7 to match PCV13 serotypes. Evidence of herd immunity is based on international comparisons and immunogenicity. Data quality of effectiveness of 2+1 against non-invasive disease is especially limited. There is great uncertainty about how important the otitis media outcome is, and that turns out to be a key input for the cost-effectiveness model, so depending upon what weight is assigned to each ear infection determines how cost-effective policy change would be. This does not model continuing 3+1 for high risk groups.

The following table attempts to put the PCV schedule change in the context of other changes. This analysis imagines a world in which there is a 2+1 schedule and consideration is being given to moving to a 3+1 schedule. Adding the third dose in the primary series would cost $300,000/QALY saved. This is more expensive than other routinely recommended preventive interventions, including lime disease in areas with very high attack rates, which was estimated to be about $200,000/QALY saved. If a larger weight is placed on the otitis media parameter and the assumption is made that preventing an ear infection is worth giving up about 4 days of life, the cost per QALY decreases to about $140,000. Conversely, if less weight is placed on the otitis media parameter and it is assumed that the schedules are identical against otitis media, the cost per QALY is just under $4 million:

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Sensitivity Analysis: Increases in PCV13 Coverage

	Base Case Coverage (83.3%)	Expanded Coverage (86%)	Expanded Coverage (93%)
Cases			
IPD	44	(82)	(410)
Hospitalized pneumonia	1,453	831	(780)
Non-hospitalized pneumonia	10,136	8,091	2,790
Tymp. tube placement	2,318	(450)	(7,624)
Otitis media	261,324	201,596	46,745
Deaths	2.5	(0.5)	(8.1)
Total Cost (savings) in millions	($421)	($434)	($466)
Savings/QALY lost	$300,000	$446,000	Cost Saving
Savings/Life-year lost	$6,014,000	Cost Saving	Cost Saving

Coverage denotes coverage with complete recommended schedule. 19

In conclusion, compared to a 2+1 schedule, the current 3+1 schedule is less cost-effective than other routinely recommended preventive services. The cost-effectiveness of the third dose in the 3+1 schedule could fall into the range of other routinely recommended services if the QALY loss associated with otitis media were 0.011 (4 days) instead of 0.005 (1.8 days). If the effectiveness of 2+1 and 3+1 against otitis media are equivalent, then the cost-effectiveness of the 3+1 schedule falls far outside the range of other services considered to be cost-effective.

Discussion Points

Dr. Karron pointed out that acute otitis media is a “moving target,” and she assumed that with PCV13 and increasing herd immunity, the proportion of otitis media that is pneumococcal-associated will continue to decrease. In the model, some of the assumptions about the burden of pneumococcal-associated disease were from 2003. But the current status may be an emerging era in terms of pneumococcal otitis media burden.

Dr. Stoecker clarified that for otitis media, disease inputs were assumed from the prior PCV7 and applied PCV7 effectiveness to those disease rates. He thought they did a pretty good job of matching the impact of the vaccine with the disease rates that were prevalent when that impact was measured. The reasons this was done is because there was a large otitis media burden before PCV7 was introduced, and then introduced this effective vaccine with a 3+1 schedule, but the concern is that scaling back to a 2+1 effectiveness, which is about half as effective for this particular age group, potentially the burden would increase by a much large amount since it is being based on the large baseline disease incidence rate from before 3+1 significantly reduced it. These are very conservative assumptions about when the disease started, and what vaccine effectiveness to apply to those. The model started with the largest possible disease burden in order to determine the maximum possible difference between the two schedules as a conservative assumption.

Dr. Kimberlin (AAP) noted that the first of the six key assumptions is that both schedules have similar direct effects against IPD, but on slide 15 with a base case of 83% coverage, there are 44 increased cases of IPD. If it was assumed to be similar, it was not clear how there could be increased cases.

Dr. Stoecker referred to the last line of slide 9 showing that for 0 to 1 year olds vaccine effectiveness was assumed to be 90% in both schedules, and the difference is 98. For everyone over age 1, it was assumed that the 2+1 schedule only prevents 98% of vaccine-type IPD and the 3+1 prevents 100%. That is why it is similar, not identical.

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Dr. Moore (AIM) inquired as to whether any consideration was given to antimicrobial resistance and those concerns with respect to treating acute otitis media rather than preventing it with vaccine. Although it is not a QALY issue, antimicrobial use and resistance patterns are making it more difficult to treat. She also requested clarification on whether the benefit of expanded coverage was the benefit over the current status with the 3+1 schedule at 83% or 93% 3+1 compared to 93% 2+1?

Dr. Stoecker responded that it was somewhat complicated. In the model, it was assumed that there are different coverage rates—one for the primary series and one for the booster dose. This is a composite of the two options Dr. Moore laid out. In the model, the primary series has a coverage rate of 93%. This is when those with a primary coverage of 3 go down to 2 and a booster dose is added for them. This is increasing those who adhere to the schedule up to 86%. He deferred the antimicrobial resistance question to the disease experts.

In terms of the assessment of QALY loss, Dr. Bennett noted that the assumption was varied for otitis media and how much QALY loss it causes in order to show that it would fall within a more reasonable range. She wondered whether they did this for any others, because she was struck by the way that QALY losses cluster essentially and are not as great as she would have expected them to be for some of the outcomes.

Dr. Stoecker responded that for the ranges on the QALY inputs, the ranges were used from the surveys. If there was a 95% confidence interval around the resulting QALY loss, that was used. Otitis media is a special case because an alternative study was conducted to assess how much parents would give up to avoid a case of otitis media in their child. The 0.11 number came from this study, so it was used in the model to determine how it would impact the results. The investigators were not completely confident about using that particular study as the base case since they were worried that parents may have been answering that question not as an acute case, but as an ongoing condition. There was a range in answers that parents would give up about 8 months of their life to avoid an ear infection in their child, so there was concern that there might be some issues in the survey.

Regarding the limitation that the model does not take into account the impact to high risk groups, Dr. Brady (AAP) pointed out that there are very high risk groups for pneumococcal infection. Another moderate risk group is based on race and ethnicity, which actually represents a relatively large proportion of the population. He wondered whether that could be modeled, because use of the vaccine has significantly altered the disparity in pneumococcal disease for the strains that are in the vaccines. He would hate to lose that, and would like to know if it would significantly impact the cost-effectiveness. He also said he thought there were a lot of problems with the QALYs. A parent who says that otitis media is about the same severity as inpatient pneumonia did not seem right. While a lot of parents with a child who has many episodes of otitis media will always be upset about that, having to admit a patient into the hospital is more than .001 more severe than otitis media.

Dr. Stoecker agreed, pointing out that the QALY results showed that inpatient was only about 20% more severe than an ear infection. That is .006 over .005.

Dr. Brady (AAP) said he assumed that deafness and disability were not included, but having a patient in the hospital for 10 or more days compared to otitis media seemed like it would be more than just 4 times.

Dr. Stoecker acknowledged Dr. Brady's concerns, and said that it would be possible to model high risk groups separately.

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Dr. Foster (APhA) recalled that when ACIP was discussing meningococcal vaccine, the QALY costs were quite significant and the committee decided to continue with that on the schedule because of practice issues as well. ACIP has had no discussions in the past about removing something from the schedule, and if they do that, it was likely to raise other issues.

Dr. Stoecker called everyone's attention to the slide in his presentation that included one of the results from the MCV4 discussions, which was about $160,000 per QALY.

Dr. Decker (sanofi pasteur) pointed out that sometimes ACIP considers making an off-label recommendation that increases protection, and sometimes considers making an off-label recommendation that could possibly decrease protection. In either case, there is either a good likelihood that the companies will align the labels with the recommendation in a reasonable timeframe. However, there is very little hope of that every happening. He thought the committee needed to be sensitive to how those different situations play out, because they are very different. For example, ACIP recommended that the number of doses of rabies vaccine in the event of an acute exposure be decreased from 5 to 4. There is no chance whatsoever that the label will ever align with that recommendation because it is impossible to provide to the FDA the type of evidence necessary for a label change. Thus, it is a permanent situation now that when the manufacturer is contacted by those who cite the ACIP recommendation, as they are regularly, they tell them it is simply wrong and that 5 doses are required in the US. That is the label. That is the law. They are forbidden to say anything else. He believes that is what will occur if the number of doses of pneumococcal vaccine is reduced. A counter example is the situation as with meningococcal vaccine for which ACIP decided to recommend a booster at 5 years. In that case, it is assumed that protection will be increased. That case puts the manufacturer in a somewhat different stance, but more importantly, sanofi pasteur immediately began the studies necessary to include that in the label. It was clear how to do that. They filed it with the FDA, and the FDA has generally been very permissive about sanofi pasteur explaining that ACIP has a recommendation that has moved ahead of the label, but that sanofi pasteur is headed that way. Not only does sanofi pasteur answer all of the calls at 1-800-Vaccine for its products and a similar number for others' products, hundreds of people in doctors' offices every day are forbidden by law to from telling patients that ACIP's recommendation differs from the package insert. He emphasized that this must be kept in mind.

Dr. Pickering indicated that CDC also receives calls from physicians about off-label use of various vaccines. Either before or about the time the 2+1 schedule was being discussed, CDC developed a collaboration with investigators at Emory University School of Medicine and Dr. Sun specifically to initiate a project based on two hypotheses: 1) there are numerous discrepancies between FDA licensure requirements and ACIP recommendations for many vaccines in children and adults dating back to 2000 .; and 2) healthcare providers are aware of and concerned about discrepancies between ACIP recommendations and FDA licensure indications. These two hypotheses led to three specific aims of this study: 1) summarize the FDA licensure requirements and the ACIP recommendations for all vaccines licensed since the year 2000 for use in all ages in the civilian population in the US; 2) enumerate discrepancies between the vaccine products licensed by the FDA for use under the US FDA Biologic License Application (BLA) program and the ACIP recommendations for the same vaccines; and 3) assess the knowledge, attitudes, and practices of pediatricians, family physicians, and OB/GYN physicians regarding discrepancies in FDA licensing and ACIP recommendations and determine whether the FDA licensure or the ACIP recommendations are being followed. The preliminary review of these data indicates the following three categories: 1) agreement, 2) the ACIP recommendations extend beyond the licensure, and 3) ACIP recommendations do not meet the full licensure of the FDA. These preliminary findings are not surprising because FDA and ACIP

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follow different mandates with regard to vaccines. These data are being analyzed and will be presented in the near future.

Dr. Duchin requested further information about how/if it is illegal for vaccine manufacturers to provide ACIP guidance when it is in conflict with the FDA package label, and whether it was illegal for the FDA to provide ACIP guidance to the public. For example, if someone requested guidance from the FDA on how to use the rabies vaccine.

Dr. Schuchat replied that their marketers must follow the labels, but clinician organizations, ACIP, and others who educate providers and the public follow ACIP, AAP, ACOG, or other standards of care. The drug representatives are not allowed to market outside of what is on the label. The pneumococcal vaccine was initially licensed for invasive bacterial disease and otitis media, and did not receive an indication for pneumonia because the initial studies did not meet the FDA's requirements for demonstrating protection against pneumonia. Therefore, the company was not allowed to market the vaccine as effective against pneumonia. Whether the vaccine representatives are the primary source of health promotion and education for clinicians is unclear. The other bodies (ACIP, AAP, ACOG, et cetera) are considered standards of care for practices, and educate based on the annual schedule voted on.

Dr. Sun (FDA) clarified that the FDA does not regulate medical practice. It regulates products that it approves that have been demonstrated to be safe and effective. What a physician does as part of medical practice with FDA-licensed products is considered practice and FDA does not regulate that. However, a company cannot advertise or promote any use that is outside of what is included in the label. It would be untenable for patient safety. Some FDA labels include ACIP recommendations; however, there if there is a difference between the FDA label and an ACIP recommendation, FDA has to follow the label because that is based on the evidence FDA reviewed.

Dr. Decker (sanofi pasteur) added that one exception to a manufacturer's "gagging" on anything that is outside a label is that an individualized conversation between medical professionals, such as with Dr. Duchin and himself meeting in Dr. Duchin's office, is that he can talk about anything as long as he makes it clear what is off-label. However, nobody involved in sales has that flexibility.

In terms of the feedback requested by the working group, Dr. Temte summarized that there was a great deal of differences of opinion in the room, which he thought was very appropriate for this. They heard that there are reasons to seriously consider a reduction in doses in terms of some parental issues, potential cost issues, et cetera. There were also significant concerns in terms of immunization programs. The interruption of a successful program, especially as it concerns high risk individuals who could be seriously impacted by a change.

Dr. Baker pointed out that there are two recommended vaccines for pregnant women with no labels. Even though at the time the recommendations were made, there was no pathway in the FDA for licensure in pregnant women because they have been protected from vaccine and other medication trials. While she anticipated that this would change in the future, sometimes from a policy and disease burden point of view, recommendations must be made that do not match the label of an available vaccine. She did not think that ACIP should do this very often. There has been great harmonization between the recommending bodies, pediatricians, family practitioners, et cetera. Most of the time, everyone agrees. Pediatricians wait for the AAP recommendations, and family practitioners probably wait for the AAFP recommendations before they implement practice. With this partnership, policy should be in a situation favorable to implementation.

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Dr. Pickering acknowledged that differences raise important issues. When ACIP made recommendations for pregnant women for influenza and Tdap vaccine use, pharmaceutical representatives who were asked by physicians whether they could administer these vaccines to pregnant women, told the physicians they could not because these indications were not in the package inserts. That is a deterrent.

At this time, Dr. Temte called for public comment related to pneumococcal vaccine.

Public Comment

Joshua Raby
Meningitis Angels

My name is Joshua Raby This is my wife, Bianca Raby. We are with the Meningitis Angels. We have no conflict of interest. On October 24, 2010 I laid down with my son Zachary. He was approximately 2 years old, and a little shy. But, we laid down watching football. He laid down for a while and he woke up and started having a little fever. I gave him some Tylenol®, called the pediatrician who said, "Give him a little bit of Tylenol® and see how does." He perked up, and the next day I made an appointment. Our child went there and they diagnosed him with the flu. They said, "Give him some medication. Go home. If he's not better within the night, come back in the morning." The night progressed and he got worse, and worse, and worse. We took him back to the doctor. They immediately admitted him. They admitted him, gave him fluids, said he was dehydrated, and said he perked up within probably a couple of hours or so. They administered the fluids. By the time we got him back into the room and they started administering fluids, he was completely lethargic. He didn't move. We couldn't get him to react to a voice. We couldn't get him to do anything. The nurse started noticing rashes forming, little black blotches, forming on his legs. We got the doctor to take a look at it. Immediately they called in a flight team from Cooks Children's Hospital, which was approximately 3 hours away, and said, "We need to get this little boy there." So, they took off, and they would only let one parent ride, so I took off there. About 30 minutes down the road, my wife gave me a call and said, "You need to get back right now. I was just praying dear God, no." My wife has never held details from me. I went to the hospital room and as soon as I got there, my wife was in a separate room right beside of us, and I went in the room and my wife was just sobbing and the nurses were around her. By the time I got settled in, a nurse came in and said they had been performing chest compressions on my son for approximately 10 minutes, and they asked if I wanted them to stop. I remember saying, "Just a couple more minutes. Just a couple more minutes." And they tried. They tried their best and they couldn't get him to come back. We went in there to say goodbye to my son, and I'll never forget seeing him laying there. He was just totally black. Just absolutely lifeless. Looking back, we were in the transition of a move to Abilene, Texas and in that move, we were getting a new pediatrician for my son. As soon as we got down there, the doctor said that basically he was due for his final dose or his 4th dose of Prevnar®, and said he was also due for the flu shot and said they would push out and go ahead and do the flu shot at the next appointment, and in the following they would go ahead and finish with Prevnar®. But he didn't make it to that appointment. So, it is our opinion that the 4th dose is very important. My son would be right here with me, and I wouldn't be here talking to you guys about this. I just pray that no other family has to experience what we had to experience, and I know that it is a small number, I know, comparatively, but that small number could be your child. Your daughter, or your son, grandchild, nephew, niece. That is a situation that I do not pray on my worst enemy. There is nothing like the loss of a child. Thank you all.

Frankie Milley

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Founder / National Director
Meningitis Angels

Hi. I am Frankie Milley and the National Director of Meningitis Angels. What most people don't realize is that 35% to 40% of our Angel Network are pneumococcal families. I know you covered the 10% death rate, and I did see that you covered some of the disabilities. But I can tell you that yes, maybe 10% dies, but there are a lot of kids out there within our network, hundreds, that have serious after effects of pneumococcal meningitis. Serious. They're blind. They're deaf. They have forms of what is diagnosed as autism syndrome. They have seizure disorders so horrible that you can't even imagine. One of my moms told me that her greatest fear 8 years after pneumococcal is she will walk in the room and her baby will be dead. Her child will be dead. These families—some of these kids have up to 10, 15, 20 seizures a day. It's non-stop. These kids are 24-hour a day 7-day a week care. Now, I've testified once in 12 years of coming to ACIP meetings on pneumococcal, and you know why I haven't? Because you guys always did the right thing. I believe that you always do the right thing, and you try your best to do the right thing in all cases. But, we have a saying in Texas, "If it ain't broke, don't fix it." That's kind of how I feel about this. We have had wonderful success with pneumococcal vaccine just the way it is, so let's don't fix it. It ain't broke. But, if we delete that 4th dose, it might be broke. I want to be able to go back in the month ahead and assure my families that are dealing with children that live horrible lives with these kids that are seriously disabled from pneumococcal meningitis that you guys are going to do the right thing. One of the things Josh didn't say to you is that they're expecting another baby. They have a 2-year old who has had 4 doses of Prevnar®, so they feel safe, but they're expecting a baby in the spring and he is horrified that you guys may delete that 4th dose and he may have to go through this once again. So, again, I want to say to all of you, thank you so much for the work and the dedication that you guys do. I know you're going to do that right thing. I know that. As for meningococcal, we'll take that up another day.

Shannon Duffy Peterson, Parent
Parents of Kids with Infectious Diseases (PKIDs)

I am Shannon Duffy Peterson. I am here on behalf of PKIDs, but I am a parent. I'm going to read it because this is very difficult: Her children are worth every penny. A life-changing event, one involving her children, will make any parent regret what they could have or should have done. I have personal experience of this. I held my daughter, Abigail, in my arms while she died of one of the world's biggest vaccine-preventable killers of children—pneumococcal disease. Abigail was just shy of her 6th birthday. I am a parent of 4 children, a business owner, and through PKIDs, an advocate for immunization and keeping children healthy. My younger children are at home in Sleepy Eye, Minnesota and my oldest daughter, Abigail, is up in Heaven with her grandparents. In 2001, my 5-year old daughter became a statistic when she died of a vaccine-preventable disease. Abigail became infected with pneumococcal bacteria during the 2001 influenza vaccine shortage. She was not vaccinated for either disease. When our children were born, my husband, Dwain, and I were adamant about vaccinating our children. We wanted our children to be protected against everything, and we wanted healthy children. At that time, we had a pediatrician who did not push vaccination, and did not recommend the most recent vaccines available. Consequently, my children did not have their chicken pox, flu, or pneumococcal vaccinations.

February 18, 2001 came as a normal Sunday. We took the children to Sunday school, went to church together, played throughout the day, danced with them to music, and then relaxed with them before bedtime by playing a board game. Abigail said she suddenly wasn't feeling well and had a headache. We had her lie down and took her temperature, it was 101.5, and gave

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her some Motrin®. She started to vomit up the medicine. We thought she had the flu. We thought this was strange because she had had the same illness and a sinus infection two weeks earlier, but she was okay and we knew that there were many germs that kids were passing around. We became alarmed when a rash developed all over her body that we'd never seen before, but we suspected it to be a high fever rash. I called the emergency room and was told that there was a flu going around with high fever, vomiting, and diarrhea and to just treat the fever ultimately with Motrin® or Tylenol® and a tepid bath. Abigail was tired when we put her to bed, planning to check on her quite frequently, but hoping that she would sleep off the flu. Throughout the night, we kept changing her bedding and bathing her to break the fever even though she seemed pretty lethargic, and ended up sleeping with her to comfort her. We woke later to her crying "mommy" as she had fallen out of bed while attempting to make it to the bathroom. It was then while cleaning her up that my husband noticed the tremendous blotches on her skin and said, "This is not normal. We have to get her to the emergency room right away." We woke up our little boy, got them both in the truck, and drove as fast as we could 21 miles to Newell, Minnesota and called the hospital on the way to say we were coming and prayed for the best. I sat in the back with the children comforting Abigail, and when she said to me, "Mommy, I hurt so bad all over," I assured her it was from the sickness and held her in my arms the best that I could while we were all bucked up. Those were the last words I would ever hear from my beautiful little girl. She died in my arms while we were driving. When we arrived at the hospital, they called a "Code Blue" and attempted for one hour to revive her. Her heart never started and they were breathing for her. She was pronounced dead at 7:20 Monday, February 19th.

Our hearts broke that day as our son, Abigail's little brother, witnessed all of this, so we had to tell him that his playmate and his bedtime companion had died and there was nothing mommy, or daddy, or the doctors could do to save her. It doesn't end there, though. Two hours later, after we arrived home from saying goodbye to our first born, our son started to experience some of the same symptoms as his sister, and we rushed him to the clinic. They got us in immediately and started running tests. While we were waiting for results, Samuel, our son, started to vomit. I couldn't believe this was happening all over again. I was holding him on the floor in our doctor's office when our pediatrician came in with Abby's preliminary autopsy results stating that she had overwhelming sepsis caused by streptococcus pneumonia, congenital asplenia, and hemorrhagic adrenal glands. I thought I would lose both my children that day. While my daughter's death happened quite quickly and I wasn't able to save her by rushing her to the hospital, I was able to save my son by hospitalizing him directly after her death for two days as he was extremely sick. With hospitalization and medication, he recovered enough to be released from the hospital in time to attend his sister's funeral.

My world changed in those life-altering three days. I now understand the importance of vaccines and how children's lives depend on them. I'm asking all parents to make sure kids are kept healthy and vaccinate them. If we do this, we'll save lives. It's our responsibility as parents and medical professionals to protect our children and to protect all children. It's not okay in my opinion to reduce the number of pneumococcal conjugate doses children get based on cost, or even the fact that we have thankfully a full immunization schedule. We listened to our pediatrician. We didn't vaccinate, and we lost our Abigail and we almost lost our son, Samuel. I'm sure all of you follow the recommended vaccine schedule. If a primary dose of the pneumococcal vaccine is removed, it will save some dollars and be one less vaccination for our kids, but it will also mean more kids will die, more kids will be hospitalized, and more kids will be in pain. If you follow such a schedule and your child is hospitalized, or if you should lose your child to this cost-saving measure, well that would be unthinkable. It's not acceptable to risk your family, or mine, or anyone else's. Why would we ever choose to increase infection when we can decrease the number of cases through a simple vaccination? Thank you.

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Dr. Temte thanked the public commenters for sharing very, very difficult stories.

Herpes Zoster Vaccine

Introduction

Jeff Duchin, MD
Chair, Herpes Zoster Work Group

Dr. Duchin reviewed plans for the Herpes Zoster Working Group update on use of zoster vaccine in older adults. Currently, ACIP recommends the routine vaccination of all persons aged 60 years of age and older with 1 dose of herpes zoster vaccine (HZV). That recommendation was originally made in 2006. In 2011, the FDA approved HZV for 50 through 59 year olds. In June 2011, ACIP declined to recommend the vaccine for adults aged 50 through 59 years and reaffirmed the current recommendation. That was based on the shortfalls in the bulk product used to manufacture the vaccine, and limited data available on long-term protection of HZV. ACIP planned to continue to monitor supply issues and reconsider recommendations for adults aged 50 through 59 years when an adequate and stable supply of the vaccine was assured.

The terms of reference for the Herpes Zoster Vaccine Working Group are to review the supply and uptake of HZV, review new data on long-term protection, and consider revision of existing recommendations to include vaccination of 50 through 59 year olds. Regarding supply and uptake of HZV, beginning in 2007, Merck experienced production shortfalls of the bulk product used to manufacture varicella zoster virus (VZV)-based vaccines. There has been uninterrupted vaccine supply since January 2012, and the working group assumes that there will be a continued stable vaccine supply for the target population. Nevertheless, vaccine uptake is not optimal and the coverage rate for adults remains very unsatisfactory at this point [NIS, 2007; NHIS, 2008-2012].

The key issue regarding the recommended age of vaccination is the fact that the burden of herpes zoster disease increases with age. The primary consideration during the working group's deliberations was that the vaccine should provide protection during the period of highest incidence of herpes zoster and herpes zoster-related complications, which is standard practice for targeting populations for vaccination recommendations. Dr. Duchin indicated that Merck would present results during this session from its long-term persistence study (LTPS) on vaccine effectiveness 7 through 11 years after vaccination.

The Herpes Zoster Working Group does not propose changes to the existing recommendation for routine vaccination of persons 60 years of age and older. The rationale for this conclusion is that herpes zoster vaccine administration should be timed to achieve the greatest reduction in the burden of herpes zoster disease and its complications. There is insufficient evidence for long-term protection offered by the herpes zoster vaccine, and persons vaccinated under 60 years of age may not be protected.

Regarding next steps, the working group will continue to monitor data on duration of protection as it becomes available, evaluate the optimal age for vaccination, and evaluate the need for revaccination.

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Vaccine Supply

Eddy A. Bresnitz, MD, MSCE
Executive Director, Adult Vaccines
Global Vaccine Medical Affairs and Policy
Merck Vaccines

Dr. Bresnitz reported that while there had been supply constraints a few years ago, Merck has resumed routine supply of all varicella-based vaccines in the US, while expanding the global availability for VARIVAX® and ZOSTAVAX®. Merck returned ZOSTAVAX® to normal shipping in the US at the end of 2011 and has shipped more than 6 million doses since then. ProQuad® was re-introduced in the US in 2012, and an uninterrupted supply has been maintained of both ProQuad® and VARIVAX®. ZOSTAVAX® is now available in over a dozen countries, with 10+ more launches planned in 2014. Merck's commitment to expanding access and supply of ZOSTAVAX® remains strong.

Merck has invested over $1 billion in new manufacturing capabilities to increase capacity, improve reliability, and create redundancy to better ensure long-term supply. An important milestone was achieved when Merck received FDA approval of its Durham plant for varicella bulk production on September 4, 2013.

Regarding Dr. Duchin's observation about uptake not being optimal based on the NHIS data, the Healthy People 2020 target is 30%. In 2012, Merck implemented a very active promotional campaign for ZOSTAVAX®, and uptake is still only at 20%. It is not only the issue of supply, but it is also the issue of access and ability to cover the vaccine. The reimbursement process for vaccine is very complex in the US, particularly for ZOSTAVAX®. Having enough supply is not adequate to ensure that there is appropriate uptake of this very important vaccine.

Long-Term Persistence Study

Dr. Janie Parrino
Merck Vaccines

Dr. Parrino presented information regarding the LTPS. This study was conducted by the Department of Veterans Affairs' Cooperatives Study Program, with Dr. Michael Oxman serving as the study chair. Before discussing the LTPS study results, Dr. Parrino provided an overview of the two predecessor studies to the LTPS.

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The Shingles Prevention Study (SPS) was the pivotal efficacy study conducted in adults 60 years of age and over that enrolled over 38,000 individuals and assessed vaccine efficacy of three endpoints: incidence of herpes zoster, incidence of post-herpetic neuralgia (PHN), and the burden of illness. The median age at enrollment into the SPS was 69 years. Median follow-up time was approximately 3.1 years. The vaccine efficacy on the incidence of herpes zoster was 51%, on PHN 67%, and burden of illness 61%. The study demonstrated that the benefit of vaccination persisted through the four years of follow-up. There was a pre-specified lower bound success criterion of 25%, which was exceeded by each of the three study endpoints.

