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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 20-21, 2012
Atlanta, Georgia

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Table of Contents	Page
Agenda	4
Acronyms	6
Wednesday: June 20, 2012	
Welcome and Introductions	8
Dr. Frieden Keynote Address	12
Farewell to Dr. Baker	14
Pneumococcal Vaccines • Introduction • Impact of PCV13 Use in Children • PPSV23 for Adults with Immunocompromising Conditions: Background, Review of Data, and GRADE • PCV13 for Adults with Immunocommpromising Conditions: Background, Review of Data, and GRADE • Cost-Effectiveness of PCV13 for Adults with Immunocompromising Conditions • Recommendations for PCV13 Use Among Immunocompromised Adults	18
Influenza • Introduction • Influenza Activity / Surveillance Update • Vaccine Effectiveness • Vaccine Safety Update • Proposed Recommendations	38
Hepatitis B Protection for Healthcare Personnel (HCP) • Introduction • Overview of Hepatitis B Protection Among HCP • Risk of Exposure and Antibody Levels Over Time • Hepatitis B Protection Among HPC: Cost-Effectiveness Considerations • Future Considerations	58
Pertussis Vaccines • Update: ACIP Pertussis Vaccine Working Group • Update: Pertussis Outbreak in Washington State	78
Meningococcal Vaccines	85
Vaccine Supply	87
Development of Evidence-Based Recommendations Using GRADE • Development of ACIP / CDC Vaccine Recommendations Using GRADE • Strategic Advisory Group of Experts on Immunization (SAGE) Approach to Updating WHO Vaccine Position Papers • Update on GRADE	89
Public Comments Day 1	98

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Thursday: June 21, 2012	
Agency Updates • CDC • Center for Medicare and Medicaid Services (CMS) • Department of Defense (DoD) • Department of Veteran's Affairs (DVA) • Food and Drug Administration (FDA) • Heath Resources and Services Administration (HRSA) • Indian Health Services (I HS) • National Institutes of Health (NIH) • National Vaccine Advisory Committee (NVAC) • National Vaccine Program Office (NVPO)	99
IOM Vaccine Committee Report	103
Adult Immunization • Introduction • Non-Influenza Vaccination Rates among US Adults • Plans for Expanding Vaccine Coverage Tracking for US Adults Using BRFSS • Report on First National Adult Immunization Summit	110
Human Papillomavirus (HPV) Vaccines • Introduction • IIS Sentinel Site Data: Uptake of HPV Vaccine in the US • HPV Vaccine Update	119
Anthrax Vaccine Adsorbed (AVA)	129
Measles, Mumps, Rubella (MMR) Vaccine • Introduction • Epidemiology of Rubella and Congenital Rubella Syndrome (CRS) in the US • Post-Exposure Prophylaxis for Measles with Immune Globulin • Review of Policy Considerations Pertaining to MMR Vaccine	132
Public Comment Day 2	153
Certification	154
ACIP Membership Roster	155

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

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), Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30333
June 20-21, 2012