The Short-Term Persistence Study (STPS) extended the follow-up from the SPS to approximately 8 years after vaccination. This study enrolled about 14,000 individuals. There was no hypothesis testing in the STPS. There was a break in surveillance of herpes zoster cases from the completion of the SPS and the start of the STPS. In addition, there was more follow-up time in the vaccine group than in the placebo group, because placebo recipients were offered vaccine under another amendment of the SPS study while the STPS was ongoing. The median age at enrollment into the STPS was 73 years, with a median follow-up time of approximately 1.2 years. Data contributed to analyses were collected primarily from Year 4 to Year 7 post-vaccination. For the STPS time period, vaccine efficacy on the incidence of herpes zoster was 40%, PHN was 60%, and burden of illness was 50%. In addition, pooled analyses with the SPS were also performed. The data analyses for vaccine efficacy for each year, Year 1 to Year 7 post-vaccination, for the combined SPS and STPS studies demonstrated that the efficacy for zoster vaccine, for herpes zoster burden of illness, and incidence of herpes zoster was statistically significant for each year through the end of Year 5. Point estimates for Year 6 and Year 7 suggested continued efficacy for herpes zoster burden of illness and the incidence of herpes zoster, but the results were not statistically significant, except for burden of illness in Year 7. There are small numbers of cases in later years that reduce the power to detect true differences. With regard to PHN, the efficacy of zoster vaccine for incidence of PHN appeared to persist. However, because of the small number of cases of PHN, there is not a statistically significant difference beyond two years post-vaccination.

The LTPS extended the follow-up time from the SPS to approximately 12 years after vaccination. The objectives of the LTPS study were to estimate the duration of vaccine efficacy on the incidence of herpes zoster, the incidence of PHN, and the herpes zoster burden of illness. The primary safety parameter was the incidence of vaccine-related SAEs. This study enrolled 6867 subjects. It was descriptive in nature, with no hypothesis testing. There is not an unvaccinated concurrent control group for calculation of vaccine efficacy during LTPS, because the placebo recipients in the SPS were offered vaccination, which most accepted. By the time the LTPS started, there were no longer any placebo recipients to serve as controls. Instead, historic control rates were estimated using three different methods. The primary analyses are based on the whole time interval after enrollment into LTPS, and that data contributing to the analyses were collected primarily from Year 7 to Year 10 post-vaccination. The information for each year time period is limited, but annual vaccine efficacy estimates are provided as supplementary information.

The LTPS was originally designed to use herpes zoster and PHN incidence rates and burden of illness scores observed in the placebo group of the SPS, adjusted for subject age, as historical control rates for calculating vaccine efficacy. However, within the placebo group of the SPS and STPS, a significant increase in the risk of herpes zoster over increasing follow-up or calendar time was observed even after adjusting for the increasing age of the subjects. The control rate used to calculate vaccine efficacy could be underestimated if it was adjusted only for age. Therefore, calculations for expected herpes zoster incidence rate for the historical placebo reference subjects were adjusted accordingly. The primary method of analysis, also known as

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Method 1, adjusted the SPS data for both age and calendar effects, based upon this finding. Method 2, which is the most conservative of the three methods, adjusted the SPS data only for the age effect. Method 3 adjusted SPS and STPS for age and calendar effects. Of note, this increasing risk over increasing follow-up or calendar time, after adjusting for increasing age, was not noted when analyses were done for PHN. Therefore, the estimates of incidence of PHN for the historical control were only adjusted for age and there is no Method 3 analysis for PHN.

Regarding the results for the entire LTPS time period, the median age at enrollment into the LTPS was 74 years. Median follow-up time was approximately 3.9 years. There were 263 cases of herpes zoster during this time period. For herpes zoster, the observed incidence rate was 10.3 per 1000 person-years. For the primary method, vaccine efficacy was 21.1%. As expected, Method 2, which was the conservative estimate, gave the lowest rate for vaccine efficacy and Method 3 gave the highest rate for vaccine efficacy. As mentioned earlier, there were only two methods of analyses for PHN. For the primary method, vaccine efficacy was 35.4%. By Method 2, it was 33%. The incidence rate of PHN was 1.3 per 1000 person-years for that follow-up time. The incidence rate for herpes zoster burden of illness was 1.7 per 1000 person years. Vaccine efficacy based upon the primary method was 37.3%, with a range of 29.5% to 40.5% based upon the sensitivity analyses.

Regarding the results of the annual incidence of herpes zoster, a limited amount of data were available for each year. This becomes particularly evident in Years 11 and 12. In addition, the estimated incidence rate of herpes zoster for the LTPS time period was lower than the observed rate from the STPS. The point estimates have some variability from year to year, but beginning at Year 9 a lower numeric value is seen compared to the other years. In terms of the results of the annual incidence of PHN, the first thing to note is the small number of cases contributing to the analyses, so it is very important to interpret these data with caution. Regarding the vaccine efficacy for the incidence of PHN, there are very wide confidence intervals associated with the point estimates, which again is a reflection of the limited amount of data. The point estimates on vaccine efficacy for PHN are lower in Years 7 and 8 compared to some of the years, and then increase again in Years 9 and 10. Turning to the herpes zoster burden of illness data, at Year 6 vaccine efficacy is lower than in prior years and the 95% confidence interval includes zero. The point estimates then increased for the subsequent years and the 95% confidence intervals remain above zero through year 10 post-vaccination. Again, these data for the annual estimates are provided as supplementary analyses and information.

With regard to safety, no vaccine-related SAEs were reported. A total of 399 deaths were reported, none of which were determined by the study investigators to be related to the study vaccine. Of the subjects, 5.8% discontinued the study due to death, which is not unexpected due to the age of the cohort. Available results suggest that zoster vaccine is generally well-tolerated.

Concerning the limitations of the LTPS, the SPS was conducted at 22 sites, the STPS was conducted at 12 sites, and the LTPS was conducted at these same 12 sites. Thus, the LTPS was conducted at only 12 of the 22 original sites. It was a descriptive study with no hypothesis testing. There was a lack of a placebo control group, requiring estimation of historical control rates based on data from prior placebo recipients in SPS and STPS. The age and calendar time effects and incidence rates were assumed from the SPS and STPS study data. As noted earlier, the estimated control rates for Years 7 through 12 were lower than the observed rates in the placebo group for Years 4, 5, and 6, which could result in an underestimate of vaccine efficacy. In addition, there were small numbers of cases in the data for the annual estimate analyses.

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In summary, over the LTPS follow-up period, ZOSTAVAX® did continue to reduce incidence and severity of herpes zoster, although the vaccine efficacy estimates were lower than what was seen in the overall SPS and STPS study populations. The supplementary analyses on annual vaccine efficacy have limited information for each year time period of the LTPS, resulting in high year to year variability and generally broad confidence intervals. However, the vaccine efficacy on herpes zoster estimates were generally consistent with the prior years through Year 8. There was some variability in those point estimates and were numerically lower starting at Years 9 and 10. For PHN, there were small numbers of cases in each year. However, the estimates were numerically lower in Years 7 and 8 than those observed in the SPS and STPS. For Years 9 and 10, the estimated efficacy was more consistent with what occurred in prior years. For the herpes zoster burden of illness, the estimates were generally consistent with prior years through Year 10, although point estimates were higher for some years than for other years with the exception of Year 6, which was numerically lower than what was observed in the SPS and the prior years in the STPS.

Discussion Points

Dr. Stanley Plotkin (Vaccine Consultant) pointed out that if they were talking about any other vaccine, they would be looking at immunologic data. The correlate of protection for zoster is a cellular response as measured by enzyme-linked immunosorbent spot (ELISpot), but at least one could look at the glycoprotein-based enzyme-linked immunosorbent assay (gpELISA), which had a statistical correlation with efficacy. Although there is not a placebo population, the results could be compared with the results before vaccination. He would like to know what the immunologic data are for this vaccine, with specimens taken long after immunization. With respect to discussion of the pneumococcal vaccine, no data were shown on opsonophagocytic responses, a functional response, which might influence the committee's judgment regarding which schedule to use.

Dr. Parrino responded that immunogenicity data were not collected as part of the Long-Term Persistence Study (LTPS). The data from the Shingles Prevention Study (SPS) went out through month 36 post-vaccination, and was already starting show a decline as measured by both gpELISA and ELISpot . Merck conducted a booster study with two collaborators who had participated in the LTPS in which the geometric mean titers (GMTs) were assessed for individuals who were vaccinated approximately 10 years earlier in the SPS, compared to individuals who were age-matched (e.g., 70 years of age and above). Their baseline GMTs were very similar.

Dr. Temte reported that on Saturday, October 26, 2013, Dr. Plotkin would be receiving the Caspar Wistar Metal of Achievement for an individual who has had significant impact on global health.

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Burden of Disease and Effectiveness of HZV in Older Adults

Craig Hales, MD, MPH
CDC Lead, Herpes Zoster Work Group
Advisory Committee on Immunization Practices

Dr. Hales presented information on the burden of herpes zoster disease in adults, short-term vaccine efficacy and effectiveness, and long-term vaccine effectiveness. The characteristics of the burden of herpes zoster and its complications, along with the results from several studies on the short- and long-term vaccine efficacy and effectiveness were key considerations in the working group's deliberations on the use of zoster vaccine in older adults.

Acute zoster is characterized by a localized and painful rash. Zoster is usually self-limited, but pain associated with acute disease can be disabling. PHN manifests as mild to excruciating pain that persists months to years after resolution of the rash, and is the most common complication of zoster. Chronic pain associated with PHN can disrupt sleep, mood, work, and activities of daily living, adversely impacting quality of life and leading to social withdrawal and depression. Secondary bacterial infections of the skin may occur, and ophthalmic involvement can lead to ocular complications, including permanent visual impairment. Serious neurologic complications include palsies, meningitis, and stroke syndromes.

Several studies, such as a population-based study on zoster incidence in Olmsted County, Minnesota, show a rapid increase in zoster incidence beginning in the fifth decade of life and continuing beyond age 80 [Yawn 2007]. In this study, zoster incidence was 6 per 1000 person years in 60 through 69 years, almost doubling to 11 per 1000 person years in adults 80 years of age and older. Not only does the incidence of zoster increase with age, but also the risk for developing zoster-related complications increases with age. In terms of the proportion of people in the Olmsted County study with zoster who developed PHN, defined as pain continuing at least 90 days after rash onset, those 60 through 69 years of age had double the risk of developing PHN than those younger than 60. The risk of PHN doubles again in persons 80 years of age and older compared to 60 through 69 year olds. In persons 80 years of age and older, 20% of zoster cases progress to PHN. Other studies have shown similar results. The same study also showed that non-pain complications (e.g., ocular and neurologic complications, secondary skin infections, and disseminated zoster) were more common in older age groups. The SPS measured interference of activities of daily living (ADLs) caused by zoster. The study measured the mean severity of interference with the following seven ADLs over 6 months following onset of zoster: general activity, mood, walking ability, work, relations with others, sleep, enjoyment of life. The burden of interference of ADLs increased with age, with adults 80 years of age or older having over twice the burden of interference with ADLs compared to adults 60 through 69 years of age [Schmader 2010]. A study from Connecticut showed that population-based rates of hospitalization increased several fold from age 60 through age 85 and older. The study found that three-quarters of all zoster-related hospitalizations occurred in persons 60 years of age and older [Lin 2000]. Other studies of zoster-related hospitalizations show similar results.

Vaccine efficacy is defined as "the reduction of disease in vaccinated persons relative to unvaccinated persons under optimum conditions" as measured in a double-blinded, randomized, placebo-controlled clinical trial. Vaccine effectiveness is defined as "reduction in disease in vaccinated persons relative to unvaccinated persons under 'real world' conditions" typically measured in observational studies. Two studies have evaluated the short-term efficacy of the zoster vaccine in adults 60 years of age and older. The SPS was an RCT with over 38,000 subjects spanning 1 to 4 years after vaccination. The short-term persistence substudy

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(STPS) was a continuation of SPS in a subset of approximately 14,000 subjects who were followed 4 to 7 years after vaccination. For prevention of zoster, the SPS found a vaccine efficacy of 51% 1 to 4 years after vaccination. The STPS found an efficacy of 40% during years 4 to 7 after vaccination. For prevention of PHN, The SPS showed 67% efficacy 1 to 4 years after vaccination, and the STPS showed 60% efficacy during years 4 to 7 after vaccination, but was not statistically significant. The SPS showed that short-term vaccine efficacy for preventing zoster in persons 60 years of age and older declines the older the person is at the time of vaccination.

The SPS evaluated vaccine efficacy against PHN in subjects who developed zoster post-vaccination. Vaccinated subjects who developed zoster were less likely to progress to PHN compared to placebo subjects; however, this effect was seen only in subjects 70 years of age or older. Vaccine efficacy for the prevention of PHN in subjects with zoster was 55% in 70 through 79 years old, and 26% in those 80 years of age and older. Data on duration of protection against zoster from the combined SPS and STPS studies show a decrease in vaccine efficacy in the first year after vaccination, with relatively stable point estimates through Year 7. However, total person years of follow-up time decrease over the combined study period. By Year 6, the lower 95% confidence interval for vaccine efficacy crosses zero. Therefore, vaccine efficacy beyond Year 5 is uncertain. Data from the same studies assessed the efficacy for prevention of PHN, defined as zoster-related pain lasting at least 90 days. Because of the small number of PHN cases, estimates for vaccine efficacy are very unstable and not significant beyond Year 2 after vaccination. Therefore, it is difficult to conclude how long the vaccine protects against PHN, although point estimates for vaccine efficacy throughout the period suggest continued protection.

Two observational studies evaluated vaccine effectiveness in adults 60 years of age and older. The first was a study in a health maintenance organization (HMO) in over 300,000 individuals, with a mean follow-up time of approximately 1.5 years.[1] Vaccine effectiveness was also evaluated in a study of 766,000 Medicare beneficiaries with a mean follow-up time of approximately 2 years.[2] The two studies found vaccine effectiveness of 55% and 48% for the prevention of zoster. The Medicare study showed 59% effectiveness for preventing PHN. The HMO study showed that the vaccine was 65% effective for the prevention of zoster-related hospitalizations. In contrast to the SPS, which showed decreasing vaccine efficacy with age at the time of vaccination, the HMO study showed similar effectiveness regardless of age. The most likely explanation for the differences between these two studies is the way cases were ascertained. Active case finding in the SPS allowed ascertainment of all cases of zoster, even mild cases when the individual might not have otherwise sought healthcare. The observational study, however, found zoster cases only when an individual sought care for zoster. Therefore, the results from the HMO study show stable vaccine effectiveness for persons 60 years of age or older for preventing clinically significant zoster [[1]Tseng 2011, [2]Langan 2013].

There has been one study of vaccine efficacy in adults 50 through 59 years of age. This RCT, called the Zoster Efficacy and Safety Trial (ZEST), followed over 22,000 subjects for a mean of 1.3 years. This study showed a vaccine efficacy of 70% for the prevention of zoster. Efficacy for prevention of PHN was not studied because subjects who developed zoster were followed for only 21 days after rash onset [Schmader, 2012]. Comparing short-term vaccine efficacy for prevention of zoster in clinical trials in the ZEST study in 50 through 59 year olds to the SPS in adults 60 years of age and older, vaccine efficacy for preventing zoster was higher in 50 through 59 years compared to 60 through 69 years old. However, results from the two studies are not directly comparable because mean follow-up time from the ZEST study in 50 through 59 year olds was less than half that of the SPS study subjects vaccinated at 60 years of age and older.

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There has been one study of long term vaccine effectiveness in adults vaccinated at 60 years of age and older. The LTPS was an observational study that continued to follow a subset of almost 7000 vaccinated subjects from the SPS and STPS for 7 to 12 years after vaccination. At the completion of STPS the placebo group was offered the vaccine; therefore the LTPS had no concurrent control group, a major limitation of this study. It is also worth noting that the vaccination subjects were unblinded to their vaccination status. Vaccine effectiveness was calculated from a statistical model using zoster and PHN incidence from historical controls [Parrino, unpublished]. Zoster incidence in vaccine and placebo groups in the SPS and the STPS was compared to the vaccine group in the LTPS from 1 to 11 years after vaccination. The placebo group was offered vaccination at the completion of STPS in order to predict the zoster incidence for an unvaccinated cohort during Years 7 to 11. The investigators used a statistical model based on the original placebo group of the SPS, accounting for increasing age and the effect of calendar time. Vaccine effectiveness was calculated using these estimates. The model predicts that zoster incidence would be the same in the vaccinated and unvaccinated group by Year 11, indicating that no protection from the vaccine would remain. However, it is impossible to know whether this model accurately predicts what zoster incidence would be if the investigators continued to follow the placebo group over the entire study period. Therefore, calculation of vaccine effectiveness using this projection is suspect.

Decision and Cost-Effectiveness of HZV in Adults ≥50 Years of Age

Ismael Ortega-Sanchez, PhD
Senior Health Economist
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ortega-Sanchez discussed the policy question, decision and cost-effectiveness model, selected parameters and assumptions, base case results, and sensitivity and scenario analyses pertaining to the cost-effectiveness study of HZV in adults 50 years of age and older. He noted that this analysis went through a blind peer-review process by CDC economists, and some of their comments were incorporated in this presentation.

This analysis was conducted in order to answer the policy question, “What is the optimal age to recommend a single dose of zoster vaccine in adults 50 or older?” There are at least two ways to look at this. The first is from a public health perspective, “If the objective was to minimize the burden of zoster disease, at what age would vaccination have the greatest population impact?” The second is from an economic perspective, “At what age would vaccination produce the greatest value?” For both approaches, the objective was to evaluate the cost-effectiveness of one dose of zoster vaccine administered at age 50, 60, or 70 versus no vaccination. The approach was a cohort-based decision analysis model, the population was immunocompetent persons 50 years of age and older, the analytic horizon was to follow subjects from 50 years of age using a mean life expectancy, and a societal perspective was used.

For this analysis, the investigators resorted to a previously constructed decision tree model to compare the four strategies. A fraction of the decision tree model is depicted in the following illustration:

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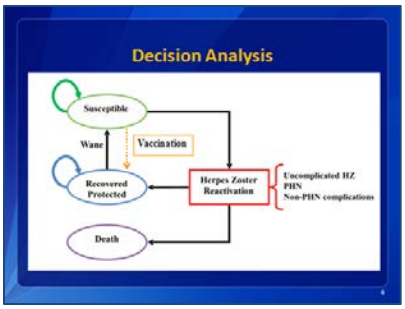
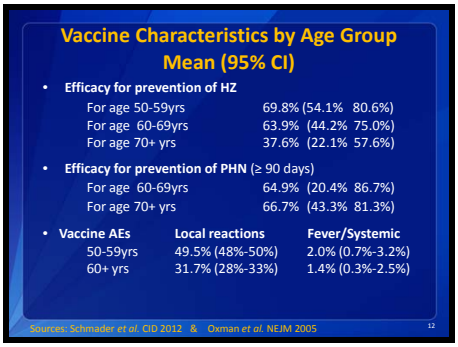


The model describes herpes zoster disease reactivation and specific outcomes (e.g., uncomplicated zoster, PHN, and non-PHN complications). To deal with uncertainties, the model is also designed with a Monte Carlo simulation. The simulation allowed the investigators to calculate not only the most likely or base case estimates for health benefits and costs, but also the ranges around these estimates.

Because of the nature of herpes zoster disease, the primary outcomes were QALYs gained and cost per QALY saved. The secondary outcomes were cost per outcome averted in terms of the cost per case of zoster and the cost per case of PHN; and the number needed to vaccinate in order to avert one case of herpes zoster and one case of PHN.

Regarding selected parameters and assumptions, the best available data were included. The data were updated on the epidemiology of the disease, age-specific when available; healthcare utilization costs; vaccine characteristics; and the quality of life during herpes zoster disease and complications. Herpes zoster incidence rates by age groups were included as reported in publication during the last 30 years (1982-2011). Likewise, the proportion of herpes zoster disease with PHN and non-pain complications were incorporated in the model. The following table shows the vaccine characteristics used in the model:



Based on data from the studies presented earlier (SPS, STPS, LTPS) for vaccine efficacy, the waning of vaccine efficacy was modeled. This waning was normalized as residual vaccine efficacy, so it begins with 100 and drops down to zero. This was used for all of the age groups.

A number of other key assumptions were used in this analysis. QALY loss was calculated from duration of pain, pain intensity, and health utility from various health states. All of this was weighted by people who suffered these specific scenarios. Another base case assumption was no recurrent herpes zoster. The age-specific health-related quality of life correction was used (HUI-III). The direct and indirect costs of herpes zoster and PHN for the acute phase of zoster, non-pain complications, long-term costs for PHN, and work loss to pain and productivity loss to death. The discount rate for all costs and health outcomes in ratios was 3%. Vaccination coverage was assumed to be 100%, and vaccine cost was based on 2013 private sector prices

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of $165/dose + the cost of AEs, which is age specific + $20 administration fees for an approximate total of $190 per vaccine.

Turning to the preliminary base case results, Analytic Approach 1 assessed the question regarding the age at which vaccination would have the greatest population impact. Four cohorts of 1 million people were followed from 50 years of age and were comprised of those not vaccinated at all, those vaccinated at age 50, those vaccinated at age 60, and those vaccinated at age 70. Dr. Ortega-Sanchez emphasized the difference in terms of prevention of zoster cases comparing no vaccination to vaccination at age 50, 60, or 70, all of which seem to be in the same range. However, vaccination at age 60 seems to prevent more zoster cases when looking at the cumulative number of cases of zoster. Of course, due to mortality rates in the population, the size of the cohort will be reduced as some will die before reaching the age at which they would have been vaccinated. In fact, 1 million people will be less than 50% when they reach age 70. The cumulative number of PHN cases in a cohort of persons 50 years of age who complete their lives unvaccinated were compared to persons who completed their vaccinations at age 50, 60, and 70. Unlike zoster, there is a much greater impact when people are vaccinated at age 70.

The results for each one of the strategies in Analytic Approach 1 are shown in the following table:

Outcomes *Prevented* Compared to No Vaccination Program

	Vaccinate at 50	Vaccinate at 60	Vaccinate at 70
# HZ cases	19,765 (9.9%)	26,147 (15.0%)	21,269 (15.2%)
# PHN cases	1,012 (3.7%)	4,045 (15.0%)	8,055 (31.4%)
# Deaths	0.2 (0.3%)	0.7 (1.0%)	2 (2.2%)
Ambulatory Visits	37,839	89,169	133,128
ED Visits	8,940	8,193	12,317
Hospitalizations	435	1,492	2,535
# Days in hospital	678	6,693	10,666
# Prescriptions	46,516	90,964	126,357
Lost work (hours)	625,817	506,110	413,058

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Except for lost work hours, outcomes prevented are higher when waiting to 70 to vaccinate followed by waiting to 60 to vaccinate. From the prevention point of view, vaccinating at 50 produces smaller numbers than the other scenarios. In general, the prevention shown in proportions above are very low.

Analytic Approach 2 addressed the question regarding the age at which vaccination would produce the greatest value, if a million doses of vaccine were available, by assessing the cost-effectiveness of vaccinating a cohort of adults 50 years old versus a cohort of adults 60 years old versus a cohort of adults 70 years old compared to no vaccination in these cohorts. This analysis was somewhat different. This analysis includes three cohorts starting at the same time: 1 cohort of a million people 50 years of age, 1 cohort of a million people 60 years of age, and 1 cohort of a million people 70 years of age. Each cohort could be vaccinated or not.

The savings in costs and QALYs from vaccination compared to no vaccination, with all costs in thousands and discounted at 3%, are shown in the following table. Again, savings are much greater when the cohort of 1 million adults at 70 years of age are vaccinated versus vaccinating a cohort of 1 million adults at 60 years of age, followed by vaccinating a cohort of 1 million adults at 50 years of age. That is the same pattern observed when analyzing the number QALYs saved:

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Savings in Costs and QALYs from Vaccination Compared to No Vaccination Program
(All costs in *thousands and discounted at 3%*)

	Vaccinate at 50	Vaccinate at 60	Vaccinate at 70
Direct medical costs	$7,307	$15,858	$23,726
Direct non-medical costs	$319	$1,188	$1,909
Indirect costs	$9,241	$7,274	$6,329
Total costs	**$16,867**	**$24,319**	**$31,964**
QALYs saved*	948	2,609	4,780

* Discounted at 3%

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Considering the costs of the vaccine dose plus administration, local reaction, and fever/systemic reactions, vaccinating at age 50 would cost approximately $3 million more than vaccinating at age 60 or 70. That is primarily because of the local and systemic reactions, mostly due to the age-specific rates of adverse events included in the model. Once vaccination costs were considered, following the US Panel on Cost-Effectiveness for Health and Medicine Recommendations, the net costs and the cost-effectiveness ratios were calculated. The following table summarizes the cost-effectiveness by strategy from the societal perspective. Based on this summary, vaccinating at age 70 results in approximately $38,000 per QALY saved; whereas, vaccinating at age 50 is approximately 7 times higher at $271,713 per QALY saved:

Cost-Effectiveness Summary by Strategy (Societal Perspective)

	Vaccinate at 50	Vaccinate at 60	Vaccinate at 70
Net cost*	**$178.5 Million**	**$169.0 Million**	**$162.9 Million**
Cost per HZ prevented	$11,255	$8,455	$9,989
Cost per PHN prevented	$61,084	$19,761	$9,607
Cost per QALY saved **	**$271,713**	**$79,967**	**$38,191**

* *NC = Cost of Vaccination Program - Savings in Cost-of-Illness from Vaccination*

** Does not including indirect cost savings

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Basically the same pattern is observed when estimating the average number needed to vaccinate (NNV) by strategy for one herpes zoster case, one non-PHN complication, one PHN case, and one QALY saved.

A number of sensitivity and scenario analyses were conducted to try to deal with the uncertainties in the parameters used and the data that were incorporated into the model. The selected parameters for the scenario analyses on which Dr. Ortega-Sanchez focused for this presentation included the following:

- Duration of vaccine efficacy
  - Upper and lower 95% CI from SPS, STPS, and LTPS data
- Vaccine efficacy for PHN in 50 through 59 year olds
  - Assuming same efficacy reported for PHN in 60 through 69 year olds
- Patient perspective for QALYs
  - Patient responses on health state evaluations from Zoster Utility Evaluation project
- Vaccine effectiveness for prevention of herpes zoster
  - Observational study in a HMO (Tseng et al. JAMA 2011)

The duration of vaccine efficacy was modeled for the upper and lower 95% confidence intervals from the SPS, STPS, and LTPS and assumed same efficacy for all age groups. Although there

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was no resource for vaccine efficacy for PHN for persons 50 through 59 years old, the same vaccine efficacy reported for PHN in those 60 through 69 years old was used for the 50 through 59 age group. The following table reflects cost-effectiveness for selected scenario analyses:

Cost-Effectiveness
Selected Scenario Analyses

	Vaccinate at 50	Vaccinate at 60	Vaccinate at 70
Base-case	**$271,713**	**$79,967**	**$38,191**
Duration of Vaccine Efficacy – *Lower 95%CI*	$802,356	$215,034	$103,886
Duration of Vaccine Efficacy – *Upper 95%CI*	$227,168	$69,113	$32,864
Vaccine Efficacy for PHN in 50-59 year olds	$226,186	$80,005	$38,210
Patient perspective for QALYs	$222,380	$66,906	$31,991
Vaccine *Effectiveness* for HZ	$336,073	$95,349	$34,739

When using the lower bound, the duration of vaccine efficacy significantly increases the cost per QALY across all age groups compared to the base case, but the increase is the greatest (i.e., less cost effective) in those vaccinated at age 50. The duration of vaccine efficacy decreases the cost per QALY across all of the strategies compared to the base case across all age groups when using the upper bound. Vaccine efficacy for PHN in those 50 through 59 years old decreases the cost per QALY for those vaccinated at 50 years of age, but increases the cost per QALY in those vaccinated in 60 and 70 years of age. The patient perspective for QALYs, which is more sensitive to the specific pain and suffering, decreases the cost per QALY across all age groups somewhat. In terms of vaccine effectiveness for herpes zoster, which was from the post-implementation study, the cost per QALY increased because they presented lower vaccine effectiveness than that reported in the clinical trials.

There are several study limitations in the model. Among the most important ones is the uncertainty in the duration of vaccine protection against HZ and PHN. There are limitations in the LTPS results due to lack of concurrent control group. Longer protection against PHN could increase the attractiveness of earlier vaccination. QALY-loss due to mild, moderate, and severe adverse events among vaccine recipients were not included, although some of the medical costs to treat these adverse events are part of the vaccination costs. Including these QALYs could increase the attractiveness of vaccination at a later age. Herpes zoster incidence rates may be increasing over time. This may increase the attractiveness of later vaccination. There is uncertainty in the specific QALY loss due to herpes zoster and its complications, which could affect the results for the policy question in any direction. The results of the scenario analysis increase confidence somewhat. The strengths are that the study includes data on duration of protection through 11 years after vaccination, and the assumption of key parameters was updated based on recent studies relating to zoster and zoster vaccine.

In conclusion, substantially greater reduction of disease burden, healthcare utilization, and costs are achieved with vaccination at age 70 or 60 compared to vaccination at age 50. Results were robust, based on the magnitude of the differences among vaccination strategies, the consistency of the public health and economic perspectives, and the consistency of the results from the scenario analyses. These conclusions are consistent with those found in other published analyses.

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Discussion Points

Dr. Jenkins inquired as to whether there were differences by gender in terms of health utilization and mortality rate differential.

Dr. Ortega-Sanchez replied that gender would create some differences, but that was not the question that was analyzed in this analysis. The problem could certainly be approached using differential models based on gender. It is known that the incidence for women is much higher than for men; however, those results were not available at this point.

Dr. Kempe said she thought that Dr. Ortega-Sanchez was making assumptions that the efficacy was the same between 50 through 59 and 60 through 69, but clearly a lot of the data suggested that efficacy was not the same at 70. She inquired as to whether different efficacy was used in the model for the 70 plus age group. She noted that one of the other speakers made the point that the health maintenance organization (HMO) study was perhaps not as accurate, but that Dr. Ortega-Sanchez used the HMO study rather than the other one that showed more dramatic changes with age.

Dr. Ortega-Sanchez indicated that for the base-case scenario, vaccine efficacy was based on published reports from RCTs, and he agreed that the HMO study was observational. However, for the base case analysis, data from the RCTs were used, while the observational study published by the HMO was used only for the sensitivity analysis.

Working Group Considerations for Use of HZV in Adults 50 Through 59 Years of Age

Craig Hales, MD, MPH
CDC Lead, Herpes Zoster Work Group
Advisory Committee on Immunization Practices

Dr. Hales indicated that the Herpes Zoster Working Group considered the epidemiology of zoster, short-term and long-term vaccine efficacy and effectiveness, and results from the decision and cost-effectiveness analysis in its deliberations on use of the vaccine in 50 through 59 years olds. The results from several studies show that the burden of zoster increases rapidly after age 50. Not only does the incidence of zoster itself increase with age, but of those who develop zoster, the proportion of zoster progressing to PHN, the proportion of zoster with non-pain complications, interference with ADLs, and the proportion of zoster hospitalizations also increase with age. The working group concluded that vaccination should continue to protect older adults during periods of high risk for zoster and its complications. A woman who is vaccinated at age 50 can expect to live another 33 years on average. A 60 year old woman can expect to live another 24 years, and a 70 year old woman another 16 years. The younger a person is at the time of vaccination, the longer a period of time the vaccine needs to provide protection against zoster and its sequelae.

Regarding the working group's conclusions on short-term vaccine protection, zoster vaccine provides protection against zoster and zoster-related complications in adults 60 years of age and older. Vaccine effectiveness from large observational studies is consistent with vaccine efficacy from RCTs. Evidence from RCTs shows that efficacy against zoster lasts at least 5 years. . Efficacy for preventing zoster in adults 50 through 59 years of age was demonstrated in one RCT, with mean follow up time of 1.3 years; however, is no available evidence on efficacy for preventing PHN or other complications in 50 through 59 year olds. There is also no

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available evidence on duration of protection against zoster or PHN for persons vaccinated at 50 through 59 years of age.

With respect to the working group's conclusions on long-term protection in persons 60 years of age and older, the LTPS results show waning protection over 11 years. However, the working group concluded that due to lack of concurrent control group, data from the LTPS are insufficient to determine duration of protection. Effectiveness of zoster vaccine administered to persons 60 years of age and older for preventing zoster beyond 5 years remains uncertain.

The results of the decision and cost-effectiveness of zoster vaccine showed that a substantially greater reduction of zoster burden, healthcare utilization, and costs can be achieved through vaccination of older adults who have higher incidence of zoster and zoster-related complications. The analysis shows that the cost per QALY saved is high with vaccination at age 50 because of limited impact on prevention of severe disease.

Working group members were in agreement not to propose changes to the existing recommendation for routine vaccination of persons 60 years of age and older. The rationale for this decision was that zoster vaccine administration should be timed to achieve the greatest reduction in burden of zoster and its complications. There is insufficient evidence for long-term protection offered by the zoster vaccine. Persons vaccinated under 60 years of age may not be protected when the incidence of zoster and its complications are highest. The working group also recognized that some 50 through 59 year olds may wish to be vaccinated. HZV is approved for use in 50 through 59 year olds; therefore, providers can still offer vaccine to adults in this age group. However, providers should counsel persons who are vaccinated under 60 years of age that the duration of protection offered by the vaccine is uncertain, and that they may not be protected when the incidence of zoster and its complications are highest. The working group also discussed the potential role of revaccination, and reviewed partial results on safety and immunogenicity of a second dose of the vaccine, but no data on efficacy are available. Because duration of protection offered by the vaccine is uncertain, the need for revaccination is not clear. The working group also noted that a second dose of vaccine is not licensed. The working group will continue to monitor data on duration of protection as it becomes available, evaluate the optimal age for vaccination, and evaluate the need for revaccination.

Discussion Points

Dr. Temte inquired as to whether any trials were being conducted for revaccination, and what interval was being considered.

Dr. Parrino responded that a booster dose study is currently ongoing that is being conducted with two of the investigators from the SPS from the LTPS, which is assessing safety and immunogenicity data and the results for the 6-week time period for the gpELISA, which was the primary objective of the study. These results are available at clinicaltrials.gov and show non-inferiority in terms of an immune response for the booster dose recipients, compared to first-time vaccinees who are the same age. Regarding additional studies to evaluate the duration of vaccine protection, a database study is being conducted by Merck's epidemiology group in conjunction with Kaiser Permanente that is following individuals 50 years of age older for 10 years or so following vaccination to assess duration of protection. In terms of revaccination interval, the booster dose study was conducted at 10 years after a first vaccination in the SPS. Preliminary results are also available for interferon gamma (IFNγ) ELISpot, which was also performed as part of the immunogenicity assays in the study. The gpELISA is the primary

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objective, but the data currently available on the ELISpot currently supports the data from the gpELISA.

Dr. Pickering asked whether there were sufficient data pertaining to recurrence of zoster to figure into the age recommendations or the cost-effectiveness analysis.

Dr. Hales responded that because there are limited data on recurrence, it was not figured into the cost-effectiveness analysis. They also did not believe it would substantially impact the results.

Dr. Harrison noted that the immunogenicity data at 10 years suggested a return to baseline, which the imperfect observational analyses suggested as well in terms of protection. Thus, it seemed that at 10 years, there would be basically no protection.

Dr. Parrino clarified that in the SPS, at 36 months the gpELISA was already starting to return to baseline. Thus, it appears that there is a return to baseline earlier than the vaccine efficacy being observed.

Dr. Hales indicated that the working group considered the results from the LTPS, which showed the possibility of waning over 10 or more years. However, because there was no concurrent control group in that study, they did not feel that it was strong enough evidence to demonstrate the extent to which vaccine efficacy is waning or how many years of protection there are. In order to consider revaccination, stronger data are needed with regard to duration of protection.

Dr. Bresnitz (Merck) pointed out that the cost-effectiveness analysis was modeling, and that changes could be made to the assumptions that would change the calculations. For example, uptake of vaccine is approximately 6% per year based on the National Health Interview Survey (NHIS) data versus the 100% coverage used in the model. Other assumptions could be modeled as well that would achieve somewhat different results. Regarding the last statement Dr. Hales made regarding physicians advising their patients to delay getting the vaccine or advising them not to get the vaccine, 20% of herpes zoster rates in this country occur in the 50 through 59 year old population on an annual basis (N=~200,000 individuals). Their risk of post-herpetic neuralgia PHN is not as high as in an older population, but when they have acute zoster, their pain is the same as someone who is 60, 65, 70, or older. It is the prolonged pain that perhaps differs in the two populations. Individuals 50 to 59 years of age do experience prolonged pain as well, but just not as frequently. The efficacy of the vaccine in the population of 50 through 59 year olds is substantially higher than in the older population. Thus, it is known that there is an efficacious vaccine in that population and the safety profile is essentially no different. It was unusual to make a statement that physicians may want to council their patients against getting the vaccine because its durability is unknown. There are many vaccines that are newly licensed or for which there is a new indication, but for which durability is unknown. However, a recommendation is not made to wait to obtain these vaccines because there may be a higher benefit in the future. Instead, the vaccine is offered and based on epidemiologic data, policy recommendations may be revised. By adopting a statement for physicians to council, they were basically saying to people, “Don’t get vaccinated and be at risk for getting herpes zoster.”

Dr. Hales responded that the statement was not intended to advise people not to get the vaccine. It was intended to make people 50 through 59 years of age aware of the risks and benefits of getting vaccinated at an earlier age, given that their highest risk for zoster and complications will be higher later in life.

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Dr. Duchin added that if they knew who would get herpes zoster at age 50 to 59, vaccinating adults in this age group would make a lot of sense. Considering the entire population and that the burden of severe zoster PHN and debilitating disease is going to be in the older age groups and there is only one shot to prevent herpes zoster and its related complications at this time, he thought they should focus the intervention on the period when the risk is greater, which would be persons over 60 years of age.

Dr. Hales pointed out that when assessing zoster cases only, vaccination at 50, 60, or 70 looks similar. However, the risk of complications from zoster increase rapidly after age 60. That was why we saw a large difference in terms of PHN, healthcare utilization, and QALYs between vaccination at 50 compared to vaccination at 60 and 70. While it is true that there is a large number of cases of zoster in 50 through 59 years, these cases are not as severe as in older patients.

Dr. Campos-Outcalt said he was supportive of the action recommended, which was to take no action at this point. However, he was somewhat troubled by some of the inconsistencies being applied that had not been applied elsewhere. This statement represented a discrepancy with the Food and Drug Administration (FDA), which ACIP did not like to do. The committee has approved other vaccines in the past without knowing what the duration of protection would be, and over time determined whether a booster or second dose would be needed. Also troubling to him was the 20% adherence rate, the reason for which he thought was because this vaccine is not covered by many private insurance companies. It is covered by Medicare for some strange reason under Part D, which creates a tremendous barrier for people to get the vaccine in the office. It will now be covered under the Affordable Care Act (ACA) at age 50, which would eliminate the potential for a disparity based on income. He wondered whether better results would be achieved by having higher rates of vaccine acceptance between ages 50 and 60 versus a lower rate after age 60. Another inconsistency was that while zoster incidence is increasingly higher with age, the incidence at 50 years of age was shown to be 5 per 1000. ACIP has recommended vaccinating against a number of diseases far rarer than that. At this point, he said he was comfortable not countering the recommendation, but he did find aspects of it to be troubling.

Dr. Schuchat elaborated that for those 60 through 65 or those 65 and older with private insurance who are not on Medicare, the vaccine is covered under ACA with no co-pays or deductibles when given by an in-network provider. While many people are frustrated about the challenges of Medicare Part D for vaccines and the zoster barriers, now that supply is no longer a barrier, it is important to communicate that people at least 60 years of age with private insurance do not have to worry about the co-pays and deductibles for this pretty expensive vaccine that is routinely recommended.

Dr. Duchin noted that the primary use of this vaccine was being viewed as prevention of the severe complications of zoster, not just zoster per se. Severe PHN and other debilitating complications occur more frequently in the older age groups. Duration of protection is not known and no booster dose efficacy studies are being planned. Therefore, the working group based the recommendation on the fact that there is one opportunity to prevent severe zoster-associated illness and the best time to do that. The best information available was used to make the best recommendation possible, but the working group will continue to evaluate data as they become available on immunogenicity and potential booster, and is very open to reconsidering and refocusing the strategy. However, based on the currently available data, the best strategy appears to be in vaccinating older adults.

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Dr. Temte added that it was important to keep in mind that the demographic projections for this country show that the over 65 population is exploding. They are going to be living longer, healthier, and having higher expectations in terms of health care as time goes on—especially if they are more prone to debilitating disease. In his practice, he sees zoster from age 8 and one of his co-workers in her 30s had zoster. However, the people who have the problems and who are hospitalized in his experience are almost always elderly and have significant issues.

Particularly given the demographic trends in the US, Dr. Reingold was surprised that there were not more studies planned to assess the efficacy of a second dose. While he was not clear whether ACIP could make recommendations to manufacturers, he expressed his hope that someone would conduct such studies.

Dr. Bennett found the coverage data to be shocking, and it was unclear to her why it was so poor in those 60 through 65 as well as those over 65 years of age. She wondered whether any work was being done to increase coverage.

Dr. Campos-Outcalt pointed out that part of the problem is that many physicians do not carry this vaccine in their offices. Because of the Medicare Part D issue, they do not get reimbursed, so they simply do not carry it to administer to 60 to 65 year olds who have private insurance.

Dr. Kempe indicated that several national surveys have been conducted about this, and the cost and payment issues are significant. People are not stocking the vaccine because they do not have a portal for pharmacy.

Dr. Hales agreed that there are many barriers to obtaining the vaccine. The first few years after introduction of the vaccine, there were supply issues. However, those have been resolved for at least the last year and a half or so. Some studies have shown that many people are still not aware of their risk of zoster. There are now television announcements that are attempting to raise awareness about the disease, and which are helping to educate people about their risk of zoster.

Dr. Bresnitz (Merck) pointed out that uptake is pretty good among those 60 to 64 years of age who are covered by commercial insurance because it is first dollar coverage. It is in the Medicare population where there are problems. It is a pharmacy benefit. Half of vaccines are given in pharmacies currently. Depending upon the plan or benefit design under Medicare Part D, someone may have a higher or lower co-pay, the deductible may be different, and whether it is December or January may impact the charge. There are data showing that if someone's co-pay is less than $50, they are more likely to be vaccinated than if their co-pay is over $50. This is observed in claims reversals in pharmacies where people receive a prescription, go to the pharmacy, find out how much it will cost, and then decide not to get the vaccine. Regarding durability data, the vaccine was licensed in 2006 for those 60 years of age and older. Because of supply constraints, provision of vaccine to the marketplace took several years. Unconstrained supply did not begin until 2012. Assessing durability in an observational study like an HMO, where data lag behind for a couple of years because it is a database study, good observational data will not be seen in the 60 and over population for several years yet. The indication for the 50 through 59 year old population was not approved until 2011, and there is not a recommendation for that age group, so there is limited vaccination in that population. Therefore, durability data for that population will not be seen until after 2020. Essentially, except for in the US and Canada, this vaccine is just beginning to be used globally. Thus, durability data based on observational data will not be available any time soon, because there are no other studies underway except for what Merck is conducting, which is going to take a long time. Regarding public awareness, the marketing campaign was created in 2012. A Merck

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team presented the campaign to the ACIP working group before launching it. The NHIS data showed 20% uptake in the 60 and over population, with a Healthy People 2020 target of 30% uptake. Despite a very intensive campaign, which did show good response in terms of uptake, the surveillance data show only a 20% uptake. Part of it has to do with financial barriers, physicians not assessing patients for risk, and physicians not making a strong recommendation when they do assess risk. The statement regarding the 50 through 59 year old population will reduce doctors' recommendations. Ultimately, doctors only advise rather than order patients about what to do. Very often, it is a "pocket book" decision.

Regarding durability, Dr. Karron said she was troubled about saying that there is only one shot at this. She inquired as to what the evidence was to suggest that 50 through 59 was the same as 60 to 69, and that durability of antibody would not be long enough.

Dr. Schuchat noted that it had been an interesting day with lots of contrasting data, reviews, and recommendation considerations. It sounded as though industry was considering revaccination. She pointed out that one thing to remember about this disease, unlike every other disease against which vaccination is recommended, is that this vaccine is against reactivation versus infection. While there are a lot of immunologic data, it would be very helpful to know what clinical protection revaccination would provide against a reactivation disease. If the company would pursue that type of testing, it would be very easy for ACIP to review data about multiple vaccinations. As she understood it, the working group limited their consideration to a single vaccination.

Dr. Bresnitz (Merck) said that while he did not recall the antibody response in the 50 through 59 year old group verses the older group, the geometric mean fold of the ELISA was somewhat higher at about 1.7 in those 60 years of age and over population and 2.1 in those 50 through 59 years of age. Conducting an efficacy trial for revaccination is prohibitive and is just not possible. There are 38,000 people in the SPS, which was why Merck limited their investigation to immunogenicity and safety in the ongoing booster trial. There are a few hundred people in that trial. To conduct an efficacy trial, many people would be needed. Attrition would likely be high because many people, because they are elderly, would die of some competing disease.

Day 1: Public Comment

Dr. Deborah Wexler
Executive Director
Immunization Action Coalition

I'm Dr. Deborah Wexler, Executive Director of the Immunization Action Coalition (IAC). We received funding from all of the vaccine companies pretty much, and we're proud of it, and happy about it, and also from CDC, several foundations, and many private donors.

I'm here today because I wanted to let ACIP and all of you know about IAC's new campaign. It's called "Give Birth to the End of HepB." The campaign is based on the ACIP recommendations of the year 2005 to make sure that all infants are given a birth dose of hepatitis B prior to hospital discharge. The reason we're on this campaign is because right now, about 1 out of 3 infants are not receiving that birth dose before they leave the hospital. This is resulting in approximately 800 babies becoming chronically infected with hepatitis B during their first year of life. This campaign is to help stop that. What we have done is created a book that's about 85 pages long that's a resource guide about what hospitals can do to protect newborns.

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It's been endorsed by CDC, AAP, AAFP, and ACOG. It is available free on our website through the "Give Birth to the End of HepB" campaign at www.immunize.org/protect-newborns. I hope you'll look at it.

In addition to creating the book and materials to help hospitals and educate them about the recommendations, because what we've found is that a lot of hospitals aren't aware of this guidance to give the birth dose prior to discharge, and that it's a recommendation of all of these professional societies and CDC, we also created something called "The Hepatitis B Birth Dose Honor Role." That is a listing on IAC's website of hospitals that have implemented policies to give the birth dose to every newborn prior to hospital discharge. It's to honor those hospitals that have achieved a 90% or greater rate of vaccinating all newborns before hospital discharge. I'm happy to say that was just launched in July and we just started adding more hospitals in September. We have 20 hospitals right now that we've honored on our website that are achieving the rate of 90% or more over a one-year period, and that have written policies in place to give the birth dose. If any of your hospitals qualify for the Hepatitis B Birth Dose Honor Role, I urge you to look at the website. I hope we'll see many, many more hospitals on the honor role. Thank you.

Yellow Fever Vaccine

Joseph A. Bocchini, Jr, MD
ACIP, Workgroup Chair
Japanese Encephalitis and Yellow Fever Vaccines Working Group

Dr. Bocchini reviewed the work completed by the Japanese Encephalitis (JE) Vaccine Working Group, and indicated that the additional work underway related to JE vaccine is the revision of the current statement. In addition, there was a recent change by WHO in its recommendation for a booster dose of yellow fever (YF) vaccine. The JE Vaccine Working Group was asked to add a review of this issue to its agenda and present recommendations to the full ACIP.

YF-VAX®, a live-attenuated YF vaccine, is the only YF vaccine licensed for use in the US. This vaccine is recommended for people residing in or traveling to YF endemic areas. In accordance with International Health Regulations (IHR), ACIP recommends a booster dose every 10 years. ACIP recommendations for use of YF vaccine were updated in 2009 and published in the *MMWR* in 2010.

In April 2013, based on a systematic evidence review, WHO's Strategic Advisory Group of Experts (SAGE) concluded that a single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease and that booster doses of YF vaccine are not needed. Countries can still require YF vaccine booster doses under IHR.

The JE Vaccine Working Group will be restructured to form the JE and YF Vaccines Working Group. The objectives will be to 1) review long-term immunogenicity and vaccine failure data for YF vaccine; and 2) develop recommendations regarding YF vaccine booster doses in US travelers and laboratory workers. An ACIP vote is anticipated on the YF vaccine booster dose in 2014.

Discussion Points

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Dr. Campos-Outcalt said he assumed that since SAGE already conducted a systematic review, ACIP would simply use and update that review.

Dr. Bocchini responded that the working group would assess that review, and determine whether there were any additional published or unpublished data to add to it. A determination would also need to be made regarding whether the ACIP GRADE review requirements are different from those used by SAGE.

Dr. Temte added that Dr. Abramson would be presenting an update on global perspectives of immunization during the second day of the ACIP meeting.

Global Immunization Update

Jon S. Abramson, MD
Chair, Department of Pediatrics at Wake Forest School of Medicine
Chair, WHO Strategic Advisory Committee of Experts on Immunization (SAGE)

Dr. Abramson explained that the Eight Millennium Development Goals (MDGs) set a bold vision for the entire international community to work toward a common end so that human development reaches everyone. Many of these goals are only partially health-specific. Some deal with education and some deal with poverty. The MDGs were adopted by over 190 countries in 2000. The goals use 1990 data as the starting point, and are set to be achieved by 2015. The MDGs include 21 quantifiable targets measured by 60 indicators. If all MDGs are achieved, world poverty would be cut by half, which has already occurred. Also, tens of millions of lives would be saved. While millions of lives have been saved, the ten million goal has not yet been reached.

Focusing on MDG Goal 4 (MDG4), which is to reduce mortality by two thirds in children less than 5 years of age, Dr. Abramson pointed out that the goals were created in 2004. In 1990, the mortality rate in children less than 5 years of age was approximately 160/1000 in low-income countries as compared to 8/1000 in developed countries. By 2012, the mortality rate in low income countries was reduced by 45% to approximately 88/1000 in children less than 5 years of age. Global deaths decreased from about 12 million to 6.6 million. Approximately 17,000 fewer children less than 5 years of age died every day in 2012 than in 1990, but about 18,000 children less than 5 years of age still died every day in 2012. Many of the deaths in children less than 5 years of age in low income countries continue to be due to vaccine-preventable diseases, which is where SAGE spends almost all of its time. As of 2012, most of the issues are occurring in Africa and Asia.

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Since 1990, 90 million lives have been saved. However, 216 million children died before age 5 from 1990 through 2012. If MDG 4 is achieved on target, an additional 3.5 million children's lives would be saved between 2013 through 2015. If current trends continue in all countries, the world will not meet the MDG4 target until 2028. By then, an additional 35 million children will die.

In terms of why SAGE was formed, the WHO has a mandate to provide leadership on global policies and standards and norms, and to support countries in applying these to national programs to improve health. SAGE was established by the WHO Director General in 1999 as the principal advisory group to the WHO for vaccines and immunization. SAGE provides recommendations on global policies and strategies for all vaccine-preventable diseases. SAGE is comprised of 15 independent experts from around the world serving in a personal capacity. They represent a broad range of disciplines, including epidemiology, public health, vaccinology, pediatrics, internal medicine, health economics, infectious diseases, immunology, drug/vaccine regulation, program management, immunization delivery, healthcare administration, and vaccine safety. There is a spectrum of professional affiliation geographically and in terms of diversity, which is considered to be very important. The initial term is for 3 years, with a provision for one additional term. The chair serves for 3 years.

Numerous other committees deal with global immunization. SAGE collaborates with global, regional, and national advisory bodies including the following:

<u>WHO Immunization Advisory Committee</u>
Global Advisory Committee on Vaccine Safety
Expert Committee on Biological Standardization
Initiative for Vaccine Research Advisory Committee
Immunization and Vaccines-Related Implementation Research Advisory Committee
Immunization Practices Advisory Committee

<u>WHO Regional Technical Advisory Committees</u>
Regional policies, strategies, priority-setting, monitoring
6 WHO Regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, Western Pacific
2 people are elected from each region to give input to SAGE

<u>National Immunization Technical Advisory Groups</u> (NITAGs)
Country-level policies, strategies, priority-setting, program implementation, monitoring

SAGE's recommended process for committee meetings is to meet two times per year, with additional meetings as required (e.g., pandemic influenza, DoV planning). The meetings are convened in an open forum to ensure transparency. Observers include United Nations Children's Fund (UNICEF), Global Alliance for Vaccines and Immunisation (GAVI), Secretariat, Chairs of WHO Regional Offices, and TAGs. SAGE working groups address complex questions and are comprised of at least two SAGE members, WHO staff, and additional external subject matter experts. SAGE considers working group recommendations. SAGE recommendations are made by consensus and not by majority vote. The resulting evidence-based recommendations provide the basis for WHO vaccine position papers, which inform country-level decision-making and program implementation. These recommendations also assist partner organizations (e.g., GAVI, non-profit organizations, and international professional associations).

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To assess the quality of evidence, SAGE uses the broadly endorsed GRADE approach. This rating method assesses the quality of evidence based on levels of confidence in estimate of effect (very little confidence, limited confidence, moderately confident, very confident). Also assessed is the strength of recommendations in terms of whether they are *Strong* (benefits do, or do not, outweigh risks and burdens) or *Weak* (benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks). Regarding how WHO processes SAGE recommendations, the SAGE Chair briefs the WHO Director General on the proceedings of each meeting. Conclusions and recommendations are published in WHO's *Weekly Epidemiological Report* within two months. In addition to GRADEing, the Developing and Evaluating Communication Strategies to Support Informed Decisions and Practices Based on Evidence (DECIDE) research project was launched in 2011. Sometimes people using GRADE are frustrated because this process does not tell the entire story. Thus, the DECIDE mechanism is another way of assessing impact. SAGE's Varicella Working Group is the first to try to use the DECIDE plot on top of GRADE to determine what the impact would be on various recommendations.

An independent review of SAGE in 2008 investigated the effects of recommendations formulated by SAGE and concluded that, "SAGE recommendations have become a necessary step to the introduction and use of vaccines, especially in developing countries and, as a consequence, have clear and significant impact." The independent review recommended that WHO take immediate steps to consolidate and build on the successes of SAGE; rapidly disseminate recommendations at the country level; and ensure that immunization policies are coordinated within the wider framework of other possible preventive interventions.

To a great extent, the Decade of Vaccines (DoV) started because the Gates Foundation was willing to contribute $10 billion to move this forward. The DoV vision is, "We envision a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases" and its mission is, "To extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live." Many countries and individuals contribute to GAVI as well, so the funds are not only coming from the Gates Foundation. GAVI Secretariat, Seth Berkley, is an incredibly effective fund raiser and comes from a public health background. There is a very symbiotic relationship between GAVI, Bill Gates, and WHO. They are independent, but the relationship works well. It is a unique moment in time where increased funding meets scientific opportunity, there is increased country ownership, there is improved coordination of partners, that are increased resources from government and international partners, and there is a robust pipeline of new vaccines (e.g., malaria, dengue, TB, HIV). The goals of DoV are to 1) Achieve a world free of poliomyelitis; 2) Meet vaccination coverage targets in every region, country, and community; 3) Exceed the Millennium Development Goal 4 target for reducing child mortality; 4) Meet global and regional elimination targets; and 5) Develop and introduce new and improved vaccines and technologies.

Regarding the relationship to the Global Action Plan (GVAP), the previous Global Immunization Vision and Strategy (GIVS) plan is now being replaced with the GVAP. The GIVS was created as a way to help meet some of the MDGs, but is no longer adequate to deal with the robust vaccine pipeline and the need to add newer vaccines into national programs. The GVAP will be used to achieve the five DoV goals that contain six objectives. This is a collaborative effort by the international vaccine community to extend, by 2020 and beyond, the full benefits of immunization to all people. The GVAP was endorsed in 2012 by 194 member countries at the 65th World Health Assembly, which is WHO's decision-making body. SAGE recommendations are used to support the WHO's contributions to the GVAP. A new vaccine plan was developed for the DoV, given that there continued to be unmet needs and many challenges. Opportunities exist to do much better including: 1) Elimination (e.g., measles) and eradication (i.e., polio)

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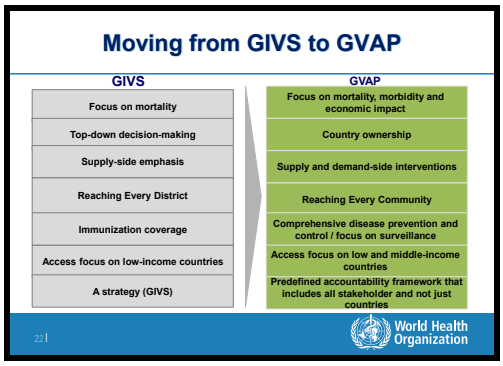
goals are not on target; 2) More rapid introduction and uptake of recently introduced vaccines would further decrease the number of deaths; and 3) More rapid introduction and uptake of new vaccines this decade (e.g., malaria). A comparison of the two plans is illustrated in the following table:



GVAP Guiding Principles include the following:

Country Ownership
Countries have primary ownership and responsibility for establishing good governance and for providing effective and quality immunization services for all.