AGENDA ITEM	PURPOSE	PRESIDER / PRESENTER(s)
Wednesday, June 20, 2012		
8:00 AM - Welcome and Introductions		Dr. Carol Baker (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
8:30 AM - Pneumococcal Vaccines		
Introduction	Information & Discussion	Dr. Nancy Bennett (ACIP, WG Chair)
Impact of PCV13 use in children		Dr. Matthew Moore (CDC/NCIRD)
PPSV23 for adults with immunocompromising conditions: background, review of data, and GRADE		Ms. Tamara Pilishvili (CDC/NCIRD)
PCV13 for adults with immunocompromising conditions: background, review of data, and GRADE		Dr. Kathleen Dooling (CDC/NCIRD)
Cost-effectiveness of PCV13 for adults with immunocompromising conditions		Dr. Charles Stoecker (CDC/NCIRD)
Recommendations for PCV13 use among immunocompromised adults	Vote	Ms. Tamara Pilishvili (CDC/NCIRD)
10:15 AM - *Break*		
10:45 AM - Influenza		
Introduction	Information & Discussion	Dr. Wendy Keitel (ACIP, WG Chair)
Influenza activity/surveillance update		Dr. Lyn Finelli (CDC/NCIRD)
Vaccine effectiveness		Dr. David Shay (CDC/NCIRD)
Vaccine safety update		Dr. Tom Shimabukuro (CDC/NCEZID)
Proposed recommendations	Vote & VFC Vote	Dr. Lisa Grohskopf (CDC/NCIRD)
12:00 PM - *Lunch*		
1:15 PM - Hepatitis B Protection for Healthcare Personnel (HCP)		
Introduction	Information & Discussion	Dr. Mark Sawyer (ACIP, WG Chair)
Overview of hepatitis B protection among HCP		Dr. Sarah Schillie (CDC/NCHHSTP)
Risk of exposure and antibody levels over time		Ms. Meredith Reilly (CDC/NCHHSTP)
Hepatitis B protection among HCP: cost-effectiveness considerations		Dr. Tom Hoerger (Senior Fellow, RTI International)
Future considerations		Dr. Sarah Schillie (CDC/NCHHSTP)
3:15 PM - *Break*		
3:45 PM - Pertussis Vaccines		
Update: ACIP Pertussis Vaccines Work Group	Information	Dr. Mark Sawyer (ACIP, WG Chair)
Update: pertussis outbreak in Washington State		Dr. Jeffrey Duchin (ACIP; Chief Communicable Disease Epidemiology & Immunization Section, Public Health-Seattle & King County)
4:10 PM - Meningococcal Vaccines		
Update: Meningococcal Vaccines Work Group	Information	Dr. Cody Meissner (ACIP, WG Chair)
4:25 PM - Development of Evidence-Based Recommendations Using GRADE		
Development of ACIP/CDC vaccine recommendations using GRADE	Information & Discussion	Dr. Jonathan Temte (ACIP)
Strategic Advisory Group of Experts on Immunization (SAGE) approach to updating WHO Vaccine Position Papers		Professor David Durrheim, University of Newcastle, Australia; SAGE Member
Update on GRADE		Dr. Faruque Ahmed (CDC/NCIRD)
5:10 PM - Vaccine Supply	Information	Dr. Jeanne Santoli (CDC/NCIRD)
5:25 PM - Public Comment		
5:40 PM - Adjourn		

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

AGENDA ITEM	PURPOSE	PRESIDER / PRESENTER(s)
Thursday, June 21, 2012		
8:00 AM - Unfinished Business		Dr. Carol Baker (ACIP Chair)
8:15AM - Agency Updates		
CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH		CDC and *Ex Officio* members
8:30 AM - IOM Vaccine Committee Report		
Identifying and prioritizing new preventive vaccines for development	Information & Discussion	Dr. Guruprasad Madhavan, Dr. Tracy Lieu (IOM Committee on Identifying and Prioritizing New Vaccines for Development)
9:00 AM - Adult Immunization		
Introduction	Information & Discussion	Ms. Kristen Ehresmann (ACIP, WG Chair)
Non-influenza vaccination rates among US adults		Dr. Walter Williams (CDC/NCIRD)
		Dr. Walter Williams (CDC/NCIRD)
Plans for expanding vaccine coverage tracking for US adults using BRFSS		
Report on first National Adult Immunization Summit		Dr. Carolyn Bridges (CDC/NCIRD)
9:30 AM - Human Papillomavirus (HPV) Vaccines		
Introduction	Information & Discussion	Dr. Joseph Bocchini (ACIP, WG Chair)
IIS sentinel site data: uptake of HPV vaccine in the US		Dr. Karen Cullen (CDC/NCIRD)
HPV vaccine update		Dr. Lauri Markowitz (CDC/NCHHSTP)
10:30 AM - *Break*		
11:00 AM - Anthrax Vaccine Adsorbed (AVA)		
Considerations for AVA post-exposure prioritization		Dr. Nancy Messonnier (CDC/NCIRD)
	Information	Dr. Raymond Strikas (CDC/NCIRD)
11:30 AM - Measles, Mumps, Rubella (MMR) Vaccine		
Introduction	Information & Discussion	Dr. Jon Temte (ACIP, WG Chair)
Epidemiology of rubella and congenital rubella syndrome (CRS) in the United States		Dr. Huong McLean (CDC/NCIRD)
Post exposure prophylaxis for measles with immune globulin		Dr. Mark Papania (CDC/NCIRD)
Review of policy considerations pertaining to MMR vaccine		Dr. Huong McLean (CDC/NCIRD)
12:45 PM - Public Comment		
1:00 PM - Adjourn		