Shared Responsibility and Partnership
Immunization is an individual, a community and a governmental responsibility that transcends borders and sectors

Equitable Access
Equitable access to immunization is a core component of the right to health

Integration
Strong immunization systems, which are part of the broader health systems and closely coordinated with other primary health care delivery programs

Sustainability
Informed decisions and implementation strategies, appropriate levels of financial investments, and improved financial management and oversight

Innovation
The full potential of immunization realized only through learning, continuous improvement, and innovation across all aspects of immunization.

Regarding some highlights of DoV progress to date, global coverage estimates from 1980-2012 are at a fairly good level for some vaccines (DTP1, DTP3, Measles, HepB3). Uptake is slower for the most recent vaccines introduced (Hib3, PCV3, Rota3). Part of what the DoV is about is to make the curve much sharper upward.

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New WHO vaccine recommendations since 2010 include the following:

- ❑ Conjugated Meningococcal A: Focus on the African meningitis belt with an inexpensive ($0.50) vaccine
- ❑ Conjugated Pneumococcal: Widespread global use with the help of GAVI price shaping
- ❑ Dengue: Not recommended due to lack of efficacy for serotype 2
- ❑ Hepatitis A: Decreasing the cost by recommending one dose instead of two
- ❑ Influenza: Pregnant women given highest priority
- ❑ Rotavirus: Removal of age restriction allows additional lives to be saved
- ❑ Tick-borne encephalitis: Consider use based on geographical disease incidence
- ❑ Yellow fever vaccine: Only one dose needed, and use in pregnant and lactating women should be considered based on risk-benefit assessment

With regard to meningitis, 430 million people live in the "Meningitis Belt" of sub-Saharan Africa. The meningococcal meningitis belt in sub-Saharan Africa spans from Senegal in the West to Ethiopia in the East. Epidemics due to serotype A occur every 7 to 12 years. In 2009, there were approximately 88,000 cases and about 10,000 deaths. In conjunction with the Gates Foundation, a massive immunization program using a conjugated meningococcal A vaccine ($0.50/ dose) has been initiated in this region for everyone 1 through 29 years of age. In the 6 countries where the vaccine has been used to date, the disease incidence has decreased by more than 95%.

The following table depicts how the conclusion was reached regarding the use of influenza vaccine in various risk groups:

Assessment of Influenza Risk and Influenza Vaccine Characteristics in Various Risk Groups

Risk Group	Feasibility of Delivery	Disease Severity	Vaccine Effectiveness	Indirect Benefits
Pregnant women	++	+++	+++	++
Healthcare workers	++	+	+++	+
Children, 2-5 yrs	+	++	++	-
Children, < 2 yrs	++	+++	+	-
Elderly	+	+++	+	-
Underlying Health Conditions	+	+++	+	-

29 | World Health Organization

In countries using or considering introducing seasonal influenza vaccination SAGE recommends the following:

- ❑ Influenza vaccination of all pregnant women as the highest priority group.

- ❑ Based on local circumstances (e.g., burden of disease, vaccine availability, cost-effectiveness considerations, competing priorities, and programmatic constraints), countries consider annual influenza vaccination of healthcare workers, children (< 2 yrs and 2-5 yrs of age), the elderly, and individuals with underlying health conditions. Countries should decide the relative priority to assign to targeting these groups for influenza vaccination.

In 2009, the WHO recommended that rotavirus vaccine for infants be included in all national immunization programs. In countries where deaths due to diarrhea account for 10% or greater of mortality among children less than 5 years of age, the introduction of the vaccine is strongly recommended. Due to concerns about intussusception, the first dose should be given before 15

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weeks, and the last dose by 32 weeks. In 2013, this age restriction was removed to enable children with delayed immunizations to receive the vaccine.

The risk-benefit considerations for removing the age restrictions for rotavirus vaccine are depicted in the following table:

Risk-Benefit Considerations for Removing the Age Restrictions for Rotavirus Vaccine?

	Median (5th and 95th percentiles)	
	Rotavirus Deaths Averted	Associated Intussusception Deaths
Restricted	156,100 (110,100 to 201,800)	288 (99 to 688)*
No age restriction	199,200 (140,700 to 255,400)	605 (310 to 1,133)*
[illegible]	43,100 additional rotavirus deaths averted (30,600 to 53,600)	317 additional IS deaths associated (211 to 445)

321 World Health Organization

In April 2013, SAGE reviewed its previous recommendation on YF vaccine and made the following changes to its recommendations:

1) Only one, rather than 2 doses, is needed to provide lifelong protection and that the vaccine should be considered for use in pregnant and lactating women based on risk versus benefit in the particular setting.

   – The vaccine is very effective, with only 12 suspected cases of YF disease detected in vaccinated people since the introduction of YF vaccination in the 1930s, and the duration of protection due to YF vaccine is at least 20 years and probably for life.
   – A systematic review identified 6 studies indicating that a high proportion of vaccine recipients (>90%) have detectable levels of serum neutralizing antibodies >20 years post YF vaccination.
   – In a study of antibody levels in US World War II veterans, >80% had neutralizing antibodies 30 to 35 years after a single dose of YF vaccine.

2) Based on the high mortality due to YF disease the vaccine should not be contraindicated in pregnant or lactating women, but rather the use of the vaccine in this population should be based on the risk of contracting disease in the particular geographical setting.

   – Mortality rates due to YF are 10% – 30% with ~30 000 deaths currently occurring per year (90% in Africa).
   – Over 540 million doses of YF vaccine have been administered and there have been no reports of vaccine-related viscerotropic or neurotropic disease in pregnant women.
   – There have been 3 cases of viscerotropic disease in newborns of lactating women who received the vaccine.

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Current SAGE working groups and topics include the following:

- GVAP WG (ongoing, first report out during November 2013 SAGE meeting)
- Hepatitis E WG (just formed, because China has a HepE vaccine that it might market globally)
- Japanese Encephalitis vaccine WG (just formed)
- Malaria vaccine (preliminary data from RTS,S/AS01 trial reviewed)
- Pertussis vaccine (global switch to acellular pertussis vaccine has been put on hold)
- Polio vaccine- pre- and post-eradication issues
- Pregnancy and lactation (expanding use of vaccine in this population)
- Varicella-Zoster vaccine (recommendations to be presented in April 2014)
- Vaccine Hesitancy (working for about a year, ongoing)
- Vaccine non-specific effects (ongoing)

Currently, there is a major outbreak of polio cases in Somalia. However, over 12 months have passed without a case of polio in India for the first time in history. This is a major step forward, which had to do with bivalent oral polio vaccine (OPV) and accountability. There are inaccessible areas now where very difficult issues are occurring. For example, PAHO workers have been killed. Afghanistan and Pakistan are still endemic countries. Two eradication deadlines for polio eradication have passed, and the global effort is now costing greater than $1 billion per year. In 2011, the eradication of polio was designated by the WHO to be a global emergency and the World Health Assembly made the following statement:

> "Loss of this opportunity to eradicate polio would be extremely tragic and unacceptable and a waste of the considerable investment already made in polio eradication with consequences for all of immunization activities, especially in the poorest countries. Any diminution of polio eradication activities due to a lack of funds is completely unacceptable. We urge all governments and partners to act immediately to meet the polio eradication funding needs if we are to wipe out this crippling disease."

The groups have oversight over polio. SAGE currently has the oversight responsibilities for the pre- and post-vaccination recommendations. Currently, the polio program is the most integrated with other services. Further integration of other vaccine and services will enhance the impact of the DoV.

During the past few years SAGE has been asked to consider the use of vaccines that, while not always specifically aimed at pregnant and lactating women, could benefit them and their infant. Examples of this include use of the conjugated A meningococcal vaccine in the SIA campaigns in Africa, influenza vaccine, yellow fever vaccine, and pertussis antigen-containing vaccines. This issue has existed for a long time with no real progress. The companies exclude pregnant women from vaccine trials due to litigation concerns. The regulatory agencies, given essentially no data for pregnant women, have little leeway in how the vaccine is labeled. Pregnancy registries are required, but decades go by and the labeling rarely changes. This is similar to what occurred for a very long time with many of the drugs used in children in the US until finally, a law was passed that give the FDA authority to require studies in children, which has resulted in a substantial number of drug labeling changes specifically related to use of these drugs in children. SAGE has repeatedly expressed its concerns that the current regulatory labeling hinders the use of these vaccines in pregnant or lactating women to protect themselves and/or their baby from vaccine preventable diseases are not an appropriate assessment of the risk/benefit analysis, at least for all inactivated vaccines. At the November 2013 meeting, SAGE will be discussing what further role it can have to move this issue forward.

Discussion Points

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Dr. Duchin requested further information on the surveillance component, which is a formal piece of the approach to measles/rubella initiative and whether that is integrated with what is required through the revised international health regulations.

Dr. Abramson replied that it is better, though they are never happy with it. There will be a session during the November SAGE meeting regarding how to improve surveillance. Part of the issue regards where to spend money. With rotavirus, surveillance was required in every country before making recommendations. SAGE does not subscribe to that equation.

Given the success of the A conjugate vaccine, Dr. Harrison was curious about SAGE members' thoughts about the emergence of serogroup W disease in the Meningitis Belt as well as local outbreaks of serogroup X disease.

Dr. Abramson responded that one line of thinking is that if serogroup A is eliminated, more of another serogroup will be observed. Numerous other serogroups are potentially present. It was not clear yet whether the answer to this question is known. They are trying to move through the process of addressing serogroup A. If anywhere near the rate of another serotype is observed as was seen with serogroup A, they will likely reconsider. There are many more vaccine companies globally. A lot of work is being done about market shaping and how to work with companies to reduce the cost but still satisfy them with volume and other parameters. There is significant discussion with regard to this. The serogroup A vaccine was contingent upon purchasing this vaccine for $0.50.

Dr. Baker asked how they manage to get people in the developing world to immunize pregnant women. Though recommendations are made in the US, this just does not happen. The idea of maternal immunization has been presented to companies for more than 30 years. For about the first five years, she heard a lot about litigation, which was completely fair. But then some wise people said, "Well you need to get Congress to do it." There are some diseases that could be prevented for both mothers and babies. Influenza is a great example, but there are others. However, there is not a pathway to licensure of new vaccines that might prevent maternal and infant disease based on efficacy trials, because some of these diseases have a low incidence in the US because there are other measures (e.g., hygiene, nutrition, antibiotic prophylaxis, et cetera). However, in the developing world, the problem is ascertainment and all of the noise involved in trying to conduct an efficacy trial in pregnant women. A pregnant woman's life is AEs, so assuring safety with all of the noise—actually getting blood draws from mothers and babies, or even doing blood or viral cultures in babies—is a major problem. While it is nice that regulatory agencies are listening to some extent, it is still a challenge.

Dr. Abramson replied that PAHO has led the way in this. Argentina and Brazil recently reported out that in their first year of SAGE's recommendation, they achieved only 50%—similar to what the US achieved. In the second year, they achieved 90%. There is mass campaigning, communication that fits the country and community. Plus, it is not just communication to doctors. Regarding vaccination of pregnant women, he could not predict what SAGE would do in November as this would be their first discussion about this issue. One consideration involves assessing inactivated vaccines separately from live vaccines, and adjuvanted vaccines. When they came to him to ask how he could use a meningococcal serogroup A vaccine in a lactating women, he asked under what biologically plausible reason they were telling him he could not do that. That is the framework. SAGE did not know how to lobby Congress. They went to AAP to get some help.

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Dr. Plotkin (Vaccine Consultant) noted that he did not see a goal for rubella elimination in Dr. Abramson's list, despite the fact that measles is being pushed and there is a great opportunity to address both diseases. He wondered whether SAGE had ever seriously considered what they could do with a billion a year spent on polio eradication in the way of promoting other immunization. Everyone wants the end to polio, but this seems to be an ever ongoing venture. Two initiatives will start in 2014 focused on solving problems of vaccine immunity and immunization for the future. One is through the RWJ Foundation that is sponsoring series of meetings. The first one begins in February 2014 at Scripps Research Institute. The idea will be to attack the problems with current and future vaccines to produce prolonged and potent immune responses. The second is an initiative by NIH that will begin with meetings to assess immunological issues with respect to why some vaccines are imperfect. He also suggested that SAGE look at vaccine industry as a whole in terms of the issue of the world's supply of vaccines (e.g., where the supply will come from to immunize the entire world's population, and where innovation is going to come from). There are many new vaccine manufacturers in developing countries, but by and large, they are not conducting innovative research. Meanwhile, the manufacturers in developed countries are reducing their research and development. There is a major issue regarding whether new vaccines will come from. The world, which is essentially the SAGE committee, needs to consider this issue and how to promote innovation. If it must come from developing country manufacturers, fine, but it is an issue that is going to loom very large in the near future.

Dr. Abramson responded that SAGE has been working on measles and rubella. In fact, the working group said to stop using "measles" and only use "measles and rubella." That makes sense in many ways. The working group is still active and is still working on this. Part of the issue is not the question of elimination versus eradication, but regards whether enough funds can be garnered to immunize with an MMR vaccine on a Supplementary Immunization Activities (SIA) basis, not just through age 5 but to age 15. They are concerned about shifting ages just as in varicella. SAGE members have asked the polio question many times regarding the fact that a billion dollars are being spent currently to eliminate a couple of hundred cases a year. However, the major political/social implications of failing at this is why SAGE recommended calling it a public health emergency. If they fail at this, it will be very difficult to get anyone to think about measles eradication. The question of whether measles should have been addressed before polio is an interesting one. In many ways, that would have been technically easier. He sympathizes with the question of a billion dollars and understands it, but he believes the disease must be eradicated or prove that it can be. SAGE is using a tremendous amount of effort and energy to do this.

Dr. Schuchat pointed out that the polio eradication initiative, in addition to the intense focus on ending transmission, has a component of planning and effort focused on the legacy of polio and planning how to capitalize on enormous investments and capacities that polio eradication has created, and ensuring that there is a lasting impact of that for other benefit. The GAVI Alliance has created opportunities for the poorer countries of the world to apply for MR vaccine in campaigns that go up to age 15, so there is quite a bit of budget going into that, and the expectation for hundreds of millions of young people to get MR vaccine in the poorest countries of the world over the next five years.

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Dr. Vazquez requested further information about the expansion of age limits for rotavirus vaccine, as well as how many children are receiving the vaccine at the expanded age range.

Dr. Abramson replied that if someone presents for their first dose at 16 weeks or their second dose at 40 weeks, they receive it. The 2-dose series is used in most of the countries. SAGE just recently made its recommendation, but the surveillance is ongoing to try to determine the impact of its recommendation.

Dr. Riley (ACOG) thanked SAGE for putting pregnancy at the top of the list. This is a major issue. Dr. Helen Rees, the prior SAGE chair, made a request directly to Dr. Riley through ACOG for ACOG to help work with obstetricians and gynecologists across the world. There will be an immunization discussion during the next Federation of Obstetrics and Gynecology meeting in Seattle in 2014, so there will be some education during that meeting for all obstetrician/gynecologists who attend. Everyone is concerned about pregnant women being excluded from drug and vaccine trials. Therefore, some work is being done through ACOG and the Society for Maternal-Fetal Medicine (SMFM), which is high risk obstetricians, for which ACOG is doing the legislative work to try to build at least some capacity to do some of these things in pregnant women basically based on what AAP has done.

Dr. Alan Hinman (Task Force for Global Health) reported that the Southeast Asian Region recently passed a resolution calling for regional elimination of measles in the Southeast Asian Region, so all 6 WHO regions now have elimination targets for measles. As Dr. Schuchat pointed out, GAVI has provided support for rubella vaccine. In terms of global expenditures, the GAVI Alliance will provide $1.6 billion dollars of support in 2013 to 73 of the poorest countries in the world to introduce vaccines and to hasten the narrowing of the gap between when vaccines are introduced in developed countries, and when they are introduced in developing countries.

Dr. Reingold emphasized that as polio winds up, there is a discussion about how that infrastructure and its resources can be used to more effectively address measles and rubella. The challenge is to not create another very strong vertical disease-specific program, and to do it in an integrated fashion with routine immunization.

Dr. Temte noted that it was wonderful to get a sense of how what ACIP does dovetails with what is being done globally.

Human Papillomavirus (HPV) Vaccines

Introduction

Joseph A. Bocchini, Jr, MD
Chair, ACIP HPV Vaccine Working Group

Dr. Bocchini began with a review the HPV session from the June 2013 meeting. The HPV session included a presentation by Merck on the vaccine registry for quadrivalent HPV vaccine. Rates of spontaneous abortions and major birth defects were not greater than the unexposed population rates. FDA considered Merck's regulatory commitment for the pregnancy registry fulfilled in April 2013, and the registry was terminated. The HPV vaccine Working Group presented plans for an updated ACIP statement, including recommendations for males and females and bivalent and quadrivalent HPV vaccines. As part of this, there was discussion of HPV infection risk for research HPV laboratory workers and HPV infection risk for selected

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health care workers, since both of these topics had been discussed as part of the STD Treatment Guidelines meeting in the spring. At that time, the exact wording to be included in the statement had not been resolved. Discussions have subsequently taken place within CDC.

Since the June 2013 ACIP meeting, the working group had a few conference calls to review data on alternative schedules for the bivalent HPV vaccine. A conference call planned on the 9-valent HPV vaccine was canceled due to the government shutdown. This session included a new update on HPV vaccination coverage in the US, a presentation on the 9-valent HPV vaccine development program, and review of an updated ACIP statement. He noted that all ACIP committee members received a draft of the updated statement, and requested that they provide input related to that statement to be incorporated into the final document. Once finalized, the updated statement will be put before the full committee for a final review and vote, probably during the February 2014 ACIP meeting.

2012 HPV Vaccine Coverage Data

Shannon Stokley, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Stokley reported that it was a busy summer for CDC assembling various coverage reports. A report published in the *MMWR* in July 2013 focused specifically on HPV vaccination coverage and an update on safety. Another *MMWR* report was published in August 2013, the annual adolescent vaccination coverage report. This report provided coverage for all routinely recommended vaccines for adolescents, including HPV, vaccination coverage for boys, and state level coverage.

Within the US, HPV is one of several vaccines recommended for adolescents, with the other vaccines being Tdap, meningococcal conjugate vaccine, and an annual influenza vaccine. The majority of vaccines are administered in the primary care setting in private physician offices and public health department clinics. The HPV vaccine is widely available. Almost all pediatricians and at least 88% of family physicians stock and administer HPV vaccine [Daley et al. Pediatrics. 2010;126:425-433]. HPV vaccine is covered by most private health insurance companies and government insurance programs. With the ACA, it will be covered by all plans. According to the 2011 National Immunization Survey-Teen (NIS-Teen) data, approximately 39.4% of adolescents 13 through 17 years of age are eligible for VFC vaccine.

In the US, vaccination coverage is monitored among the adolescent population through the NIS-Teen. The NIS-Teen was implemented in 2006 and in 2008 was expanded to provide state level estimates. The NIS-Teen is a random digit dial (RDD) telephone survey of US households with an adolescent 13 through 17 years of age. Starting in 2011, the survey deployed a dual sample frame including households from landline and cell phone samples. A strength of the survey is that all analyses are limited to adolescents with provider verified immunization histories.

According to NIS-teen data from 2006 through 2012 by vaccine for adolescents 13 through 17 years of age, as of 2012, 85% of adolescents had received a Tdap vaccine and 74% had received the meningococcal conjugate vaccine. In contrast, only 53% of girls had received 1 or more doses of HPV and only 33% of girls had received all 3 doses of the HPV series. Among adolescent boys, 21% received 1 or more doses of HPV and 7% received all 3 doses of the HPV series. Each year approximately a 10 percentage point or more gain is seen for Tdap and meningococcal conjugate vaccine. However, for the past 3 to 4 years, very little increase has

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been seen in HPV for girls. In fact, from 2011 through 2012, no change was observed in coverage.

In terms of vaccination coverage levels for adolescent girls for 1 or more doses of HPV vaccine by state, there is tremendous variation in coverage across the county. Coverage tends to be lower in the Southeast and higher in the Northeast, and ranges from a low 39% in Florida to a high of 74% in Rhode Island. Regarding vaccination coverage by poverty status, among adolescent girls, vaccination coverage for the first dose of HPV is significantly higher among those living below the poverty level compared to girls living at or above the poverty level. However, no statistically significant differences were observed for 3 doses of HPV. For adolescent boys, vaccination coverage is also significantly higher among those living below the poverty level for both 1 dose and 3 dose coverage. Differences in vaccination coverage by race/ethnicity are also observed. Vaccination coverage for the first dose of HPV is significantly higher among Hispanic girls compared to white non-Hispanic girls; however, no significant differences were observed among the 3 groups for 3 doses of the series. Among boys, vaccination coverage for 1 dose of HPV is significantly higher among black and Hispanic boys compared to white non-Hispanic boys. In terms of coverage for 3 doses, Hispanic boys also have significantly higher coverage than white non-Hispanic boys. Although admittedly, coverage is low for all groups [MMWR. 2013;62;685-93].

Another important measure that is evaluated with respect to HPV is vaccine completion. “Completion” means the number of girls who actually completed the series who start the series. Nationally, 67% of girls who start the HPV series receive all 3 doses. This is actually a significant decrease from 2011. This means that 33% of girls who initiate the series do not come back to complete the series. In terms of completion by race/ethnicity, black non-Hispanic and Hispanic girls are less likely to complete the series when compared to white non-Hispanic girls. CDC is currently conducting research to better understand the barriers to completing the HPV series among different racial and ethnic groups [MMWR. 2013;62;685-93].

One issue affecting HPV vaccination coverage are vaccination intentions among parents of adolescent girls. Since 2008, CDC has assessed vaccine intentions among parents of unvaccinated girls. Each year, the proportion of vaccinated girls has increased some, subsequently decreasing the proportion who report that they are *somewhat* or *very likely* to have their daughter receive the vaccine. The proportion of parents who report that they are *not likely* to receive the vaccine within the next 12 months has remained consistently at about 25%, although in 2012 it was about 23%. There remains a core group of parents who are not expressing the intent to have their daughters vaccinated.

Within the NIS-Teen survey, parents are asked why they do not intend to vaccinate their daughter in the next 12 months. The five main reasons include: the vaccine is not needed or necessary (19.1%), the vaccine was not recommended by the provider (14.2%); concerns over the safety of the vaccine or concerns over side effects from the vaccine (13.3%); lack of knowledge about the disease or the vaccine (12.6%); and their daughter is not sexually active (10.1%) [MMWR. 2013; 62:591-5].

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When HPV vaccination practices have been studied among physicians, it has been observed that providers are less likely to recommend the HPV vaccine to their younger adolescent patients. Based on the results of a national survey of pediatricians and family physicians, only 53% of providers strongly recommend HPV for their female patients 11 through 12 years of age. The percent who strongly recommend the vaccine increases with patient age [Allison et al. Academic Pediatrics. 2013;13:466-74].

Communication of HPV vaccine during the healthcare encounter is also very important to vaccine acceptance. Several qualitative evaluations have been done regarding this issue. Common themes found from these studies show that the vaccine is often presented as optional; whereas, other vaccines indicated for adolescents are recommended. Also, some providers expressed mixed or negative opinions about the vaccine. When parents expressed reluctance to the vaccine, providers were hesitant to engage in discussion. Finally, some providers shared the parent's view that it was acceptable to delay vaccination until the teen was older [Goff S et al. Vaccine 2011;10:7343-9; Hughes C et al. BMC Pediatrics 2011;11:74].

Another important challenge is vaccination opportunities. A "missed opportunity" is defined as a healthcare encounter where at least 1 vaccine was administered, but not all indicated vaccines were administered. Based on 2012 NIS-Teen data, among girls unvaccinated for HPV, 84% had a missed opportunity. This means that the girls had a healthcare encounter and received a vaccine, but did not receive the HPV vaccine. If missed opportunities could be estimated, vaccination coverage for the first dose of HPV could be as high as 93%. Of course, eliminating missed opportunities requires that parental and provider attitudes and practices be addressed. It is possible to obtain high vaccination coverage levels for the HPV vaccine given the current vaccine delivery system [MMWR. 2013; 62:591-5].

In summary, progress with improving HPV vaccination coverage among US adolescent girls has stalled. However, vaccination coverage among boys is increasing. The main reasons parents give for not vaccinating daughters are lack of awareness and gaps in understanding the need for vaccination. Primary care providers are key to increasing vaccination coverage. It is really critical to improve communication, provide strong recommendations, not delay the vaccine, implement evidence-based strategies to improve vaccine delivery, and prevent missed vaccination opportunities.

CDC has a number of activities underway. Just before the shutdown, CDC was able to award funds to11 immunization awardees to conduct targeted activities to increase HPV coverage. A study has also been initiated to improve physicians' communication skills and comfort level with talking about and recommending HPV vaccines. Research-based outreach and education continue to be provided to parents to improve awareness and vaccine uptake. The communication group has developed additional materials for physicians, including the TIPS sheet for clinicians, which includes actual language providers can use to help answer questions from parents, which are available at (http://www.cdc.gov/vaccines/who/teens/for-hcp-tipsheet-hpv.html). A speakers bureau has been created of HPV-related cancer specialists to present to pediatricians and family physicians on the importance of HPV vaccine, and to drive home the message that HPV vaccine is cancer prevention. Work continues in media outreach through professional and parent channels as well. CDC has updated its HPV portal website where all materials can be found: www.cdc.gov/vaccines/YouAreTheKey.

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Discussion Points

Dr. Jenkins asked for a reminder about whether schools require the vaccine. Whether there is a philosophical versus a religious exemption tends to impact vaccination rates.

Ms. Stokley replied that only two states require this vaccine for school entry, DC and Virginia. Not much impact is being observed on vaccination coverage in these areas. However, 41 states require Tdap for school entry and about 14 states that require meningococcal conjugate vaccine. There is motivation for teens to present to physicians' offices for Tdap and meningococcal conjugate vaccine, which is also an opportunity to administer HPV. The Tdap and meningococcal requirements have improved coverage in the states with requirements, and there is some debate regarding whether this has had a spillover effect on HPV. More investigation is needed in that area.

Dr. Lett (CSTE) thanked CDC for all of the HPV materials on the portal. CSTE has found them to be incredibly useful. CSTE recently had its statewide pediatric immunization conference, where they utilized the slide sets and tip sheets. The participants found the sample provider conversations to be incredibly helpful.

Dr. Karron said she thought any and all efforts to improve uptake of these important and life-saving vaccines should be done. Obviously, there is a problem with uptake. However, there is also a problem with completion. In follow-up to some of the discussions the previous day, many countries throughout the world are considering 2-dose schedules for HPV. She wondered if the US would ever consider that as well.

Dr. Markowitz responded that CDC is following the data, and presented some of the early data to ACIP a year ago. The working group recently heard data and plans from one of the manufacturers about 2 dose schedules, so this is something CDC is following. The HPV vaccination program is much less mature in the US than the pneumococcal program.

Dr. Zahn (NACCHO) inquired as to whether concerns regarding vaccine safety were about vaccine safety in general, or vaccine safety specific to HPV vaccine.

Ms. Stokley replied that the question in the survey is specific to HPV vaccine; however, the way it is coded is very general. Therefore, it is unknown what specific vaccine safety concerns they have. When focus groups have been conducted with parents to better understand what they mean by "vaccine safety." Oftentimes what parents state as safety concerns are not the same as CDC would consider as safety concerns. It is more about duration of protection and a vague notion. It is very difficult to pinpoint what parents mean.

Ms. Hayes (ANA/ACNM) reported that her experience clinically is that young girls switch from the pediatrician to a reproductive healthcare provider sometime in their tweens and teens, and that they start their vaccine series with their pediatrician and then stop, and reproductive healthcare providers are not supplying the vaccine. When she offers the vaccine to teenagers, she is amazed at how often the parents are speculative, and she cannot get them to pin down why they do not want their teenager to have the vaccine. It is very frustrating, and addressing that and finding out ways to specifically address it is the biggest challenge. There is one document on the CDC website that is specific to vaccines recommended for teens that she has found to be the most helpful, because it takes HPV away from the sex question and to the indication that it is a vaccine to prevent disease.

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Dr. Harrison inquired as to whether there were any data on coverage for two doses. He wondered whether the drop-off occurred between the first and second dose or the second and third dose.

Ms. Stokley replied that in the July 2013 *MMWR* report, coverage was included for 1, 2, and 3 doses. It appears that half drop off between 1 and 2 and the other half drop off between 2 and 3. It is not one specific dose or the other.

Dr. Gorman (NIH) also thanked CDC for trying to protect his daughters from this disease. He also commended CDC's amazingly successful smoking cessation campaign, with very graphic advertisements appearing on television and radio for the last 6 months. He wondered whether a similar program had been considered for the HPV vaccine. The disease prevented is fairly dramatic. Ms. Stokley said this would be something to consider.

Dr. Schuchat indicated that she had their communication staff reach out to the smoking team, because that has been a phenomenally effective and successful campaign. They are also reaching out to cervical cancer survivors and others. Her team was stunned to find out that the smoking campaign was $50 million, and they do not currently have the resources to do this but would love to be able to follow that model.

Dr. Kempe commented on a number of studies that are being conducted from the parent perspective. Based on qualitative data, there seems to be a real concern about the 11 through 12 year old age group and the message that this confers to children. Based on her qualitative work, parents tend to be far more accepting after ages 13 through 15. This is also known from the physician perspective. Based on the results of a number of surveys, physicians are more concerned about approaching parents and children at 11 through 12 versus 13 and older. She believes they either have to change that or rethink the timing of when the vaccine is recommended. While she did not think that was preferable based on the science, this concern is consistently observed. Based on surveys of physicians, there may have to be a better plan about how this is being presented from the physician side. A lot of her surveys indicate that physicians feel in a bind about the need to discuss sexuality when talking about this vaccine with 11 through 12 year old children, and with their parents. Rather than presenting this as a cancer prevention vaccine, some physicians feel it is unethical to give this vaccine without discussing sexuality. If the profession is confused about this, a better action plan is needed.

Dr. Whitley-Williams (NMA) inquired as to whether there was any information regarding whether there is any impact on the data comparing receipt of the vaccine in the public versus the private sector.

Ms. Stokley responded that she would have to check into this, though she did know that those who are publicly insured tend to have higher initiation rates than those who are privately insured. However, the pattern does not maintain with 3 doses. She was not sure whether this had been assessed by private physician versus federally qualified health center (FQHC) or public health department.

Ms. Pellegrini asked whether there was any information about the extent to which the schedule itself contributes to either the drop off or the hesitancy as a factor. This is a very challenging schedule for parents of teenagers. She suggested that consideration be given to whether there are any messages that can be given to parents about whether there is any flexibility in the schedule.

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Ms. Stokley responded that the 2012 survey included questions to try to further understand the issue of drop off for those who initiated but did not complete. Since the data are so new, they have not had a chance to fully assess that, though it is planned. With the qualitative work, they frequently hear that a lot of parents do not even know that there are three doses. Some education needs to be done when getting the first dose. They need to be told that before they even leave the office, it is critical to schedule the second and third doses. She recognized how difficult it is for parents to remember, and to keep those appointments. One method she heard of that is being used by Kaiser is that before patients leave the office a sticker is placed on their insurance card with the date of their next appointment. That is a simple way to remind parents when to return that does not require mailing or phone calls. She encouraged providers to think about simple ways to keep it fresh in parents' memories.

Dr. Temte said he thought NIH had a study underway to examine inappropriate schedules and immunogenicity.

Dr. Bennett asked about coverage in the young adult population. Given what is known about how difficult it is with younger age groups, she wondered whether any attention was being focused on the young adult group 18 through 26 years old, and if there were any plans to do catch-up with that population.

Ms. Stokley replied that the NIS captures vaccination coverage data among young women and men. Based on those data, coverage has increased for 18 through 21 year olds. It was not clear whether that was due to vaccination during that age, or young teens aging into that group causing the coverage to increase. Coverage still remains very low in that group. The priority has been focusing on the 11 through 12 year old and the adolescent group. That was not to say that older women are not important. Obstetricians and other groups who see these patients must encourage and provide the vaccine.

Dr. Sun (FDA) wondered whether any evaluation had been done regarding why certain states were particularly successful (e.g., Nebraska, Massachusetts, California, et cetera).

Ms. Stokley responded that they have talked to some of the states. The Northeast especially tends to have strong vaccination programs in general, with high coverage for infant vaccines as well. They have very strong relationships with the healthcare community and physicians, and work very closely with them to implement vaccine recommendations. Some of it has to do with political will and support, and financial support from within the state. South Dakota used to have one of the highest rates. Their governor was very supportive, but a lot of that funding that allowed them to provide the vaccine for free to all girls has been eliminated. Coverage there is beginning to decrease.

Dr. Coyne-Beasley indicated that her research supported what Dr. Kempe reported, that there is vaccine hesitancy at a younger age among providers as well as parents. A major reason for that focus is the desire to give the vaccine to young people before they are exposed to the infection. While she agreed that young adults are really important, exposure to all sexual activity must be addressed—not just sexual intercourse. She expressed hope that at some point, this vaccine could be given at birth like hepatitis B. While it is exciting for coverage to be at 20% for boys, that is actually less than the first year of routine recommendations for girls in terms of uptake. She thinks many parents of boys still consider this to be a vaccine for girls to prevent cervical cancer. While she applauded the materials CDC developed, she emphasized the continued need to do more work regarding boys.

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Dr. Moore (AIM) reported that one thing that has been effective for her on the frontlines was paraphrasing something Dr. Frieden has been saying that every routine vaccine is given as soon as it is immunologically appropriate, and also hope that the recipient never encounters the pathogen they have been vaccinated against. There is nothing unusual about giving HPV at age 11 or 12. There is nothing to excuse. Giving the vaccine at 11 or 12 is when it is immunologically appropriate. It has nothing to do with behavior. It is just like every other vaccine. There is no reason to wait until the last second to vaccinate someone against HPV anymore than measles, hepatitis B, or anything else. That messaging seems to work well. The other thing that is working well in Tennessee is introduction of the 3-star visit. Tennessee does have a Tdap requirement for middle school, and she has been pushing the concept of 3-star visits for pre-teens. A 3-star visit is a Tdap, meningococcal conjugate, and an HPV vaccine all during the same encounter. Continuous quality improvement metrics can be done at all health departments looking at the VFC-eligible pre-teens who present for a Tdap. If they walk out the door with all three, the nurse gets a 3-star visit. These reports are being sent out monthly by county and region, and a remarkable increase has been observed in 3-star visits, because "what you measure, you accomplish." This concept seems to be resonating with the healthcare providers.

Dr. Reingold reminded everyone that Dr. Frieden pointed out in his opening remarks the previous day that the US is lagging behind Rwanda in terms of coverage. However, Rwanda vaccinates in schools. While in the US there is an emphasis on the medical home, many rich countries also use schools to immunize children. He wondered whether CDC had any demonstration projects evaluating school-based HPV vaccination.

Ms. Stokley replied that Dr. Kempe was involved with that as well. It is challenging in the US to do school-located vaccination. There are several logistical barriers in terms of just how the US healthcare system works, how vaccines paid/reimbursed for, parental consent issues, et cetera. When parents are asked about school-located vaccination, in general they are not opposed to it. However, they tend to prefer the medical home and private physician. While this has been more successful with influenza vaccine, it has been very challenging to vaccinate large groups of teens with HPV.

Dr. Middleman (SAHM) commented that schools are great sites, but it depends on the school and the make-up of the school. Houston had a vaccination program in the fall of 2012 in which 522 children participated. Over 440 HPV vaccines were given. There are varying populations in which it is acceptable to get parental consent, and there are ways of doing this. It is very geographically and culturally related, and requires more study.

Dr. Temte mentioned that in his practice, he is starting to approach the 11 through 12 year olds by asking if they wear bike helmets and if their parents are promoting that. Then he asks when they put it on—before they get on the bike, when they are riding the bike, when a car is about to hit them or after the car has hit them. He gets a unanimous "before you get on the bike."

9-Valent (9vHPV) HPV Vaccine Program Design

Alain Luxembourg, MD, PhD
Director, Clinical Research
Merck

Dr. Luxembourg reported on a new 9-valent HPV vaccine from Merck. The currently licensed vaccine has the potential to cover approximately 70% of cervical cancers (types 16/18). These numbers are worldwide. The 9-valent vaccine, which includes the 5 next most frequent types worldwide, has the potential to cover 90% of cervical cancers. In terms of pre-cancers, the 9-

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valent vaccine also has the potential to substantially increase coverage from approximately 50% with the current vaccine for high grade lesions, CIN2/3, to about 75% to 85%. This coverage essentially matches the best screening programs. The 9-valent vaccine also has the potential to substantially increase the prevention of CIN1. Cervical cancer is not the whole story. There is also substantial additional coverage for dysplasia, which certainly has a lot of impact potentially in countries with cervical cancer screening [*Sanjose et al. Lancet Oncol. 11:1048-56 (2010)*].

The goal with the 9-valent vaccine is to have something that is very similar to the quadrivalent vaccine. It is adjuvanted with the same adjuvant, amorphous aluminum hydroxyphosphate sulfate (AAHS), and it contains L1 virus-like particle (VLP). It contains the same four VLPs as the quadrivalent vaccine (6, 11, 16, 18), which are referred to as the "original types." It also contains 5 additional types (31, 33, 45, 52, 58), which are referred to as the "new types." The 9-valent vaccine is administered the same way as the quadrivalent on a 3-dose schedule. The target age is the same (males and females 9 through 26 years of age).

The product is designed to demonstrate that there is efficacy for the original types compared to the quadrivalent vaccine, that coverage is broadened to the new types, and to demonstrate that safety and duration of protection are comparable to that of the quadrivalent vaccine. The ultimate goal is to transition completely from quadrivalent to 9-valent vaccine with time. To accomplish these goals, the clinical program was designed around 5 main goals, which are to demonstrate that the 9-valent vaccine:

- ❑ Provides a similar level of protection as quadrivalent vaccine against HPV infection and disease due to the original types
- ❑ Is highly protective against HPV infection and disease caused by the new types
- ❑ Offers substantial protection against overall cervical/external genital disease, cytological abnormalities, and invasive procedures
- ❑ Has non-inferior immunogenicity in adolescents versus young women
- ❑ Has an acceptable safety/tolerability profile

Adolescents cannot be directly assessed for HPV efficacy for two reasons: 1) gynecological examinations are not feasible in that age, and 2) they are not exposed to HPV very much. Similar to studies conducted in that age range for licensure of GARDASIL®, the quadrivalent vaccine, immunobridging will be conducted between young women where efficacy is being established to adolescents.

These 5 goals will be accomplished with 6 studies for the initial filing. The pivotal efficacy study (001) is being conducted in young women 16 through 26 years of age, which is very similar to what was done previously in the quadrivalent program. This study is now completed, with extensions ongoing. The study is meant to provide dose ranging, efficacy, immunogenicity, and safety data. Two immunobridging studies (002 and 009) are being conducted in adolescents. Study 002 is being conducted in boys and girls 9 through 15 years of age, and women 16 through 26 years of age. The purpose of this study is adult-to-adolescent immunobridging. The base study is completed, with an extension ongoing for long-term effectiveness. Study 009 was conducted in girls 9 through 15 years of age, and has completed. The purpose of this study was qHPV-to-9vHPV immunobridging. Two concomitant use studies (005 and 007) have been completed. Study 005 was conducted in boys and girls 11 through 15 years of age to assess concomitant use of Menactra® (meningococal vaccine) and Adacel® (Tdap vaccine). Study 007 was conducted in boys and girls 11 through 15 years of age to assess concomitant use of Repevax® (Tdap/polio vaccine). A study in prior quadrivalent vaccine recipients (006), which has been completed, was conducted in girls and women 12 through 26 years of age to assess

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safety. Given the large number of recipients of quadrivalent vaccine, it is very likely that some of them will be interested in receipt of the 9vHPV vaccine. Protocol 003, an immunobridging study which assesses males 16 through 26 years of age, is ongoing. Data from this study should be available before the end of 2014.

There are a number of development considerations in the 9vHPV vaccine clinical program. The first consideration is that a placebo cannot be used, because there is a very effective existing vaccine and people cannot be permitted to develop pre-cancers during a clinical trial. The consequence is that an active comparator must be used, so the 9-valent vaccine is compared to the existing quadrivalent vaccine. The quadrivalent vaccine is highly efficacious, and few disease endpoints are expected with the original types. Thus, it is not feasible to conduct a head-to-head comparison based on disease endpoints or even on infection endpoints. Therefore, the strategy has been adjusted. The quadrivalent efficacy finding with respect to the original type will be bridged to the 9-valent vaccine based on the demonstration of similar immunogenicity. There has been regulatory agency concurrence on that. Disease endpoints will also be collected in order to show that there will be very few diseases, and to assess whether there is a negative trend in efficacy.

With regard to Study 001, the basis of licensure and the basis of demonstration of efficacy is different for the original types and for the new types. For the original types, it will be demonstration of non-inferior immunogenicity. For the new types, it will be demonstration of efficacy. This study is designed to answer a number of questions. The primary objective for the original types is non-inferior immunogenicity for 9-valent versus quadrivalent vaccine. The exploratory objective is incidence of 6/11/16/18-related persistent infection and disease, which includes comparison with the historic placebo arm of the quadrivalent vaccine studies. The primary objective for the new types is reduction of combined incidence of 31/33/45/52/58-related CIN 2/3+, VIN 2/3+, VaIN 2/3+, with the basis for licensure/cancer efficacy similar to that of quadrivalent vaccine. The secondary/exploratory objective for the new types is reduction of incidence of 31/33/45/52/58-related cervical, vulvar, vaginal disease (any grade), 6-month and 12-month persistent infection, and Pap test abnormalities. Irrespective of HPV, there is a secondary/exploratory objective to assess the impact of 9-valent vaccine on overall cervical, vulvar, and vaginal disease, Pap test abnormalities, and cervical and external genital procedures.

In terms of the Study 001 flowchart, there is a dose-ranging component and subjects are enrolled in two parts. Subjects enrolled in Part A were assessed for several doses, and based on that, the study was continued into the Phase III evaluation keeping only the selected dose for the long-term efficacy assessment. Subjects were enrolled in Part B with the selected dose and the quadrivalent control arm. That design allowed prompt movement to Phase III. During the efficacy evaluation, which lasts up to 4 years following the end of the vaccination period, each subject receives a gynecological examination, Pap test, and gynecological sampling. The sampling is very intensive in an effort not to miss any endpoints. The program is designed to bridge efficacy findings in young women to adolescents based on similar immunogenicity. In the GARDISIL® program, there was also immunobridging. Non-inferiority was demonstrated in girls 9 through 15 years old and young women 16 through 26 vaccinated with quadrivalent vaccine, which was the extent of immunobridging in the quadrivalent program. In the 9-valent program, immunobridging was used more extensively.

As noted earlier, Protocol 001 included immunobridging for the 4 original types in young women receiving the 9-valent compared to young women receiving quadrivalent. Protocol 002 will provide immunobridging for all 9 types between girls receiving 9-valent and young women receiving 9-valent and boys receiving 9-valent compared to young women receiving 9-valent. A

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supportive analysis will compare girls receiving 9-valent with girls receiving quadrivalent, with a comparison for the 4 original types. Finally, there will be a comparison between Protocol 001 and 002 for girls receiving 9-valent versus young women receiving quadrivalent. The design is very comprehensive in order not to miss any potential discrepancy. The goal is to demonstrate that the two vaccines perform the same.

Turning to safety, the safety database is substantial and is similar to or greater than the database previously used for the initial licensure of the quadrivalent vaccine (~13,300 subjects administered 9vHPV vaccine; ~8,000 young women, 16 to 26 years of age; ~5,300 adolescent girls and boys, 9 to 15 years of age). Safety endpoints are collected the same way as in the quadrivalent program, with methods that are equivalent to or exceed those used for the quadrivalent program (elevated temperatures; injection-site and systemic adverse experiences; systemic adverse experiences regardless of causality D1 to Mo12, (or D1 to end-of-study for studies of less than 12-month duration; vaccine-related systemic adverse experiences and deaths for the entire study period; and new medical history).

In summary, the program is designed to demonstrate that the 9-valent vaccine will broaden cervical cancer and pre-cancer coverage. The vaccine has the potential to prevent approximately 90% of cervical cancers and about 80% of high-grade cervical disease (CIN 2 or worse). The comprehensive clinical development program is based on 6 Phase III studies, which are now completed. The primary endpoints have been met for all of the studies, and Merck is now on track to submit a BLA for the vaccine with the FDA before the end of 2013. Merck plans to present the studies in November 2013 at the EUROGIN conference. Mindful of the EUROGIN embargo policy, Merck will not be able to discuss the results of the studies at this meeting, but looks forward to sharing the results with ACIP during a future meeting.

Discussion Points

Regarding the measured outcomes, Dr. Coyne-Beasley pointed out that it is currently known that the quadrivalent vaccine offers protection for anal cancer. However, there was no mention of anal cancer in this presentation. She also inquired as to whether any impact was expected on oropharyngeal cancer with the addition of the 5 new serotypes, which is particularly important since oropharyngeal cancer is expected to exceed cervical cancer in the future.

Dr. Luxembourg replied that anal cancer was not included for two reasons. When the program started in 2007 the quadrivalent trial was not completed for that endpoint. Also, the main types of anal cancer are supposed to match the original types. So, the bridging of the efficacy types will be based on immunobridging similar to cervical cancer endpoints. Serotype 16 is the main serotype found in oropharyngeal cancer. There is a small benefit by adding new types, but it is only incremental.

Dr. Duchin wondered if Dr. Luxembourg could comment on the limitations of immunobridging studies in the absence of an immune correlate of protection, which he prefaced by saying that it was not necessarily specific to Merck's vaccine. He also inquired as to whether consideration was given to evaluating a 2-dose series.

Dr. Luxembourg responded that immunobridging is an accepted method to do this. In a way, this is unprecedented because new types are being added for a vaccine where there is no threshold of response that is established to be protective. Therefore, the only way to do this is to compare two vaccines that are known to be protective. Merck hopes to demonstrate not only non-inferior immunogenicity, but also that immunogenicity is the same. Supportive analyses will assess disease endpoints, and additional immunoassays will be conducted as well. In the end,

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it will be very apparent whether the two vaccines behave similarly. Merck acknowledges that consideration of the 2-dose series is important, and is considering this.

Dr. Reingold recognized the challenge in not being able to have a placebo group, but noted that in terms of the comparison with historical controls to assess comparability of the new vaccine against the 4 types in the quadrivalent, it is known that the prevalence of HPV is decreasing. He would assume the incidence would decrease in this age group as well, so he was not quite sure he bought the comparison of historical controls from the prior trial. He asked Dr. Luxembourg whether he could convince him that he was wrong about that.

Dr. Luxembourg responded that Merck is aware of the limitations of comparing across program arms, across studies, and across programs that have been conducted across several years. It is important to keep in mind that Protocol 001 has been conducted in 18 countries, in 5 continents, in countries with substantial vaccine coverage, and in countries without substantial vaccine coverage. This is why there are supportive analyses.

Dr. Vazquez asked whether Merck foresaw that the addition of the 5 serotypes to the new vaccine would allow coverage for new types of cancers or better coverage for the outcomes that have already been evaluated with the current vaccine.

Dr. Luxembourg replied that the addition of the new types will potentially allow coverage for disease, pre-cancer, cancer, and infections that are caused by the new types that are not covered by the current vaccine. The International Association of Research on Cancer has recognized 12 HPV types as oncogenic, high risk types, and also anogenital cancers. Serotypes 16 and 18 are the two most prevalent, and the 5 new types are the 5 next most prevalent.

Thinking of the bigger picture, Dr. Schaffner (NFID) pointed out that Dr. Luxembourg used the word “boys” twice in his presentation and “young men” once. Since eventually it would be preferable for this vaccine to be used in boys and girls, he suggested including a slide at the beginning to demonstrate what cancers the additional types would address in the reproductive tracts in boys and girls, and then focus down on the issue to remind everyone that this is the beginning of a larger program designed to affect boys and girls.

Dr. Luxembourg thought this was an excellent idea. The main piece is Protocol 001 in young women, but certainly the goal is to include boys and men, and hopefully they will be part of the indications also. There are certainly incremental benefits in the male population as well. Gender-neutral vaccination will have a better outcome in general than gender-specific vaccination.

Dr. Gellin (NVPO) was encouraged that Merck is considering a 2-dose evaluation. When doing so, he suggested assessing the intervals to try to determine the optimal interval to achieve the best response.

Dr. Schuchat requested clarity regarding whether Merck is seeking an indication for boys, or if the conversation would be about some sort of off-label recommendation for boys.

Dr. Luxembourg clarified that Merck is seeking a full transition from quadrivalent to 9-valent vaccine for all indications, and for all populations for whom the vaccine is indicated. That includes boys and men.

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Dr. Markowitz indicated that the HPV Working Group would be reviewing and considering issues related to the 9-valent vaccine, and would plan to review with the ACIP some of the issues such as the burden of disease due to the additional 5 types. These vaccines will protect against the types of cancer already under consideration—not additional types of cancers. About 30% of cervical cancers are caused by types that are not covered by 16 and 18.

Updated ACIP Statement

Lauri Markowitz, MD
HPV Vaccine Working Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Markowitz reviewed the ACIP statement for the bivalent and quadrivalent vaccines. To review, the following are published ACIP recommendations for HPV vaccines:

- 2007 ACIP Statement [*MMWR* Recomm Rep 2007;56:1-24]
  - Recommendation for routine vaccination of females at age 11 or 12 years with quadrivalent HPV vaccine

- 2010 Policy Note [*MMWR* 2010;59:626-9]
  - Recommendation for routine vaccination of females with bivalent or quadrivalent HPV vaccine

- 2010 Policy Note [*MMWR* 2010;59:630-2]
  - Quadrivalent HPV vaccine may be given to males 9 through 26 years

- 2011 Policy Note [*MMWR* 2011;60:1705-8]
  - Recommendation for routine vaccination of males at age 11 or 12 years with quadrivalent HPV vaccine
  - This was the only recommendation for which GRADE was used, because GRADE had just been adopted by ACIP before that time

The objectives of the updated statement are to consolidate the recommendations for females and males; consolidate information and recommendations for bivalent and quadrivalent vaccines; harmonize wording that differed in policy notes/statement; and update background information and data regarding efficacy, safety, immunogenicity, impact monitoring, et cetera. Of note is that the work on this statement will overlap with the consideration of the 9-valent vaccine. The working group felt that having the updated ACIP statement would facilitate efforts for development of future policy.

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In terms of the construction of the updated HPV vaccine ACIP statement, the background sections are as follows:

- Biology, immunology, epidemiology and natural history

- Clinical sequelae
  - Cancers
  - Anogenital warts
  - Recurrent respiratory papillomatosis (RRP)

- Prevention, treatment, and cervical cancer screening
  - Prevention of sexual transmission of HPV, non-vaccine
  - Treatment of HPV related disease
  - Cervical cancer screening
  - Selected health care and research laboratory workers (discussed during the June 2013 ACIP meeting regarding risk and protective factors for these workers)

The background section regarding selected health care and research laboratory workers will address the following:

- Health care providers performing laser or electrosurgical procedures
  - Appropriately ventilated room using standard precautions and local exhaust ventilation (e.g., smoke evacuator)
    - Use of N-95 respirator to be discussed at upcoming Hospital Infection Control Practices Advisory Committee (HICPAC) meeting
    - Final wording will be consistent with CDC guidelines as a result of that meeting

- Research HPV laboratory workers working with wild type virus or "quasi virions"
  - Proper infection control measures; at minimum biosafety level 2 (BSL2)

The vaccine sections will be as follows:

- HPV vaccines and evaluations (a short section on the vaccines themselves and the clinical evaluations that were done for efficacy and immunogenicity that led to licensure)

- HPV vaccines: quadrivalent and bivalent vaccines

- Efficacy
  - Updated data from pivotal efficacy trials
  - Duration of protection
  - Evaluation of cross protection (not included in the previous statement)

- Immunogenicity
  - Immunobridging
  - Spacing of vaccine doses, concomitant administration
  - Persons with HIV infection

- Safety
  - Data from clinical trials
  - Post-licensure evaluations

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There will then be three short sections, including the following:

- ❑ Economic burden of HPV disease and cost-effectiveness of vaccination, which will draw largely from previously published data on cost-effectiveness of HPV vaccination
- ❑ HPV vaccination program in the US, which will review the most recent coverage data
- ❑ Summary of rationale for HPV vaccination recommendations

Recommendation sections will be included for the following:

- ❑ Recommendations for females
- ❑ Recommendations for males
- ❑ Administration, intervals, concomitant administration, interchangeability
- ❑ Special situations
- ❑ Precautions and contraindications

Recommendations for females currently in the draft are as follows:

> ACIP recommends routine vaccination of females aged 11 or 12 years with either HPV2 or HPV4 administered as a 3-dose series. The vaccine series can be started beginning at age 9 years.
>
> HPV4 and HPV2 protect against HPV 16 and 18, types that cause cervical cancer and other HPV-associated cancers. HPV4 also protects against HPV 6 and 11, types that cause genital warts.
>
> Vaccination also is recommended for females aged 13 through 26 years who have not been previously vaccinated or who have not completed the 3-dose series.
>
> If a female reaches 27 years of age before the vaccination series is complete, the second or third doses of vaccine can be administered after age 26 years to complete the vaccination series.
>
> Prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV tests, or HPV antibody) to establish the appropriateness of HPV vaccination are not recommended.

Recommendations for males currently in the draft are as follows:

> ACIP recommends routine vaccination of males aged 11 or 12 years with HPV4 administered as a 3-dose series (GRADE recommendation category: A, evidence type: 2*). The vaccination series can be started beginning at age 9 years.
>
> Vaccination with HPV4 is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated.
>
> If a male reaches 27 years of age before the vaccination series is complete, the second or third doses of vaccine can be administered after age 26 years to complete the vaccination series.

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*Recommendation category A: recommendation that applies to all persons in an age or risk-based group. Evidence type 2: randomized controlled trials with important limitations or exceptionally strong evidence from observational studies.

Comments were received from ACIP and working group members, one of which was that the male and female recommendations should no longer be separated. Dr. Markowitz shared the following mock-up of what that might look like for ACIP's consideration:

Alternative recommendation wording:

ACIP recommends routine vaccination of children aged 11 or 12 years with either HPV2 (girls) or HPV4 (boys* and girls) administered as a 3-dose series. The vaccine series can be started beginning at age 9 years.

Vaccination also is recommended for girls and women aged 13 through 26 years and for boys and men aged 13 through 21 years, who have not been previously vaccinated or who have not completed the 3-dose series. Men aged 22 through 26 years may be vaccinated.

If woman or man reaches age 27 years before the vaccination series is complete, the second or third doses of vaccine can be administered after age 26 to complete the vaccination series.

**GRADE used for recommendation: Recommendation category A: recommendation that applies to all persons in an age or risk-based group. Evidence type 2: randomized controlled trials with important limitations or exceptionally strong evidence from observational studies.*

The use of GRADE for the male recommendation will be addressed in the following two sections of the document:

- In *Methods* at beginning of document:

  "Grading of Recommendations Assessment, Development and Evaluation (GRADE) was adopted by ACIP in 2011 and recommendations for males were considered using GRADE. Factors considered in determining the recommendation included benefits and harms, evidence type, values and preferences, and health economic analysis."