Acronyms

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 Servies Administration
I H S	Indian Health Service
IIS	Immunization Information Systems (Immunization Registries)
IOM	Institute of Medicine
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NIH	National Institues of Health
NVPO	National Vaccine Program Office
PCV13	13-valent Pneumococcal Conjugate Vaccine
PPSV23	23-valent Pneumococcal Polysaccharide Vaccine
SAGE	Strategic Advisory Group of Experts (WHO)
TBD	To be determined
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
WG	Work Group
WHO	World Health Organization

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACA	Affordable Care Act
ACCV	Advisory Commission on Childhood Vaccines
ACHA	American College Health Association
ACNM	American College of Nurses and Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Events
AFP	American Family Physicians
AHIP	America's Health Insurance Plans
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AIN	Anal Intraepithelial Neoplasia
AMA	American Medical Association
ANA	American Nurses Association
Anti-HBs	Antibody to Hepatitis B Surface Antigen
Anti-HBc	Antibody to Hepatitis B Core Antigen
ASH	(United States) Assistant Secretary for Health
ASTHO	Association of State and Territorial Health Officials
BMJ	British Medical Journal
BRFSS	Behavioral Risk Factor Surveillance System
CAPITA	Community Acquired Pneumonia Immunization Trial
CDC	Centers for Disease Control and Prevention
CIC	California Immunization Coalition
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
DAIDS	Division of AIDS (NIAID, NIH)
DBD	Division of Bacterial Diseases
DoD	Department of Defense
DMID	Division of Microbiology and Infectious Diseases (NIAID, NIH)
DSMBs	Data Safety Monitoring Boards
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
ECDC	European Centre for Disease Prevention and Control
EHR	Electronic Health Record
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
EOC	Emergency Operations Center
EPINet	Exposure Prevention Information Network
EBRWG	Evidence-Based Recommendations Working Group
FDA	Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety, WHO
GAVI Alliance	Global Alliance for Vaccines and Immunisation
GBS	Guillain–Barré Syndrome
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Treatment
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCP	Health Care Personnel
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
Hib	*Haemophilus influenzae B*
HICPAC	Hospital Infection Control Practices Advisory Committee
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
IAC	Immunization Action Coalition
ICERs	Incremental Cost-Effectiveness Ratios
IDEPC	Infectious Disease Epidemiology, Prevention and Control
IG	Human Immune Globulins
IgG	Immunoglobulin G
IGIM	Immune Globulin given Intramuscularly
IGIV	Immune Globulin given Intravenously
IGSC	Immune Globulin given Subcutaneously
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IIS	Immunization Information System
ISO	Immunization Safety Office
JAMA	*Journal of the American Medical Association*
KD	Kawasaki Disease
LAIV	Live Attenuated Influenza Vaccine
ME	Mucosal/Non-Intact Skin Exposure
MMR	Measles, Mumps, Rubella
MMR-V	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NASH	Non-Alcoholic Steatohepatitis
NCATS	National Centers for Advancing Translational Sciences
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	(Eunice Kennedy Shriver) National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NITAG	National Immunization Technical Advisory Groups
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NREVSS	National Respiratory and Enteric Virus Surveillance System
NSS	National Security Staff
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OSHA	Occupational Safety and Health Administration
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PICU	Pediatric Intensive Care Unit
PI	Percutaneous Injury
PPHF	Prevention in Public Health Fund
PCV13	Pneumococcal Conjugate Vaccine
PPSV23	Pneumococcal Polysaccharide Vaccine
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
ROC	Rank Order Centroid
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts
SES	Socioeconomic
SME	Subject Matter Expert
STIKO	German Standing Vaccination Committee Ständige Impfkommission
SWOT	Strengths, Weaknesses/Limitations, Opportunities, Threats Analysis
TAGS	Regional Technical Advisory Groups (of the WHO)
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccine and Related Biologic Products Advisory Committee (FDA)
VSD	Vaccine Safety Datalink
VTEUs	Vaccine and Treatment Evaluation Units
VTrckS	Vaccine Tracking System
WA DOH	Washington State Department of Health
WER	Weekly Epidemiological Record
WHO	World Health Organization

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Welcome & Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Baker called the meeting to order, welcoming those present. She then turned the floor over to Dr. Pickering for opening remarks.

Dr. Pickering welcomed everyone to the June 2012 Advisory Committee on Immunization Practices (ACIP) meeting. He said that this meeting, although extremely exciting, was a little depressing because it would be the last official meeting for four of the members.

He indicated that the proceedings of this meeting would be accessible 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: Stephanie Thomas, Natalie Greene, Tanya Lennon, and Chris Caraway.