- In *Recommendations*:
  - Grading category and evidence type will be noted within the recommendation statement
  - A link to the GRADE evidence tables online will also be included

There are four sections to address special situations, three of which have been in previous statements or policy notes:

- Persons with abnormal Pap, genital warts, et cetera
- Immunocompromised persons
- Men who have sex with men (MSM)
- Children with history of sexual abuse or assault (new section)

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For immunocompromised persons, the wording in male and female recommendations was harmonized. The 2011 Male Policy Note states that, "For immunocompromised males, ACIP recommends routine vaccination with HPV4…and vaccination through age 26 years for those who have not been vaccinated previously…." The 2010 Female Policy Note, before there was very much data, stated that, "HPV2 and HPV4 are not live vaccines, and can be administered to females who are immunosuppressed…" For the updated draft, the language was adopted from the male policy statement stating that, "ACIP recommends routine vaccination with HPV4 or HPV2 for females and with HPV4 for males. Vaccination is recommended through age 26 for those who have not been vaccinated previously or who have not completed the 3-dose series."

In the new section in special situations for children with a history of sexual abuse or assault, a recommendation is made to start vaccination at age 9 years. The statement is also made that vaccine will not protect against progression of infection to disease or promote clearance of infection, but will protect against vaccine types not yet acquired. As a reminder, a letter was received a year ago from the Texas Pediatric Society urging ACIP to make this recommendation. ACIP felt at that time that there was already a recommendation to allow vaccination at age 9, so a separate vote was not needed. However, it was agreed that this would be included in the updated ACIP statement. Discussions were held with a variety of other groups that issue guidance for providers who are specifically caring for these types of children.

The *Precautions and Contraindications* section includes four sections (e.g., hypersensitivity or allergy, acute illness, preventing syncope, and pregnancy), all of which have been in previous ACIP statements or policy notes. These are basically unchanged, except for the pregnancy section. No change has been made in the recommendation. HPV vaccine is still not recommended for pregnant women. Mention of the quadrivalent vaccine in pregnancy registry reporting has been removed as discussed during the June ACIP meeting, but language is included to continue to report to the manufacturer and VAERS. The bivalent registry is continuing. Dr. Markowitz highlighted the fact that this was placed in the *Precautions and Contraindications* section per guidance in pregnancy developed by ACIP in 2008. In the 2007 statement, *Pregnancy* was in a separate section by itself. In the 2010 Policy Note, it was included in a *Precautions and Contraindications.* Pregnancy is listed as a "precaution" in ACIP General Recommendations Statement and in the adult schedule. Pregnancy wording, which has been in previous statements and policy notes and will basically remain the same, follows:

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

Comments received to date include the following:

- Include more post-licensure safety data, specifically about deaths that have been reported to VAERS and the interpretation
  - The Immunization Safety Office (ISO) has provided a paragraph on this that will be included in the statement

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- Reorganize wording of routine recommendations
  - In the current draft, wording is separate for females and males
  - The alternative wording is to state recommendations for 11 or 12 year olds and then discuss different vaccines, and age range for females and males

The next steps are to incorporate comments from the working group and ACIP members. Although there are no new recommendations in the statement, ACIP will vote on the updated statement in its entirety. That will probably occur during the February 2014 meeting. Dr. Markowitz invited all comments, and requested that the following questions be addressed specifically:

- Should the wording of the vaccination recommendations for females and males be separate or combined?

- Where should the *Pregnancy* section be placed within the statement?

Discussion Points

Dr. Temte reminded everyone that in the past, ACIP has made a priority of revisiting, revising, or reaffirming all ACIP recommendations on about a five-year schedule. This statement was being put forward for reaffirmation, and did not include anything new. He placed a strong emphasis on carefully reading what was sent out, and providing feedback to the writing team.

Dr. Baker noted that sexual abuse in children begins as early as the first year of life. This is a prophylactic not a treatment vaccine. She inquired of the manufacturer as to whether any studies were planned in younger children.

Dr. Friedland (GSK) responded that there is a study underway with GSKs vaccine HPV vaccine, Cervarix®, in 4 through 6 year old girls in Latin America.

Dr. Duchin supported the suggestion to combine the recommendation for females and males, but he thought it would be useful in the text to explicitly call out the benefits to the different genders so that providers with an interest in that information can readily find it in the document.

Dr. Rubin asked whether the working group had considered a preference for HPV4 over HPV2 for HIV-infected young women in recognition of the burden of genital warts and the difficulty of treatment in that population.

Dr. Markowitz responded that the working group had not discussed this specifically, but this is being raised in guidelines being written by groups that deal specifically with HIV-infected individuals. There are studies underway to address these issues, and the benefits of the vaccines. The obvious difference is that genital wart protection is not provided.

Regarding the lack of success in completion of the HPV vaccine series, Dr. Gorman (NIH) wondered whether the working group would reconsider the recommendation to delay during pregnancy.

Dr. Markowitz replied that one issue is that the focus is on the younger age group, and the problem with not completing the vaccination series is not really the result of pregnancy issues.

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Dr. Gorman (NIH) said that while he would agree with that as an assessment, making a recommendation to cease during pregnancy is another barrier to completing the series.

Dr. Temte added that the standard of care is to have a 6-week post-partum visit after delivery. Given that about two-thirds of women comply with that visit, it is a very good opportunity to catch up on things like that. This is an area that would benefit from ACIP working with its partners such as ACOG, AAF, and nurse midwives to get word out that if a dose is deferred, a natural follow-up visit is an ideal time to administer it.

Dr. Riley (ACOG) suggested that if the goal was completing the series, it should be given before they leave the hospital. There is precedence for that with rubella vaccine. The problem for almost every vaccine is knowing whether someone has actually started the series. People deliver in places where they did not receive their care, so a registry may not be helpful in this case.

Vaccine Supply

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

During this session, Dr. Santoli reported on the vaccine supply status of pertussis-containing vaccines and Hib-Hep B combination vaccine.

In terms of pertussis-containing vaccines, sanofi pasteur's pertussis-containing vaccines, Daptacel® (DTaP), Pentacel® (DTaP-IPV-Hib) and Adacel® (Tdap) have been in short supply since mid-August. There was a longer issue with Pentacel® prior to that, but there was a specific issue with regard to pertussis-containing vaccines. However, shipping of these vaccines resumed in mid-October. As production of these products continues to increase, supply will flow, but will remain constrained over the next several months.

GSK has taken steps to meet increased demand for pertussis-containing vaccines and anticipates being able to address gaps related to these supply limitations, using a combination of products and presentations. However, during this time period, backorders and delays in deliveries may occur related to Tdap vaccine, but are expected to be short in duration. Also, provider preference for vaccine presentation (syringes/vials) may not be able to be accommodated at times during this period.

Merck's Hep B-Hib combination vaccine, Comvax®, is not currently available for distribution. It is anticipated to be available again in December 2013. In the interim, Merck is able to supply sufficient quantities of the component vaccines to meet historical demand for the component Merck products as well as for Comvax® vaccine.

CDC's Vaccine Supply/Shortage Webpage can be found at:
http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

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General Recommendations

Introduction

Dr. Jeff Duchin
ACIP General Recommendations Working Group Chair

Dr. Duchin reminded everyone that the General Recommendations document is published by the *MMWR* every 3 to 5 years, and addresses a broad range of immunization issues that are relevant to all vaccines as opposed to the vaccine-specific publications. The General Recommendations are intended to address topics that cannot be attributed to a single vaccine, but that are germane to the practice of immunization in general. The General Recommendations are directed to providers who give a large variety of vaccines every day, and who come from variable backgrounds and training (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants, et cetera). The General Recommendations are intended to provide resources through text, tables, and figures that can be used as a handy and easy to interpret reference. The last version was published in January 2011. A number of topics are being revised, including the following:

- Timing and spacing of immunobiologics
- Contraindications and precautions
- Preventing and managing adverse reactions
- Reporting adverse events after vaccination
- Vaccine administration
- Storage and handling of immunobiologics
- Altered immunocompetence
- Special situations
- Vaccination records
- Vaccination programs
- Vaccine information sources

The topics addressed during this session included *Vaccination Administration and Vaccination Records*.

Specific topics in *Vaccination Administration* include the following:

- Infection Control and Sterile Technique
  - General Precautions
  - Vaccine Administration: Preparation and Timely Disposal
  - Safe Use of Needles and Syringes

- Route of Administration
  - Injectable Route
    - Intramuscular
    - Subcutaneous
    - Intradermal
  - Oral Route
  - Intranasal Route
  - Multiple Injections
  - Jet Injections

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- Infection Control and Sterile Technique
  - General Precautions
  - Vaccine Administration: Preparation and Timely Disposal (MAJOR ADDITIONS)
  - Safe Use of Needles and Syringes (MAJOR ADDITIONS)

- Route of Administration
  - Injectable Route
    - Intramuscular
    - Subcutaneous
    - Intradermal (NEW SECTION)
  - Oral Route
  - Intranasal Route
  - Multiple Injections
  - Jet Injections

- Methods for Alleviating Discomfort and Pain Associated with Vaccination

- Clinical Implications of Nonstandard Vaccination Practices (EXTENSIVE DISCUSSION – PATIENTS WITH HEMOPHILIA)

- Tables (dose/route and needle length)

Specific topics in *Vaccination Records* include the following:

- Records of Health Care Providers
- Patient Records
- Immunization Information Systems
  - NEW ADDITIONS – SPECIAL PRESENTATION ON CLINICAL DECISION SUPPORT for Immunization (CDSi)

The remaining sections to be revised include:

- Altered Immunocompetence
- Storage and Handling of Immunobiologics
- Vaccination Programs

The working group expects to present the entire document to the ACIP for a vote during the June 2014 meeting.

Update: Vaccine Administration and Vaccine Records

Dr. Andrew Kroger
General Recommendations Working Group

During this session, Dr. Kroger provided an update on the revisions under discussion during this session. He noted that ACIP members should have two draft copies for each of these sections, one with tracked changes and one clean copy.

With regard to vaccine administration, he covered the areas that engendered a lot of discussion in the working group:

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- ❑ Changes to Infection Control and Sterile Technique
- ❑ Addition of Information on Intradermal Route
- ❑ Vaccination Route: Intramuscular versus Subcutaneous

Two components of changes to infection control and sterile technique generated some discussion in the working group. The first was a new section titled "Vaccine Administration: Preparation and Timely Disposal," which appeared on Page 1, Line 13 (P1, L13) of the tracked copy. The second regarded the revision of the language surrounding Occupational Safety and Health Administration (OSHA) regulations with respect to preventing needlestick injuries. The new language for "Vaccine Administration: Preparation and Timely Disposal" reads:

> "Vaccines should be drawn up in a designated clean medication area that is not adjacent to areas where potentially contaminated items are placed. Multi-dose vials to be used for more than one patient should not be kept or accessed in the immediate patient treatment area. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment that could then lead to infections in subsequent patients. If a multi-dose vial enters the immediate patient treatment area, it should be discarded after use. (REF http://www.cdc.gov/injectionsafety/providers/provider_faqs_multivials.html)." (P1, L15-22)

Also in the "Vaccine Administration: Preparation and Timely Disposal," language is included that reads:

> "In certain circumstances in which a single vaccine type is being used (e.g. in preparation for a community influenza vaccination campaign), filling a small number (10 or less) of syringes may be considered. When syringes are filled, the type of vaccine, lot number, and date of filling must be labeled on each syringe, and the doses should be administered as soon as possible after filling, by the same person who filled the syringes. Unused syringes that are prefilled by the manufacturer and activated (i.e. syringe cap removed or needle attached) should be discarded at the end of the clinic day." (P3, L10)

These two sections taken together have recently engendered a lot of discussion in the working group. Because of the shutdown, the working group did not really get a chance to talk among themselves. However, they did have an opportunity to see the slide set and the draft and already there has been a lot of discussion. Dr. Kroger shared some summary points about why this has been an issue, noting that it basically has to do with mass clinics and how to apply these two concepts together in a mass clinic. It is important to ensure that multidose vials are free of contamination. They should not be opened near a patient, so there has to be some distance between patients and the storage facility or the area where the syringes are going to be filled. There is also a recommendation that the same person who fills the syringe may also need to administer it. It has been pointed out that there will be rotation of staffs, feasibility issues, and this will be inefficient. The language about discarding doses that have already been opened can lead to concerns about vaccine wastage.

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This information is based on guidance that is already on CDC's website, where it has been for a while. CDC's Vaccine Administration Work Group, distinct from GRWG or ACIP, addresses vaccine administration and safe injection practices. It is true that that is a broader discussion that goes beyond vaccines, but there has been discussion about incorporating this content into the vaccine-specific "Pink Book" as CDC guidance, so this plays into the general recommendations as well. There is very strict guidance involving the use of multidose vials. As mentioned, the pre-filling of syringes must occur at a distance from patient presumably close to the storage unit. But what about satellite clinics where the storage unit is close to the patient? What to do about this is an important discussion point, keeping in mind that the other half of the guidance about pre-filling syringes is specific ACIP guidance. Manufacturer pre-filled syringes are preferred, but the end user can also pre-fill 10 syringes at a time perhaps from one multidose vial only and take those to the administration area. Another aspect that is less controversial is defining "same day" as "same clinic day," which has been a useful concept in general immunization practices. That is also new in this section.

Another issue regarding "Preparation and Timely Disposal" involves changes that were made with respect to needle safety. The goal here was to remove what previously existed in the 2011 recommendations, which was both a strong and a weak recommendation in the same place with respect to use of needle-shielding syringes or needle-free injectors. The strong recommendation read, "These federal regulations require that safety-engineered injection devices (e.g. needle-shielding syringes or needle-free injectors) be used for injectable vaccination in all clinic settings" (P4, L6 of current draft). The weak recommendation read, "Safety-engineered needles and syringes or needle-free injection devices are preferred and should be encouraged to reduce risk for injury" (P4, L19). The weak recommendation has now been struck.

In terms of vaccine route, the last general recommendations were published in January 2011 right before there was a lot of use of Fluzone® intradermal, so there was nothing on intradermal vaccination in the general recommendation. An entirely new section has been added on this (P11, L3) to accompany a discussion on intramuscular, subcutaneous, oral, and intranasal administration of vaccines. Language has been added to this based on communication with manufacturers, which is specific information about invalidating a dose of vaccine for one age group, and validating a dose given off label to another age group:

> "Intradermal influenza vaccine injection of someone 9 through 17 years of age can be counted as a valid dose on the presumption that their skin thickness is similar to someone 18 through 64 years of age. A dose of intradermal vaccine given to someone younger than 9 years of age or older than 64 years of age should not be counted as valid" (P11, L8).

A change was made to the needle length table, Table 10, for intramuscular injections in children 18 years of age and younger and adults 19 years of age and older. Children 3 through 18 years of age used to be combined with respect to the needle length for the specific injection site. This has now been split into children 3 through 10 years of age and children 11 through 18 years of age on the current table based on two publications on the ability to use these vaccines in an alternate site, the anterolateral thigh, and variation on the maximal needle length that would be allowed, which differs for the two age groups [Jackson LA, Yu O, Nelson JC, et. Al. The 15 fifth dose of Diphtheria, Tetanus and Acellular Pertussis Vaccine. Pediatrics 16 2011:127(3), p. e580-e588; Middleman, 1 A, Anding R, Tung C, Pediatrics 2010: 125(3), p. e1-e5].

Also with respect to route, there has been ongoing discussion about the clinical implications of non-standard vaccination practices (P15, L16). While ACIP does not recommend changing the

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route of administration, but does make some vaccine-specific recommendations with respect to whether the dose is counted. The 2011 General Recommendations state, "Hepatitis B administered by any route other than intramuscular, or in adults at any site other than the deltoid or anterolateral thigh, should not be counted as valid and should be repeated." In earlier discussions in the working group, this topic was addressed somewhat when special situations and vaccination of persons with bleeding disorders were discussed. The working group reaffirmed that providers should be given discretion. If they do not feel comfortable with the bleeding risk, they have the option of not vaccinating intramuscularly. In 2013, based on discussions involving vaccination of persons with bleeding disorders, the working group left the following permissive language:

> "When hepatitis B or any other intramuscularly administered vaccine is indicated for a patient with a bleeding disorder, the vaccine should be administered intramuscularly if a physician familiar with the patient's bleeding risk determines that the vaccine can be administered by this route with reasonable safety."

This raised the question regarding whether subcutaneous doses of hepatitis B vaccine to persons with hemophilia need to be repeated. This led to collaborations with ISO, other vaccine-specific groups, and hepatitis B vaccine subject matter experts (SMEs). There have been some HPV vaccine issues with this as well. The 2011 general recommendations allows subcutaneous administration of meningococcal vaccine based on CDC immunogenicity studies conducted in 2006 when the conjugate vaccine was introduced. The conjugate was intramuscular instead of subcutaneous like the polysaccharide vaccine, and a lot of errors occurred. The studies showed that this intramuscular vaccine could be administered subcutaneously [*MMWR* 2006;55:101-7]. However, this section is silent on other vaccines except hepatitis B vaccine, which must be repeated.

Data were found on hepatitis A that demonstrated good immunogenicity if administered subcutaneously [Ragni MV, Lusher JM, Koerper MA, et. Al. 20 Safety and Immunogenicity of Subcutaneous Hepatitis A Vaccine in Children with 21 Hemophilia. Hemophilia. 6: 2000, p. 98-103 (ADDED P16, L6)], so that was added to meningococcal conjugate vaccine for which a dose given subcutaneously would be accepted. However, there is insufficient evidence for other vaccines to add them to the list with hepatitis A and meningococcal vaccine. The package insert for HPV vaccine specifically states intramuscular administration. There has been a lot of guidance given that subcutaneous dosing of HPV vaccine should not be counted. That language remains in the general recommendations. The evidence is mixed for hepatitis B vaccine. There are ongoing discussions to conduct studies with the National Center for Birth Defects and Developmental Disabilities (NCBDDD) to assess patients with hemophilia and their immunological response to subcutaneous dosing of hepatitis B vaccine. It is common practice for providers to administer the doses subcutaneously on the order of 20%.

Shifting to vaccination records, a couple of changes were made. With respect to the provider records section, the working group wanted to add some language to clarify which specific vaccines are covered by the National Vaccine Injury Compensation Program (VICP). Thus, the following language was added:

> "This Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, whether administered to a child or adult, and even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine)" (P1, L13)

This is relevant because there are specific recording requirements for the National Vaccine Injury Compensation Act, including: date the vaccine was administered; the vaccine

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manufacturer; the vaccine lot number; the name, address, and title of the person administering the vaccine; and the date of the Vaccine Information Statement (VIS) administration and the fact that the VIS was given.

Also pertaining to vaccine records, new language has been placed in a section on "Immunization Information Systems" (IIS) that highlights what functions are carried out by an IIS, which are as follows:

- ❑ Prevent duplicate vaccinations
- ❑ Forecast when the next dose is due (NEW)
- ❑ Limit missed appointments
- ❑ Allow recall for those who missed appointments (NEW)
- ❑ Determine when vaccines need to be repeated (evaluation) (NEW)
- ❑ Reduce vaccine waste
- ❑ Reduce staff time required to produce or locate vaccination records or certificates

IIS should maintain interoperability with other electronic health record tools as part of an effort to improve the quality of care, reduce health disparities, engage patients and families in their health, improve the coordination of care, improve population health, and ensure adequate privacy and security protection for personal health information www.cdc.gov/ehrmeaningfuluse/introduction.html) (P2, L19). Depending upon the duration of the process for publishing the general recommendations, the working group may make further changes and perhaps be more specific with different phases that have occurred. However, for the most part, the working group has not gotten to this yet. This is placeholder information that is a reference to interoperability with the electronic health record, and harkens back to the Meaningful Use website.

Clinical Decision Support Resources for the Immunization Community

Mr. Stuart Myerburg
Immunization Information Systems Support Branch
National Centers for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Mr. Myerburg presented a very high level overview of the Clinical Decision Support for Immunization (CDSi) project in terms of the background of the project, the project overview and results, outcomes and evaluation feedback, and next steps and future initiatives. Clinical decision support is more commonly referred to as vaccine forecasting and evaluation within the immunization community. That function is performed by many different computer systems, such as EHR, IIS, and stand-alone applications (e.g., web-based schedulers, smart phone apps, et cetera). All of these systems work independently in developing their logic and their code, which is the reason for the CDSi project. ACIP schedule integration into computer systems is challenging. The schedules are communicated for humans to read, but computer systems cannot read a narrative or a schedule. Thus, recommendations are interpreted and integrated by technical and clinical SMEs who are developing the computer systems who interpret it and try to code off of that. Translation into technical logic can be very time-consuming. Integration occurs mostly independently, so there can be variability.

The output from evaluation and forecasting systems can vary widely and the results do not always match the expectations of clinical experts or what would be expected from reading the ACIP recommendations. This is really because each computer system (e.g., EHR, IIS) is developing its own technical approach, coding off of the language, and then trying to make their own interpretations. A 2009 study by NCIRD's Immunization Information Systems Support

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Branch (IISSB) showed that there was definitely ambiguity in interpretations of ACIP recommendations. Assessment was done of 36 IIS forecasting algorithms, and 9 test cases were run against those. The result showed that 19 of the 36 systems, or 53%, forecasted the next dose due ≥ 5 days before the minimum age [2009 CDC study (*Assessing Variability Among IIS Vaccine Forecasting Algorithms – Kelly, Bryant, Pabst*)].

Interpretation of ACIP recommendations can be challenging, and implementing changes is time-consuming. The immunization schedule is complex, the schedule changes frequently, computer systems are decentralized and do not share a common technology or logic framework, and implementation is often specific to a given application and implementation setting so there is no sharing of that information. If one system is doing it correctly, it does not mean any other systems are. Of course, there is disparity as a result of that. As mentioned before, the logic that is created for these systems is really based on humans trying to interpret the schedule and make it into code. There is no common, technology-neutral logic framework for the communication of ACIP recommendations. The schedule is published as a narrative and must be converted into logic and algorithms needed for implementation. There is lack of consensus on how best to represent CDSi guidelines in computer-interpretable formats, and many of the representation standards that are being used are proprietary.

As a result, NCIRD started this project. The CDSi resource is meant to bridge the gap between the ACIP recommendations that are published in scientific language and are human-readable, and the IT world of computer systems. CDSi is designed to work in a wide variety of computer systems, and does not require a single tool to be used. Recognizing that there is variability in the tools and codes being used by these systems, they did not want to create a tool or anything that was proprietary, so CDSi is a way to take the logic and move it into their system. The hope was to promote consistent interpretation of ACIP recommendations across computer systems. Of course, the ultimate goal is to ensure that a patient's immunization status is current, accurate, and consistent regardless of where the provider is located in the US.

The problems are really variance, complexity, and disparity. The goals were to address the variance to document the logic for applying the rules so that the computer systems would have consistent interpretation. They also wanted to make sure that when there are changes to the schedules, those can be quickly incorporated into these computer systems and that ACIP rules are cataloged consistently. To clarify, these are not new vaccine recommendations. The project really is a catalog of existing ACIP recommendations. During the first part of the project, only healthy children from birth through18 years of age were addressed to limit the scope because of time. This is not a software application that can be downloaded. It is a computable and implementation-neutral logic framework and data that can be used by a variety of different systems and configurations. It is also not a replacement for current computer systems. NCIRD recognizes that there are some very mature systems within the IIS and EHR communities that are doing very well, and they do not want to replace their systems. This was really meant to be clarification and validation for existing systems or guidelines to improve systems. If someone wanted to create a new system based on these rules, obviously they could.
The following illustrations offer a graphic representation of the before and after:

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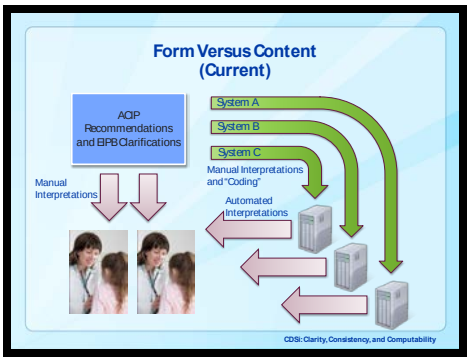

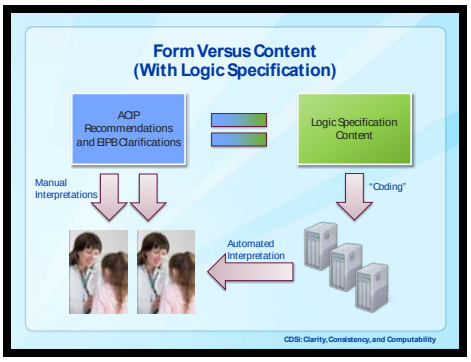

What was occurring was that each system was looking at those recommendations, getting clarifications, manually interpreting and coding, and then sending out their automated response and they were not matching up. The CDSi project hoped to take those ACIP recommendations, develop one logic specification that everyone could code off of, and then have one consistent interpretation.

The outcomes are that the CDSi system:

- ❑ Provides uniform recommendations across all entities doing immunization evaluation and forecasting
- ❑ Keeps those recommendations up-to-date and consistent
- ❑ Allows for broad use across a variety of technology platforms and public health systems by not relying on any specific computer language or software

The logic specification was published in October 2012. Early in 2013, a very informal evaluation feedback was done to determine the "pulse" of the community. Preliminary results showed that of the 42 respondents, 80% found the CDSi resources to have a *somewhat* or *very positive* impact. Of current CDSi users, 94% said they would use the Logic Specification and 100% said they would use the Supporting Data to modify their systems and/or seek clarification when new or changed ACIP recommendations are published. Thus, it is basically being used the way it was hoped the community would be using it. Others commented that they would use the resources when redesigning their CDSi systems.

In terms of the next steps, resources are in place to maintain the logic so that when there are changes or clarifications the resources can be updated. Funding was just received for adult vaccines, so the same resources will be developed for the adult schedules. As part of that program, underlying conditions will be tackled. This was tabled during the initial work due to time and resources. However, there does need to be a standard way to have consistent electronic codes for underlying conditions. That is especially relevant for the adult schedule, but it will impact that childhood schedule as well. A more formal evaluation plan will be developed to better determine impact and uptake.

With regard to ACIP take home points, the resources were designed to work with a variety of computer systems. CDSi resources are an aide to providing clarity and consistency to ACIP recommendations in computer systems. CDSi resources need to be adjusted in parallel with other clinical ACIP recommendations to speed up uptake of clinical recommendations in computers systems.

Discussion Points

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Regarding the general recommendations, Dr. Harriman wondered if under the "Vaccine Preparation" section they might want to add something about the pertussis DNA contamination issue, and the importance of preparing pertussis vaccines separately from where patient swabs are being done. The pertussis team has nice guidance that is on the web.

Dr. Kroger thought they could consider giving some concrete examples to help support that policy. While he said he was not familiar with that particular issue, he would take that back to the working group.

Regarding the recommendations, Dr. Kempe thought the phrase "inclusion of adults into IIS also would be worthwhile" should be a lot stronger. This should be strongly recommending that adults be part of IIS. There is so much evidence about the effectiveness of IIS-based tracking and recall that could be applied for adults. She has been doing a lot of work with her state registry doing centralized reminder-recall. Because of that process, and only because of their research, they became aware that different reports from the same system were recommending different children. Part of this had to do with rapidly changing codes, such as PCV7 to PCV13. All of that requires constant updating. She asked whether CDSi was capturing that type of data about changing codes for vaccines. She also wondered how conscientious assessment of these reports could be encouraged by CDC. What could be the carrot for state IISs to look critically at these reports? They are all under-funded, "under-the-gun," and working way too hard.

As far as the codes, Dr. Myerburg clarified that it is not related directly to the CDSi project, but they do keep updated code sets on their website so that it is done and available to the community. Regarding dissemination information, they have been working with numerous organizations to make sure that anytime an update is made it is distributed out to the community. There is also a place to sign up for updates whenever changes are made to the resources. Though the program is primarily in contact with the IIS community, that also will capture the EHRs who may also be interested in it. As far as the carrot, it is very time-consuming and complex, so the incentive is that it takes the burden off of the people who are working within the program. This is now there for them to just go to, and it will save them a lot of time. It is a carrot by default—just by existing.

Regarding multidose vials, Ms. Stinchfield (NAPNAP) appreciated the inclusion of some "wiggle room" for mass clinics, such as influenza vaccine clinics. However, she still thought there was some work to do on that in that it is overly prescriptive in speaking about drawing up only 10 vaccines at a time, and that the person who draws it has to be the person who gives it. In an emergency situation, that will not be followed. A way to address this is to talk about the principles, such as making sure to follow the principles of safe storage and handling, infection control, medication integrity, safe handling, et cetera. They had 6 children die of influenza in 2008 and were overrun by people wanting vaccines in January. By setting up a mass influenza clinic, they were able to vaccinate 2000 children in 3 hours. The pharmacist was drawing up the influenza vaccines, putting them in labeled buckets, and taking them to the nurses who stayed in the rooms and vaccinated. They would not have been able to manage the onslaught of people if they had to label each individual syringe. Therefore, she thought they needed to be more practical and come to the middle on that recommendation.

Dr. Kroger replied that there would be some "wiggle room" in the implementation part of any recommendation. With the discussion of needle safety, the working group did not want to be strong and weak in the same paragraph, so they became very prescriptive in that

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recommendation. However, he understood the point of erring on the side of leaving the language vague enough so that people can actually do what they need to do.

Dr. Lett (CSTE) pointed out that a number of working groups members are concerned about the language pertaining to multidose vials in the exam room. It does have preservative in it, and the goal is to try to decrease the possibility of nosocomial transmission, perhaps drug diversion, and maybe some other problems. However, a lot of vaccine could be wasted for influenza vaccine and perhaps one other vaccine that comes in a multidose vial that is given to children. Therefore, she expressed concern about that language emerging, and emerging in the "Pink Book." She welcomed the opportunity to have more discussion about that in the working group.

Dr. Duchin pointed out that it was very consistent with the new NVAC standards to promote the use of adult immunization systems. In that context, there are many fewer vaccines, but perhaps a very complicated situation with the pneumococcal vaccines. He wondered if any progress had been made around an information system for decision support for administration of pneumococcal vaccines to adults with the various vaccine formulations that are available, the various permutations of risk factors, the intervals depending on which vaccine is administered first, et cetera.

Dr. Myerburg responded that the adult project literally started the day of the shutdown, so none of those issued had been tackled yet. However, the same type of process will be done as was done for childhood immunizations. All sorts of scenarios will be gathered from SMEs across the gamut.

Dr. Moore (AIM) noted that the Meaningful Use funding is allocated to practitioners who are implementing EHRs, so she suggested flipping the IIS statement on vaccination records to read, "Electronic health record tools should maintain interoperability with the IIS." IISs are ready to receive their information, and it is up to the health record tools to work with them to make that happen. Like many states, they are a lifelong registry and definitely want all records for all ages. She also underscored Dr. Lett and Patsy Stinchfield's comments about the multidose files. A statement that "if a multidose file enters the immediate patient area, it should be discarded after use" is somewhat too prescriptive and impractical—not just in mass clinics, but also in very small clinics and health departments where there may not be a lot of different rooms in which to operate.

Dr. Caserta (HRSA) called attention to the language for the VICP stating that "This Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, whether administered to a child or adult, and even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine)." He suggested saying "seasonal influenza vaccine" because the program does not cover pandemic influenza vaccines. In addition, the statement is technically not complete, because an excise tax also needs to be imposed before a vaccine is covered, and the Secretary has to formally add it to the table through a notice in the *Federal Register*. While the statement is true, it is not technically correct. Regarding injecting into the deltoid, the VICP has had dozens of cases of bursitis where the injection is given too high in the deltoid. Thus, adding some language to say "avoid the upper deltoid" would be helpful.

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With respect to OSHA regulations, Dr. Loehr (AAFP) said that his interpretation of the statement "These federal regulations require that safety-engineered injection devices . . ." was that the statement was not true. OSHA does not require employers to use specific devices, but it does require that employers "evaluate the effectiveness of existing controls and review the feasibility of instituting more advanced engineering controls." However, they do not have to implement it. The *weak* statement is more accurate in terms of the way OSHA is interpreting the law. The *strong* statement is not what OSHA requires.

Dr. Kroger indicated that they went to the website, but that they would verify.

Ms. Groom (IHS) commended CDC on the CDSi project, which has been fantastic and IHS is grateful to have the resource and is looking forward to the work on adults, especially with regard to pneumococcal vaccine. Regarding the IIS issue, while states are working really hard on this, providers are working hard on it as well. There are situations with states that are not able to receive provider records, so the IIS-EHR interoperability is a partnership, and maybe the language could be changed to reflect that. Regarding Dr. Kempe's question about the codes, this process has progressed a long way, but there are still issues such as the quadrivalent influenza vaccine for which a new code was needed for the preservative-free and preservative-containing formulation, which did not come out until the middle of August because of the last-minute approval. There has been a lot of progress and CDC has been very responsive when those situations arise in terms of quickly getting the codes. Continuing to work on that would be great.

Regarding underlying conditions, documentation, and the electronic codes, Dr. Temte pointed out that this is a two-way street. It is inherent for the working groups to think carefully about not only the conditions, but also the ICD-9 range of codes that can help educate the programmers. There are innumerable codes, but it is actually pretty easy to do the logic. This also applies to the ability to pull medications in order to identify people who are on chronic corticosteroids. These are things that will be important for some of the vaccines.

Dr. Schaffner (NFID) wondered if interstate compatibility of the IISs had been addressed in the recommendations. Adults often move between states, and children occasionally do so, which is a real barrier in using registries in order to maintain immunization records. It would be nice to address this.

Dr. Kroger replied that the general recommendations draft does not go into that kind of detail where IIS is discussed, apart from the fact that there is language about maintaining interoperability with EHRs, which may engender cross-state issues.

Gary Urquhart (Chief of IISSB) reported that there are a couple of initiatives to address interstate data sharing. It is a very complicated issue. All states have privacy and confidentiality statutes. Interstate data sharing is not technically a major problem, but the administrative aspects of it are. IISSB has some initiatives with the Office of the National Coordinator for Health Information Technology (ONC) and others to try to find some solutions or best practices for this.

Having participated in the clinical decision support process and trying to unravel the complicated logic that the well-meaning ACIP created in its recommendations, Dr. Sawyer also requested that each working group to be very mindful of the computability of their recommendations. Even better than that, he suggested consulting with an IIS colleague before making recommendations that later have to be unraveled.

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Ms. Pellegrini emphasized that in context of the conversation about IISs, while they were thinking through the medical and scientific issues, they must also remember that there are privacy issues and people who are not comfortable with a government entity holding their medical information or this degree of their medical information. They may be comfortable with their doctor doing that in an EHR, but when it goes into what some people perceive as a large government database and there is discussion about sharing that cross state lines, people need to be told how their privacy will be protected in the process.

Influenza

Introduction

Dr. Ruth Karron
Chair, Influenza Working Group

Dr. Karron began by particularly acknowledging Dr. Lisa Grohskopf who, as a PHS member, worked very hard during the shutdown to prepare all of the material for this session.

She then reported that there had been a number of developments since the June 2013 ACIP meeting, the first of which was the publication of the 2013-2014 ACIP Influenza Statement. This year that was no small task, because in addition to the usual summary of the virus strain selections for the 2013-2014 vaccine, there was a summary of 6 recently approved vaccines (4 quadrivalent and 2 trivalent), and a revision of the egg allergy statement to include Flublok® for egg-allergic individuals 18 through 49 years of age.

In addition, FLULAVAL® vaccine was licensed, which is GSK's inactivated quadrivalent influenza vaccine (IIV4) for persons aged 3 and older. There was also a new age indication for GSK's FLULAVAL® trivalent, which is now licensed for persons aged 3 and older. FLULAVAL® trivalent was previously indicated for those 18 years of age and older. The working group also heard a preliminary discussion of the Fluzone® high-dose vaccine.

This session included an influenza surveillance update, an update on influenza vaccine distribution and coverage for the 2012-2013 season, and a presentation on Fluzone® high-dose vaccine efficacy trial results.

Update: Influenza Surveillance

Dr. Lisa Grohskopf
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Lisa Grohskopf presented a brief update on domestic influenza surveillance for the season thus far, indicating that this information came from FluView from the most current report on October 12, 2013 (Week 41). Based on the weekly influenza activity estimates reported by state and territorial epidemiologists, Puerto Rico reported regional activity, three states reported local activity (e.g., Texas, Alabama, and South Carolina), and most of the rest of the country reported either none or sporadic activity, with the exception of Nevada, which did not submit a report. It is important to note that this is a geographic spread and is not intended to be interpreted as an index of disease severity.

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Influenza positive tests are reported to CDC by WHO's National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories, which are located throughout the US. These laboratories report the number of specimens submitted and tested, and the percent that are positive for influenza. For week 41, 3541 specimens had been tested. Of those, 166 or 4.7% were positive. In terms of the breakdown by influenza type, 91% were influenza A and 9% were influenza B. Of the influenza A's, 25% were 2009 H1N1, 6% were H3N2, and 68% were not sub-typed as A's.

The US Influenza-Like Illness Surveillance Network (ILINet) is a network of over 2900 healthcare providers who report on outpatient visits, and basically report the proportion that are for ILI. ILI is defined as fever greater than or equal to 100 degrees, along with either a sore throat or cough that cannot be attributed to another known cause other than influenza. Based on ILINet data, 1.1% of visits were reported to be due to ILI for Week 41.

Pediatric deaths due to influenza have been reportable since 2004. For 2013-2014, no pediatrics death reports had been received at the time of this ACIP meeting. The total for 2012-2013 was 165 cases.

Vaccine Coverage 2012-2013

James A. Singleton, PhD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Singleton reported on 2012-2013 vaccine coverage, the results of which were released on September 27, 2013. The 2012-13 influenza season marked the third season since the universal influenza vaccination recommendation, and the third influenza season since the 2009 H1N1 pandemic. The 2012-2013 season influenza activity began early, has been moderately severe, and duration has been longer than average. There were spot influenza vaccine shortages in January 2013.

The Healthy People 2020 Influenza Vaccination Objectives (IID-12) had not been widely publicized and had not yet been updated on the website, so Dr. Singleton shared an update during this session. The 10 objectives for different groups were consolidated into four groups as follows:

- Children 6 months through 17 years (target 70% coverage, source NHIS)
- Adults ≥18 years (target 70% coverage, source NHIS)
- Healthcare personnel (target 90% coverage, source NHIS)
- Pregnant women (developmental pending data source, no target set)

No target was set for pregnant women because that was moved to a developmental objective, which means that various data sources are being developed to determine the best one to utilize to monitor coverage for Healthy People 2020. All other populations will continue to be monitored.

In terms of cumulative doses of influenza vaccines distributed by month, by season for 2003-2004 through 2013-2014, 134.9 million doses were distributed for 2012-2013, which is similar to the prior season. For 2013-2014, about 73 million doses were distributed by September 20, 2013. Manufacturers project 135-139 million doses of influenza doses will be will be produced

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during the 2013-14 season. [http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply-2012.htm].

Interim estimates were produced in November 2012 based on early season data. For the general population survey data for the general population, there were very large samples of children from NIS and Behavioral Risk Factor Surveillance System (BRFSS). Data for children 6 months through 17 years of age came from the NIS survey (n=100,829) interviews conducted from October 2012 through June 2013. Data for adults ≥18 years of age came from the BRFSS (n=348,686) interviews from September 2012 through June 2013. The online report is available at: http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm. April 2013 internet panel surveys were utilized for healthcare personnel (n=1,944)[1] and pregnant women (n=1,702)[2] [[1]*MMWR* September 27, 2013 / Vol. 62 / No. 38 / Pg. 781-786; [2]*MMWR* September 27, 2013 / Vol. 62 / No. 38 / Pg. 787-792].

Based on the NIS and BRFSS, an increasing trend was observed in the 2012-2013 season of receipt of trivalent influenza vaccine in children of 57%, adults of 42%, and the overall population of 45% [National Immunization Survey (NIS) (6 mo-17 yrs) and Behavioral Risk Factor Surveillance System (BRFSS) (≥18 yrs); trends for adults and persons ≥6 months may be affected by changes in BRFSS methodology in 2011, affecting 2011-12 and subsequent seasons (adding households with only cellular telephone service and changes to weighting methods)].

With regard to the cumulative influenza vaccination uptake by month based on data from the 2010-2011 through 2012-2013 seasons, for children there was about a 5% increase at the end of last season compared to the prior season. That increase occurred primarily in December and January. For adults, there was a 2.7% percentage point increase by the end of last season. That increase occurred primarily in January and February [http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm]. For the 2012-2013 season, coverage for children 6 months through 17 years was 56.6%. That represented a 5 percentage point increase from the prior season. As observed in prior seasons, vaccine coverage decreases as age increases. Coverage of at least one dose of influenza vaccine for children decreased with age to 76.9% for children 6 through 23 months, 65.8% for children 2 through 4 years, 58.6 for children 5 through 12 years, and 42.5% for children 13 through 17 years. Increases for the previous season were more pronounced and statistically significant for the 5 through 12 year olds and the 13 through 17 year olds by 4 to 9 percentage points [NIS].

Turning to influenza vaccination coverage by age group for the six sites participating in the IIS Sentinel Site Project in 2012-2013, fully vaccinated was calculated in two different ways: 1) a simple way based on vaccine history from 2010-2011 forward, and 2) a more complicated approach that could eliminate some of the children who need two doses. The ratio of full coverage to fully vaccinated based on the complicated approach is about 69%, 73%, and 74% respectively for the three age groups. So, a little more than two-thirds of those who received one dose were actually fully vaccinated. With the simple algorithm for 5 through 8 year olds, there was a difference of 8.8 percentage points from 20% to 29%. That occurs only in the older age group.

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Among adults 18 years of age and older, 41.5% reported influenza vaccination for the 2012-2013 season. That is about a 3 percentage point increase from the prior season. As seen before, vaccine coverage increases with age from a low of 31.1% in 18 through 49 year olds to 66.2% in persons 65 years of age and older. Increases were statistically significant in all of the age groups ranging from 1 to 3 percentage points. Coverage for persons 18 through 49 with high risk conditions was higher than all persons 18 years of age and older at 40% versus 31%. A wide variation in coverage among children and adults continues to be observed by state. The range for children was 44% to 82%, and the range for adults was 31% to 53%. Coverage is generally higher among children than adults by state as well as nationally.

In terms of racial/ethnic differences in coverage for the 2012-2013 season, non-Hispanic whites and American Indian/Alaska Native (AI/AN) had nearly similar coverage of about 54% and 53% respectively. Coverage in all other age groups was higher and statistically significant, ranging up to 66% in Asians. For adults, coverage for Hispanics, other multiple races, and blacks was lower than coverage in whites. Again, long-standing disparities have been observed in blacks and Hispanics compared to whites for adults for influenza vaccine.

Regarding the trend over time among healthcare workers, the NIS and Internet Panel Survey both are trending upward. The Internet Panel Survey tends to have slightly higher estimates, but the two are trending similarly.[1] The Internet Panel Survey also allows a timely way to assess influenza vaccine coverage by occupation and work settings among healthcare workers. There was a general increase in all occupation groups, but the highest coverage was among physicians at 92%, followed by 89% in nurse practitioners and physician assistants and 85% in nurses. The lowest was in non-clinical workers at 65%. Assessing healthcare worker uptake by work setting, highest coverage was in hospitals at 83%, followed by 73% in physician offices and clinic settings. The lowest was 59% in long-term care facilities. Generally, the trend has been increasing, but for long-term care facilities coverage has bounced around over the seasons. There is more information available in the *MMWR* article about the prevalence of different workers being under requirement for vaccination, which is highly associated with high coverage. Availability of vaccine at the worksite is also strongly associated with vaccination[2] [[1]Internet Panel Surveys - *MMWR* 2013;62(38); National Health Interview Survey (NHIS) - Lu et al. AJE in press and h ttp://www.cdc.gov/flu/pdf/professionals/nhis89_ 08fluvaxtrendtab.pdf; NHIS is data source for HP2020 objective; [2]*MMWR* September 27, 2013 62(38);781-786].

Multiple sources of data are utilized to assess coverage of pregnant women, including BRFSS, Internet Panel Surveys, National H1N1 Flu Survey (NHFS), and Pregnancy Risk Assessment Monitoring System (PRAMS). In the data for which there are time series (BRFSS, Internet Panel Surveys), an increasing trend has been observed in higher coverage than in prior years before 2009-2010. For the 2010-2011 season, when the PRAMS data were assessed from 18 states, the same estimate was observed from the Internet Panel Survey when restricted to those same 18 states. Based on the Internet Panel Surveys, about half of women who were pregnant anytime from October 2012 through January 2013 had received an influenza vaccine before or during their pregnancy. Based on the results from the Internet Panel Survey, about 50.5% overall were vaccinated. When asked if they had received a provider recommendation and/or provider offer for vaccination, 71% of those who received both, 46% who received a provider recommendation but no offer, and 16% who received no provider recommendation were vaccinated. This pattern was consistent across sociodemographic groups, as well as those with negative attitudes toward vaccination.

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Based on data reported in November 2012 from NIS and the National Internet Flu Survey (NIFS), the doctor's office or medically-related places are the most common venue for vaccine receipt for children and adults. About 6% of children are vaccinated in schools. Approximately 18% of adults are vaccinated in pharmacies or stores, and 17% are vaccinated in workplaces [October 4 – November 17, 2012 NIS data for children 6 months through 17 years of age; November 2-15, 2012 NIFS data for adults ≥ 18 years of age].

In summary, influenza vaccination coverage for the 2012-2013 season increased 5 percentage points from the prior season among children. There were higher increases for children 5 through 12 (+4.4) and 13 through 17 (+8.8) years. Coverage for adults increased 3 percentage points, and there were increases in each age group. Among children, coverage was higher in non-Hispanic whites than for Asians, Hispanics, blacks, and children of other/multiple races. Racial/ ethnic disparities among adults persist. There is wide variation in coverage among states. Last season's increases for pregnant women were maintained, and there was increased coverage for healthcare personnel. There is wide variation among healthcare workers by occupation setting, and the policies toward vaccinations in their facilities. The most common places for vaccination among both adults and children were medical settings, with retail settings and work places among other important venues for adults.

Regarding limitations, tracking trends by season is complicated by multiple data sources with different timeliness and methods. The *MMWR Surveillance Summary* of October 11, 2013 summarizes data sources, methods, and summary through the 2011-2012 season was scheduled to be published on October 24, 2013. There was a change in the definition of "vaccination status" for pregnant women in Internet Panel Surveys. Vaccinations in July were included, which was also done for the general population. Vaccinations received after pregnancy were excluded, but this does not really change the conclusion that coverage is about 50% in pregnant women. All of this is self-reported vaccination, which is not validated by medical records. It was estimated that more people were vaccinated than doses were distributed, so it is generally known that these estimates are on the high side. However, they are still very useful for tracking trends. Survey estimates may not be representative. Telephone survey response rates are low, which may also affect the estimates. The representativeness of internet panel survey estimates needs further evaluation.

Some recommendations are to:

- ❑ Increase influenza vaccination coverage among all groups
- ❑ Reduce disparities in coverage among adults
- ❑ Implement the following proven interventions to increase coverage from the Guide to Community Preventive Services [http://www.thecommunityguide.org/vaccines/index.html]
    - Enhance access to vaccination services
    - Increase community demand for vaccinations
    - Increase provider- or system-based interventions (strong provider recommendations for and offers of vaccination)
    - Implement community-based interventions in combination
    - Use IIS systems at the point of care and at the population level to guide clinical and public health vaccination decisions

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More detailed information can be found at FluVaxView, which is CDC's source for influenza vaccination coverage data at: http://www.cdc.gov/flu/fluvaxview/index.htm

Regarding the upcoming season, National Influenza Vaccination Week (NIVW) is December 8-14, 2013. CDC plans to release data from November 2013 for the general population, healthcare workers, and pregnant women sometime during that week.

Discussion Points

Dr. Bennett said she thought many of them remembered when the immunization rate among healthcare providers was abysmally low, so these data are very exciting. She wondered whether there were any data about decreased absenteeism, or other outcome data, among healthcare providers that would be useful to convince other employers to engage in more aggressive vaccination campaigns.

Dr. Singleton replied that CDC does not systematically collect that type of data; however, others may know of some studies.

Dr. Bresee (SME) confirmed that the studies CDC conducts annually for vaccine effectiveness do not measure absenteeism of healthcare workers. There have been studies in the literature that have described decreases in absenteeism among healthcare providers as a result of vaccination policies.

Dr. Temte added that Dr. Faruque Ahmed has published a systematic review on the effect of healthcare provider vaccination in reducing transmission. That was published in the summer, and was a very nice report using GRADE.

Dr. Foster (APhA) noted that while not shown on the graph, pharmacists had the second highest vaccination rates. Dr. Singleton indicated that those are split out in the *MMWR* report.

Regarding cumulative vaccination for adults and children by month, Dr. Karron noted that there was a tail for children from November on. She wondered whether that reflected complete immunization and perhaps some of the youngest children receiving a second dose, or if it was a first dose. She heard a lot from pediatricians in her community about inaccessibility and shortages. If it was a first dose, she wondered how this might be related. Regarding healthcare workers, she inquired as to what is being done right with nurses to move from 70% to 85% in two years. It was interesting that non-medical professionals were clearly lagging behind, and she wondered whether there were policies or practices that should be implemented to achieve increases in those areas as well.

Dr. Singleton replied that this was for the first dose reported for children. For children respondents are asked whether they received multiple doses and the month and year of each one. However, only the first dose was reported in the data for cumulative vaccination for adults and children by month.

In terms of how this relates to vaccine supply, Dr. Schuchat responded that there are a couple of factors. One is that NIVW events are conducted in early December. The first day of NIVW in 2012, Dr. Frieden did a press conference that highlighted that the US was experiencing an early and bad season. That is believed to have been fairly effective in raising demand. Before that, there was increased demand in a number of areas that were observing early disease. Supply availability was pretty early last year, but some formulations are always distributed later even when there is generally good supply of the particular formulations. Particular practices may not

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receive all that they want. Most doses are distributed by November, but that does not necessarily mean all of the particular doses desired are received.

Ms. Hayes (ANA) credited CDC with the increase in influenza vaccine uptake among nurses, because the agency gave a grant to the ANA a few years ago to increase vaccination among nurses. This was a large project that the ANA worked on for a couple of years. In addition, many hospitals are now requiring employees to be vaccinated. She wondered how many non-clinical personnel are working in personal care or nursing homes where they do not have the same kind of push that hospitals have. Regarding the internet survey for pregnant women, she pointed out that inherently a small population of self-selected pregnant women respond. Many of the pregnant women for whom she cares do not have access to the Internet, so she always feels like that should be a caveat in that report. She was curious as to whether insurance data are ever collected from the respondents and whether they have Medicaid or private insurance, and noted that 60% of births in Georgia are Medicaid births to low-income women. She wished that information about that population could be captured to determine their vaccination rates.

Dr. Singleton replied that health insurance status is asked about on the survey. There are some estimates by insurance status in the *MMWR* article. This information is collected and can be assessed. The BRFSS asked only whether a woman was currently pregnant. December through February interviews were assessed for women who indicated that they were pregnant during that timeframe. That data source could be further assessed. The PRAMS data are state-specific and are not collected in all states; however, these are rich data. An article was recently published from Massachusetts that looked in detail at factors associated with vaccination among pregnant women. The Internet Panel Surveys are not going to include someone who does not have internet access. Comparisons have been made to other surveys such as PRAMS and BRFSS, which are generally tracking the same as the Internet Panel Surveys. Some questions were added to the NHIS, although these data have not yet been assessed. Consideration is being given to the best way to evaluate potential biases.

Dr. Schuchat noted that one incentive that was operating recently in acute care hospitals was CMS incentive pay for reporting healthcare provider vaccination. Improvements in physicians, nurses, and nurse practitioners might be linked with that. Pharmacists are doing a great job without that kind of incentive.

Dr. Singleton added that it is possible that an increased number of facilities are instituting requirements. Though he had not yet analyzed that, he indicated that it was another hypothesis that could be considered. It has been observed that fewer long-term care facility employees are in facilities that have vaccine requirements compared to hospital employees.

Of the doses of vaccine distributed so far this year, Dr. Bocchini wondered if there was an idea of the relative number of quadrivalent versus trivalent, and particularly whether quadrivalent is available for younger children through the VFC program.

Dr. Schuchat reminded everyone that all of the Live Attenuated Influenza Vaccine (LAIV) is quadrivalent. The VFC program purchased quadrivalent and trivalent, LAIV and inactivated vaccine, though she did not readily know the totals of all of those different components.

In terms of what is occurring with nurses, Ms. Stinchfield (NAPNAP) said she thought that hospitals know about CMS and more organizations are more willing to be strict and are mandating vaccination. There is also much better recording, so it is known by role who is being vaccinated in hospitals. Also, many hospitals require that employees either get vaccinated or wear a mask. Mask-wearing is not fun, so more people opt for vaccination. She thinks splitting

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out groups in the data is much better, and requested that nurse practitioners and physician assistants be split out as well.

Dr. Singleton replied that nurse practitioners and physician assistants may not have been split out due to sample size issues.

Regarding Healthy People 2020 and the use of the NIS as the data source, Ms. Groom (IHS) pointed out that in the past, NHIS has used 19 years of age and older. However, the age grouping assessed for influenza was for those 18 years of age and older. She was curious about using the NHIS instead of the BRFSS data.

Dr. Singleton responded that the NHIS data are considered to be the most representative since it is an in-person survey with higher response rates than the telephone survey. The age split was primarily a matter of convenience and estimation because the surveys ask different age groups. Age 17 is the cutoff for a child for legal purposes for surveys, while 18 year olds can be surveyed themselves instead of the parents in most states. The data comes with that age split, although VFC includes 19 year olds. NHIS has data on those 18 years of age and older. They are included with the adults.

Fluzone® High-Dose Vaccine Efficacy Trial Results

David P. Greenberg, MD
Sanofi Pasteur

Dr. Greenberg presented the results of sanofi pasteur's Fluzone® high-dose efficacy trial. He provided background information on the rationale for developing this vaccine, presented key data from the pre-licensure Phase III safety and immunogenicity study, reviewed the results from the recently completed efficacy trial, and outlined plans to submit these data to the FDA.

In most seasons, people 65 years of age and older account for nearly two-thirds of influenza-related hospitalizations and about 90% of influenza-related deaths in the US.[1,2,3] Each year, 65% to 70% of this population receives vaccine, but studies conducted by the CDC and others have demonstrated that influenza vaccines protect older adults less well than younger adults.[3,6] This was evident again last season when influenza vaccines offered limited protection against the H3N2 strain among seniors [[1]US Census Bureau. http://www.census.gov.newsroom/ releases/ archives/2010_census/cb11-cn192.html. Accessed August 26, 2013. [2]Thompson WW, et al. *JAMA*. 2004;292(11):1333-1340. [3]CDC. *MMWR*. 2010;59(RR-8):1-62. [4]CDC. *MMWR*. 2012;61(22):414-420. [5]CDC. http://www.cdc.gov/ injury/ wisqars/ pdf/10LCID_All_ Deaths_By_Age_Group_2010-a.pdf. Accessed August 26, 2013. [6]Monto AS, et al. *Vaccine.* 2009;27(37):5043-5053].

Relatively lower protection in older adults may be due to immunosenescence resulting in lower antibody responses. In a typical example from one of sanofi pasteur's annual studies, Fluzone® vaccine generated lower geometric mean antibody titers (GMTs) to all 3 strains among older adults than in younger adults. The question regards whether lower antibody responses really matter in the prevention of influenza disease [Sanofi Pasteur Inc. Data on file (Annual study GRC41), November 2009. MKT20203].

Available data point to a clear correlation between resistance to influenza infection and levels of antibody to hemagglutinin. Many studies demonstrate a direct correlation between post-vaccination or post-infection HAI titers and protection against infection upon exposure to

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influenza virus [[1]Potter CW, Oxford JS. *Br Med Bull.* 1979;35(1):69-75. [2]Hannoun C, et al. *Virus Res.* 2004;103(1-2):133-138].

With the preceding facts in mind, sanofi pasteur set out to manufacture and license a vaccine that would induce higher antibody titers and provide better protection for this vulnerable population. Fluzone® High-Dose vaccine contains 60 mcg of hemagglutinin per strain, 4 times the amount contained in Fluzone® vaccine [Fluzone High-Dose vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2013].

Before presenting data from the efficacy trial, Dr. Greenberg quickly reviewed the pivotal pre-licensure Phase III study that compared the safety and immunogenicity of Fluzone® High-Dose vaccine with Fluzone® vaccine among adults 65 years of age and older. Nearly 4000 participants were randomized in this double-blind study to receive either Fluzone® High-Dose or Fluzone® vaccine in a 2:1 ratio. Solicited injection-site reactions within 7 days of vaccination were reported more often among the Fluzone® High-Dose recipients compared with Fluzone® recipients by about 10 percentage points for pain and 3 to 4 percentage points for erythema and swelling. Solicited systemic reactions within 7 days of vaccination were reported by Fluzone® High-Dose recipients by just 1 to 4 percentage points more often than the Fluzone® recipients. Further, the 6-month safety data demonstrated comparable rates of unsolicited adverse events and serious adverse events in the two vaccine groups. Post-vaccination geometric mean antibody titers were statistically significantly higher after vaccination with Fluzone® High-Dose vaccine compared with Fluzone® vaccine against all 3 strains. Based on FDA-agreed pre-specified criteria, Fluzone® High-Dose induced superior antibody responses compared with Fluzone® for the H1N1 and H3N2 strains, and noninferiority was demonstrated for the B strain [Fluzone vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2013; Falsey A, et al. *J Infect Dis.* 2009;200(2):172-180].

In summary of the pre-licensure study, Fluzone® High-Dose vaccine resulted in higher rates of solicited injection-site and systemic reactions, but serious adverse events occurred at comparable rates to those after Fluzone® vaccine. Importantly, Fluzone® High-Dose induced statistically higher antibody responses against all 3 strains as assessed by GMTs, seroconversion rates, and seroprotection rates compared with Fluzone®, and it met pre-specified criteria for demonstrating immunologic superiority to the two A strains.

The FDA licensed Fluzone® High-Dose vaccine in late 2009 under the Accelerated Approval Process with the hope of providing improved protection against influenza among seniors, based on the vaccine's superior immunogenicity. In the first three seasons of use, 13 million doses were distributed. However, despite its superior immunogenicity, as of last season, only 19% of vaccinated seniors received this vaccine, largely because healthcare providers and advisory groups have been waiting for the results of the post-licensure efficacy trial.

The post-licensure efficacy trial, FIM12, was a blinded efficacy trial of approximately 32,000 community dwelling individuals at least 65 years of age who were randomized to receive Fluzone® High-Dose or Fluzone® vaccine on a 1:1 ratio. Participants were not necessarily healthy, and many had chronic underlying diseases. The study was conducted over two seasons, concluding at the end of the 2012-13 season. Participants were enrolled in 126 clinical sites, with wide geographic distribution in the US and Canada.

The primary objective was to compare the clinical efficacy of Fluzone® High-Dose to that of Fluzone® against laboratory-confirmed influenza (defined as PCR- or culture-positive) caused by any influenza viral type or subtype associated with the occurrence of a protocol-defined influenza-like illness (defined as the occurrence of at least one pre-specified respiratory

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symptom and at least one pre-specified systemic symptom). The secondary objectives included an assessment of relative clinical efficacy based on various clinical illness definitions, methods of influenza confirmation, and similarity of the case strains to the vaccine strains. Because previous studies have demonstrated clinical benefit of vaccination against certain influenza-associated complications, the observational objectives included a description of rates of pneumonia, cardio-respiratory conditions, healthcare visits, and medication use in the 2 vaccine groups. Participants were enrolled and randomized at the beginning of each season, and individuals who participated both years were re-randomized at the time of enrollment into the second season.

Passive surveillance was conducted throughout the study, starting 14 days post-vaccination. Participants were asked to contact study personnel if they experienced any respiratory symptoms. Active surveillance involved contacting each participant, also starting 14 days post-vaccination. The frequency of contact was weekly through the end of December, twice a week during January and February, and weekly during March and April. A final contact was made in mid-May of each season. A nasopharyngeal swab was obtained as soon as possible and no later than 5 days following the onset of a respiratory illness. PCR-positive samples underwent genomic sequencing for assessment of similarity to the vaccine strains. Viruses grown in culture underwent HAI testing with ferret antisera for determination of antigenic similarity to the vaccine strains. If results of both assays were available, the ferret antisera data took priority. Participants were similarly distributed between the 2 vaccine groups with regard to gender, age, racial origin, and ethnicity.

Turning to the results of the study, Fluzone® High-Dose vaccine met the pre-specified criterion for the primary analysis, demonstrating superior clinical efficacy compared with Fluzone® vaccine against laboratory-confirmed influenza associated with a protocol-defined influenza-like illness by any viral type or subtype, regardless of similarity to the vaccine strains. Fluzone® High-Dose reduced the incidence of clinical influenza by 24.2% compared to Fluzone® vaccine. The lower bound of the 95% confidence interval was 9.7%, which is above the FDA-agreed pre-specified lower limit of 9.1% to demonstrate superior clinical benefit.

In several tables shown by Dr. Greenberg, the relative efficacy for the primary objective (24.2%) was shown in the uppermost table and the relative efficacies for sub-group analyses were shown below it. It is important to keep in mind that because the numbers of cases were small in some of these sub-group analyses, the 95% confidence intervals were wide compared to the primary analysis, but the point estimates were all positive and in the same range. For example, in the sub-group analysis of benefits demonstrated across study years, the clinical benefit of Fluzone® High-Dose vaccine was demonstrated, with relative efficacy point estimates of approximately 45% in Year 1 and 21% in Year 2.

The clinical benefit of Fluzone® High-Dose was demonstrated across influenza types, with relative efficacy point estimates of approximately 24% against type A and 27% against type B. As one would expect, the clinical benefit of Fluzone® High-Dose was somewhat better against influenza strains that proved to be similar to the vaccine strains, with a relative efficacy point estimate of approximately 35%. The clinical benefit was demonstrated across age groups, with relative efficacy point estimates of approximately 20% among participants 65 through 74 years of age and 32% among those 75 years of age and older. The relative efficacy of Fluzone® High-Dose was slightly higher in the older age group, due in part because of the modestly decreased protection afforded by Fluzone® among this older cohort.

The clinical benefit was demonstrated across illness definitions, with relative efficacy point estimates of approximately 21% against laboratory-confirmed influenza associated with a

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modified CDC ILI, which required fever plus cough or sore throat, and 18% against laboratory-confirmed influenza associated with any symptoms of a respiratory illness. The clinical benefit was demonstrated not only against influenza that was laboratory-confirmed by either polymerase chain reaction (PCR) or culture, which was the primary analysis, but also against influenza that was restricted to culture confirmation, with a relative efficacy point estimate of approximately 23%.

Regarding the relative risk of developing pre-specified health outcomes within 30 days of an illness associated with symptoms consistent with protocol-defined ILI, modified CDC ILI, or respiratory illness, all cases shown in the two tables presented by Dr. Greenberg represented laboratory-confirmed influenza. The numbers of cases were small, but all of the relative risk ratios were less than 1, suggesting that Fluzone® High-Dose vaccine offered better protection against influenza-associated pneumonia compared with Fluzone® vaccine. In the lower portion of each set of tables, the illnesses were without regard to laboratory confirmation of influenza. Again, all of the relative risk ratios were less than 1, some statistically significant, indicating that Fluzone® High-Dose offered better protection against pneumonia after any study illness. Undoubtedly, a substantial number of these cases must have been associated with influenza but the infection was not laboratory confirmed. A similar pattern was observed for cardio-respiratory conditions, suggesting better protection afforded by Fluzone® High-Dose vaccine against cardiac and respiratory-related complications. Hospitalizations occurred less frequently in the Fluzone® High-Dose group compared to the Fluzone® group within 30 days of either laboratory-confirmed influenza or within 30 days of a study illness without regard to laboratory confirmation.

With respect to safety information collected throughout the study period, severe adverse events (SAEs), including all hospitalizations of any cause, were reported less frequently in the Fluzone® High-Dose group compared with the Fluzone® group, primarily because of the lower frequency of various illness-associated complications. SAEs judged by the investigator to be related to Fluzone® High-Dose were one case each of a left cranial 6th nerve palsy that started 1 day post-vaccination, hypovolemic shock associated with diarrhea 1 day post-vaccination, and acute disseminated encephalomyelitis (ADEM) 117 days post-vaccination. Adverse events of special interest in the Fluzone® High-Dose group included one case each of Bell's Palsy, encephalitis/myelitis, and Stevens-Johnson Syndrome (SJS) that developed 53, 117, and 166 days post-vaccination respectively. Deaths due to any cause occurred at similar rates in the 2 groups.

In conclusion, the study demonstrated that Fluzone® High-Dose provides superior protection compared to Fluzone® vaccine against laboratory-confirmed influenza of any viral type or subtype among seniors 65 years of age and older. Fluzone® High-Dose vaccine reduced the incidence of symptomatic influenza by 24% relative to Fluzone®, and the lower bound of the 95% CI of the point estimate met the pre-specified criterion for demonstrating clinical superiority. This clinical benefit was demonstrated across the 2 study years, against type A and type B strains, among participants above and below 75 years of age, against all strains and those similar to the vaccine strains, across various clinical illness definitions, and regardless of the method of laboratory confirmation. In addition, the data of this post-licensure efficacy trial suggest better protection against complications, such as pneumonia, cardio-respiratory disease, and hospitalizations. The results of this and other post-licensure studies have consistently demonstrated the safety of Fluzone® High-Dose vaccine and improved immunogenicity against all 3 viral strains, confirming the results of the pre-licensure studies. As might be imagined, the FIM12 database is very large and the project team is continuing to analyze the data. The team's focus for now is to submit a clinical study report to the FDA as soon as possible, no later than early 2014. At the same time, a revised PI containing key data from this trial will be

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submitted supporting the superior clinical benefit. Finally, the team will develop a series of manuscripts from this rich database.

Current indications and safety information for Fluzone® and Fluzone® High-Dose vaccines are as follows.

Indication

Fluzone® Vaccine
Fluzone® vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Fluzone® High-Dose Vaccine
Fluzone® High-Dose vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Approval of Fluzone® High-Dose vaccine is based on superior immune response relative to Fluzone® vaccine. Data demonstrating a decrease in influenza disease after vaccination with Fluzone® High-Dose vaccine relative to Fluzone® vaccine have not yet been reviewed by FDA.

Safety Information

Fluzone® and Fluzone® High-Dose Vaccines
The most common local and systemic adverse reactions to Fluzone® and Fluzone® High-Dose vaccines include pain, erythema, and swelling at the vaccination site; fever, headache, malaise, and myalgia. Other adverse reactions may occur. Fluzone® and Fluzone® High-Dose vaccines should not be administered to anyone with a severe allergic reaction (e.g., anaphylaxis) to any vaccine component, including egg protein or thimerosal (the multi-dose vial of Fluzone® vaccine is the only presentation that contains thimerosal), or to a previous dose of any influenza vaccine.

The decision to give Fluzone® or Fluzone® High-Dose vaccine should be based on the potential benefits and risks, especially if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine. Vaccination with Fluzone® or Fluzone® High-Dose vaccine may not protect all individuals.

Before administering Fluzone® and Fluzone® High-Dose vaccines, please see full Prescribing Information.

Dr. Greenberg concluded by emphasizing that this is an extremely important study because it proves once and for all that Fluzone® High-Dose vaccine truly reduces the incidence of clinically relevant influenza compared with Fluzone® vaccine among this highly vulnerable population of persons 65 years of age and older.

Discussion Points

Dr. Temte requested that Dr. Bresee remind everyone what the approximate attack rate is for adults 65 years of age and older who are not vaccinated.

Dr. Bresee (SME) responded that CDC does not have good active ongoing estimates of rates of disease or clinic-based disease among the elderly from its surveillance systems. CDC does

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survey for hospitalizations. Over the last 10 years, the rate of hospitalizations has been about 1 per 1000. Last year it was 150 per 100,000. It is known from the community studies in the early 1970s that the annual rate of overall influenza is about 5% to 15% or 20% of the population. It is certainly known in the elderly that the rates of acquisition of disease are on the low end of that. He indicated that while he would determine a more definitive answer to submit to the ACIP members, the annual attack rate was probably in about the 5% range or so.

Dr. Kempe inquired as how the investigators dealt with the fact that many people were involved in both seasons, and that they may have been randomized to different arms. She also thought she heard Dr. Greenberg state that a lot of the clinical outcomes were significantly different, when a lot of the risks appeared to cross 1, so she was confused about that conclusion.

Dr. Greenberg replied that regarding the individuals who participated in both years, that was considered before the trial took place. An extensive analysis was done to assess whether that would somehow skew the results, which showed that it was not expected to occur. Now that the study is over, the groups have been unblinded, and the analyses are taking place, the analyses for all of the parameters are being evaluated over time with regard to those who did and did not participate both years. It turns out that, in fact, many individuals did participate both years. However, various issues that have been evaluated so far such as the point estimates of relative efficacy appear to be the same for those who participated both years as well as those who did not. Thus, there appears not to be any substantial influence of that. As mentioned at the beginning, the study was powered for the primary analysis. Therefore, there is no question that in the smaller sub-group analyses there will not be enough in each group to necessarily have confidence intervals that do not cross 1. What is important is that just by that fact, the point estimates are all in that general range of 20% to 30% for most of the analyses. While a study could have been conducted of 100,000 people over 5 influenza seasons, everyone wanted results. The primary endpoint of the number of cases was achieved.

Dr. Karron said that while she understood the rationale for not using CDC-defined ILI because fever does not always occur in the elderly, if she understood this endpoint correctly, anybody with a runny or stuffy nose who is found on active surveillance would have counted in the numbers because there were weekly telephone calls. She suggested that what they are probably trying to prevent is medically relevant illness—illness that reaches the level of going to a provider. She wondered whether he had any data on that.

Dr. Singleton responded that the clinical endpoint definition for what was referred to as “respiratory illness” in this presentation was the situation Dr. Karron described in which a person could have any single respiratory symptom (sneezing, cough, sore throat). The protocol-defined ILI included at least one systemic symptom as well. The modified CDC ILI mandated fever greater than 99 degrees and cough or sore throat. The full spectrum of illness definitions were used, and the relative efficacies described were quite consistent across all three. In terms of the respiratory illness definition that is then eventually found by PCR culture to be positive, the relative efficacy was somewhat lower in that analysis at 18% versus 24% for the protocol-defined ILI, and was similar to the modified CDC ILI. This was taken into account, and by insisting on having at least one respiratory symptom and at least one systemic symptom, and then CDC mandating that one systemic symptom be fever, the full range of possibilities was covered.

Given the concern among the elderly regarding duration of protection and early vaccination, Dr. Karron wondered if there were any data stratified by time of vaccination versus time of illness, or immunogenicity data to assess durability of the immune response.

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Dr. Greenberg responded that the team is continuing to analyze the data from this rich database, so some of the results just became available in the last couple of days and he was unable to incorporate it into his presentation. He indicated that they would be happy to share more information with the working group in the coming weeks and months. This was assessed, at least initially, on a break point of 90 days after vaccination. The clinical efficacy, the relative efficacy point estimate, was very similar for disease that occurred prior to 90 days after vaccination and 90 days plus. At least with that one early analysis, no difference was observed throughout the season less than or greater than 90 days post-vaccination.

Given that the methods mentioned testing within 5 days of symptom onset, Dr. Duchin wondered whether there was any difference in the two groups with respect to the timing of their diagnostic testing. He also inquired as to whether Dr. Greenberg was aware of any other studies of the effectiveness of this vaccine that are in progress or that are planned, particularly assessing the more significant health outcomes. One of the things he has been impressed with as he learns more about influenza is how each influenza season is so different with respect to the viruses that circulate, the virulence, and the relative protection offered by the strains in the vaccine. He wondered what Dr. Greenberg's thoughts were about how the two vaccines may compare with respect to the influenza B and A components over a number of years, particularly with better immune response to the B component and the greater appreciation of the impact of Type B disease on adults.

Dr. Greenberg replied that with regard to the five-day requirement, samples for all of the cultural or PCR confirmed cases were obtained within the five-day period. There may have been a few stragglers beyond five days, but the study teams across the sites tried to adhere to the five-day requirement. In terms of other health outcomes, there are more data in this study that have not yet been analyzed. Various other outcomes and complications are being evaluated, as well as how that might relate back to the cost. The numbers are not absolute, given that they did not review databases to find the cost of each hospitalization or each pneumonia. Certainly they have a very good sense of poor health outcomes and will try to translate that in future analyses. Regarding the variance in influenza seasons, the nice thing about the FIM12 study and the two seasons it covered was that the two seasons were amazingly very different. The first season was described by CDC as the lightest influenza season essentially on record. From other influenza studies conducted over the decades, sometimes no differences or clinical benefits of influenza vaccine are found when it is a very light season. However, in this study, great clinical benefit was described. The second year was a very heavy year, but the strain such as the H3N2 was not necessarily greatly matched to the vaccine strains, and the FIM12 study still showed additive clinical benefit of the high-dose vaccine compared to Fluzone®. For the A and B strains, the data seem to indicate that protection was afforded to both A and B strains. In terms of similarity to the vaccine strains, a greater clinical benefit of Fluzone® High-Dose is demonstrated when the circulating strains match the vaccine strains. While these two seasons were perhaps not representative of all seasons, there was a great comparison of two seasons that were quite different, and relative efficacy held up in both years.

Given that some people over 65 years of age are healthy and some may have underlying conditions, Dr. Reingold requested information about clinical protection and its variation by how sick subjects may have been at baseline. He also wondered about correlates of protection and what Dr. Greenberg could report about the immune response in the sicker elderly in terms of whatever the right correlate of protection is in this study.

Dr. Greenberg responded that information was collected on co-morbidities. While early analyses have been done, he did not have time to include them in this presentation. The relative efficacy of Fluzone® High-Dose compared to Fluzone® was very similar among

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participants with and without co-morbidities. Many of the participants did have co-morbidities. Two-thirds of the participants had at least one influenza-related co-morbidity and one-third of the subjects had two or more co-morbidities. Both immunogenicity and clinical effectiveness relative to efficacy were the same among those who had co-morbidities. At least within this context, it appears that protection is provided in both. There will be analyses looking for correlates of protection, which is one of the aims of the study. However, those analyses have not yet been done. In terms of how the vaccine performs among even sicker individuals, such as those who are in long-term care facilities, a study conducted by Zimmerman at the University of Pittsburgh in nursing homes and long-term nursing care facilities showed superior immunogenicity of Fluzone® High-Dose compared to Fluzone®. That was not an efficacy study, but they followed safety, which was fine, and then superior antibody responses.

Dr. Loehr asked whether sanofi pasteur is working on a quadrivalent high-dose vaccine. Regarding the primary analysis for FIM12, it appeared that for every 1000 people vaccinated with Fluzone® High-Dose compared to Fluzone®, there will be 4.6 fewer cases of influenza.

Dr. Greenberg responded that they are working on a quadrivalent high-dose vaccine, and recognize that people will be expecting this. Clinical studies must be conducted, but it is in the clinical development program. With regard to the primary analysis, he confirmed that the incidence of laboratory-confirmed incidence for the two groups was about 1.4 for Fluzone® High-Dose and about 1.9 for Fluzone®. There is a diminution of the number and incidence rates of influenza in the Fluzone® High-Dose group compared to the Fluzone® group. There was no placebo group in the study.

With no further questions or business posed, Dr. Temte reminded everyone that registration for the February 2014 ACIP meeting was live and functioning. He wished everyone safe travels home, and thanked them for their attention and attendance.

Day 2: Public Comment

No public comments were offered during this session.

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Certification

Upon reviewing the foregoing version of the October 23-34, 2013 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACIP Membership Roster

CHAIR
TEMTE, Jonathan L. M.D. Ph.D.
Professor of Family Medicine
University of Wisconsin School of Medicine and Public Health
Madison, WI
Term: 07/01/11-06/30/15

EXECUTIVE SECRETARY
PICKERING, Larry K., M.D.
Senior Advisor to the Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS

BENNETT, Nancy, M.D., M.S.
Professor of Medicine and Community and Preventive Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY
Term: 07/01/2011-06/30/2015

BOCCHINI, Joseph A., Jr., M.D.
Professor and Chairman
Department of Pediatrics
Louisiana State University Health Sciences Center
Shreveport, LA
Term: 07/01/2011-06/30/2015

CAMPOS-OUTCALT, Douglas, M.D., M.P.A.
Chair
Department of Family, Community and Preventive Medicine
University of Arizona College of Medicine - Phoenix
Phoenix, AZ
Term: 07/01/2011-06/30/2015

COYNE-BEASLEY, Tamera, M.D., M.P.H.
Director, NC Child Health Research Network
Associate Director, Community Engagement NC TraCS Institute - Child Health Core
Professor of Pediatrics and Internal Medicine
Division of General Pediatrics and Adolescent Medicine
University of North Carolina School of Medicine
Chapel Hill, NC
Term: 10/04/10-06/30/14

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DUCHIN, Jeffrey, M.D.
Chief, Communicable Disease Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine
Division of Allergy and Infectious Diseases
University of Washington School of Medicine
Seattle, WA
Term: 10/04/10-06/30/14

HARRIMAN, Kathleen, Ph.D., M.P.H., R.N.
Chief, Vaccine Preventable Disease Epidemiology Section
Immunization Branch
California Department of Public Health
Richmond, CA
Term: 07/01/2012 – 06/30/2016

HARRISON, Lee H., M.D.
Professor of Medicine and Epidemiology
Infectious Diseases Epidemiology Research Unit
University of Pittsburgh
Pittsburgh, PA
Term: 07/01/2012 – 06/30/2016

JENKINS, Renée R., M.D.
Professor and Chair Emeritus
Department of Pediatrics and Child Health
Howard University College of Medicine
Washington, DC
Term: 10/06/2010 – 06/30/14

KARRON, Ruth A., M.D.
Professor and Director
Center for Immunization Research
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Term: 07/01/2012 – 06/30/2016

RUBIN, Lorry, M.D.
Director
Pediatric Infectious Diseases
Steven and Alexandra Cohen Children's Medical Center of New York
North Shore-Long Island Jewish Health System
New Hyde Park, NY
Professor of Pediatrics, Hofstra-North Shore LIJ School of Medicine, Hempstead, NY
Term: 07/01/2012 – 06/30/2016

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SAWYER, Mark H., M.D.
Professor of Pediatrics
University of California, San Diego School of Medicine
San Diego, CA
Term: 04/23/08-06/30/13

VÁZQUEZ, Marietta, M.D.
Associate Professor of Pediatrics
Department of Pediatrics
Yale University School of Medicine
New Haven, CT
Term: 07/01/2011-06/30/2015

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification
Centers for Medicare and Medicaid Services
Baltimore, MD

Department of Defense (DoD)
GEIBE, Jesse, M.D., M.P.H., M.B.A.
CDR, Medical Corps
Defense Department Liaison Officer
Centers for Disease Control and Prevention
Atlanta, GA

Department of Veterans Affairs (DVA)
KINSINGER, Linda S., M.D., M.P.H.
Chief Consultant for Preventive Medicine
Office of Patient Care Services
National Center for Health Promotion and Disease Prevention
Durham, North Carolina

Food and Drug Administration (FDA)
SUN, Wellington, M.D.
Director, Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Food and Drug Administration
Rockville, MD

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Health Resources and Services Administration (HRSA)
CASERTA, Vito, M.D, M.P.H.
Acting Director
Division of Vaccine Injury Compensation
Director, Countermeasures Injury Compensation Program
Healthcare Systems Bureau
Health Resources and Services Administration
Rockville, MD

Indian Health Service (IHS)
GROOM, Amy, M.P.H.
Immunization Program Manager
Indian Health Service
Albuquerque, NM

National Vaccine Program Office (NVPO)
GELLIN, Bruce, M.D., M.P.H.
Director
National Vaccine Program Office
Department of HHS, Public Health and Science
Washington, DC

National Institutes of Health (NIH)
GORMAN, Richard L., M.D.
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases/NIAID
National Institute of Health
Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
LOEHR, Jamie, M.D., F.A.A.F.P.
Cayuga Family Medicine (Owner)
Ithaca, NY

American Academy of Pediatrics (AAP)
Chair, Committee on Infectious Diseases
BRADY, Michael T., M.D.
Professor and Chair, Department of Pediatrics
The Ohio State University and Nationwide Children's Hospital
Columbus, OH

American Academy of Pediatrics (AAP)
Red Book Associate Editor
KIMBERLIN, David, M.D.
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, M.P.H., PA-C

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Senior Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
TURNER, James C., M.D.
Executive Director
Department of Student Health and National Social Norms Institute
Professor of Internal Medicine
University of Virginia School of Medicine
Charlottesville, VA

American College of Obstetricians and Gynecologists (ACOG)
RILEY, Laura E., M.D.
Associate Professor, Obstetrics, Gynecology and Reproductive Medicine
Harvard Medical School
Maternal Fetal Medicine
Massachusetts General Hospital
Boston, MA

American College of Physicians (ACP)
POLAND, Gregory A., M.D.
Mary Lowell Professor of Medicine and Infectious Diseases
Mayo Clinic
Rochester, MN

American College of Physicians (ACP) (alternate)
FRYHOFER, Sandra Adamson., M.D., MACP
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American Geriatrics Society (AGS)
SCHMADER, Kenneth, M.D.
Professor of Medicine-Geriatrics
Geriatrics Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
NETOSKIE, Mark J., M.D., M.B.A., F.A.A.P.
Market Medical Executive, CIGNA
Houston, TX

American Medical Association (AMA)
Vacant

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American Nurses Association (ANA)
BREWER, Katie, M.S.N., R.N.
Senior Policy Analyst
American Nurses Association
Silver Spring, MD

American Osteopathic Association (AOA)
GROGG, Stanley E., D.O., FACOP
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
FOSTER, Stephan L., Pharm.D., FAPhA
Professor and Vice Chair, Department of Clinical Pharmacy
University of Tennessee Health Sciences Center, College of Pharmacy
Memphis, TN

Association of Immunization Managers (AIM)
MOORE, Kelly, M.D., M.P.H.
Medical Director, State Immunization Program
Tennessee Department of Health
Nashville, TN

Association for Prevention Teaching and Research (APTR)
McKINNEY, W. Paul, M.D.
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

Association of State and Territorial Health Officials (ASTHO)
MONTERO, José, M.D., M.P.H.
Director, Division of Public Health Services
New Hampshire Department of Health and Human Services
Concord, NH

Biotechnology Industry Organization (BIO)
LEWIN, Clement, Ph.D., M.B.A.
Head, Medical Affairs and Immunization Policy
Novartis Vaccines and Diagnostics
Cambridge, MA

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, M.D.
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization
Idaho Department of Health and Welfare
Boise, ID

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Canadian National Advisory Committee on Immunization (NACI)
WARSHAWSKY, Bryna, MDCM, CCFP, FRCPC
Associate Medical Officer of Health
Middlesex-London Health Unit
London, Ontario, Canada

Department of Health, United Kingdom
SALISBURY, David M., CB, FRCP, FRCPCH, FFPH
Director of Immunisation
Department of Health, London
London, England, U.K.

Healthcare Infection Control Practices Advisory Committee (HICPAC)
ELWARD, Alexis Marie, M.D.
Associate Professor of Pediatrics
Department of Pediatrics, Division of Infectious Diseases
Washington University School of Medicine
St. Louis, MO

Infectious Diseases Society of America (IDSA)
NEUZIL, Kathleen M., M.D., M.P.H., FIDSA
Vaccine Development Global Program (PATH)
Clinical Professor
Departments of Medicine and Global Health
University of Washington School of Medicine
Seattle, WA

Infectious Diseases Society of America (IDSA) (Alternate)
BAKER, Carol J., M.D.
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, M.D.
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A., R.N., M.S., C.P.N.P.
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

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National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, M.D.
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Immunization Council and Child Health Program, Mexico
Vacant

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, M.D.
Professor and Chair
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

National Vaccine Advisory Committee (NVAC)
ORENSTEIN, Walt, M.D.
Chair, NVAC
Associate Director, Emory Vaccine Center
Emory University
Atlanta, GA

Pharmaceutical Research and Manufacturers of America (PhRMA)
BRAGA, Damian A.
President, sanofi pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., M.D., M.P.H., M.S.Ed.
Associate Professor of Pediatrics
Baylor College of Medicine
Houston, TX

Society for Healthcare Epidemiology of America (SHEA)
KEYSERLING, Harry L., M.D.
Professor of Pediatrics
Emory University
Atlanta, GA

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