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 at this meeting will be posted on the ACIP website approximately one to two weeks after the meeting concludes, the live webcast will be posted within three weeks following the meeting, and meeting minutes will be available on the website three months or 90 days following this meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized several visitors, organized by the Pan American Health Organization (PAHO) of the World Health Organization (WHO), who were in attendance. The delegation included 6 members of Argentina's Immunization Commission, including the Executive Secretary of the committee, accompanied by technical staff from the PAHO office in Washington, DC. The previous day, the PAHO group, Dr. Jean Smith, and CDC staff from the Global Immunization Division held a working meeting to finalize an internal policy document laying out the Argentina committee's policies and operational procedures. This document draws on ACIP terms of reference as one example, as well as PAHO Operational Guidelines for National Immunization Technical Advisory Groups (NITAGs). The Argentina committee also began drafting an article for publication on their national immunization policymaking process. The committee hopes to share lessons learned from the process of developing and standardizing evidence-based approaches for immunization policy in their country with other countries in the region and around the world. Dr. Pickering requested that members of the delegation stand to be recognized. He noted that in Argentina, the immunization schedule is on all of the milk cartons, which is a wonderful idea. On behalf of ACIP and CDC, Dr. Pickering expressed appreciation to the Sabin Vaccine Institute, which provides financial and logistic support for participation of National Immunization Committee members from Latin America to attend ACIP meetings.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Also attending this meeting was a delegation from the Ministry of Health of Japan, including Dr. Yosuke Kita, Medical Officer for the National Immunization Program, Division of Tuberculosis and Infectious Disease Control, Ministry of Health, Labour, and Welfare; and Dr. Hajime Kamiya, Medical Officer, National Institute of Infectious Diseases, Infectious Disease Surveillance Center, Tokyo, Japan. Dr. Pickering requested that they stand to be recognized. Upon his return to Japan, Dr. Kita will continue discussions with the Ministry of Health regarding establishment in Japan of a national committee on immunization.

Dr. Pickering then recognized the following *ex officio* members and liaison representatives:

***Ex Officio* Members**

- Dr. Linda Kinsinger, Department of Veterans Affairs (DVA) and Ms. Mary Beth Hance, Center for Medicare and Medicaid Services (CMS), joined the meeting by telephone to answer questions and present their agencies' updates.

Members

- Ms. Sara Rosenbaum was scheduled to arrive later in the morning.

Liaison Representatives

- Dr. Laura Riley, American College of Obstetricians and Gynecologists (ACOG), was not present. Dr. Richard H. Beigi was in attendance on her behalf.

To avoid disruptions during the meeting, Dr. Pickering instructed those present to conduct all business not directly related to discussion of ACIP activities in the hall and to turn off all cell phones or place them in the vibrate mode. Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting. He reminded members that the annual ACIP group photo would be taken in the auditorium before lunch.

Dr. Pickering explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the end of the day in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room to have Stephanie Thomas record their name and provide information on 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 deliberations or committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

participate in a discussion with a proviso that he or she abstains on all votes related to the vaccines of that company.

Since the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is a new process to ACIP, educational materials have been placed on the ACIP website. In addition to the information shown on the slide, the GRADE handbook for development of evidence-based recommendations has been posted on the ACIP website. Dr. Pickering indicated that there would be a discussion of the GRADE process during this meeting.

Applications for ACIP membership are due no later than November 16, 2012 for the 4-year term beginning July 2013. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP website:

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

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

Dr. Pickering noted that at every meeting, an update is provided on the status of ACIP recommendations. Links to these recommendations and schedules can be found on the ACIP web site. A listing of recommendations that have been published since the February 2012 ACIP meeting follows:

ACIP Recommendations Published Since February 2012

Title	Publication Date	MMWR Reference
Recommended Adult Immunization Schedule — United States, 2012	2/3/12	2012;61:1-7
Recommended Immunization Schedules for Persons Aged 0 Through 18 Years — United States, 2012	2/10/12	2012;61:1-4
New Framework (GRADE) for Development of Evidence-Based Recommendations	5/11/12	2012;61:327
Licensure of 13-Valent Pneumococcal Conjugate Vaccine for Adults Aged 50 Years and Older	6/1/12	2012;61:394-395

The following resource information was shared pertaining to ACIP:

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

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

Next ACIP meeting: Wednesday – Thursday, October 24-25, 2012
Registration Deadline: Non-U.S. Citizens *and* US Citizens October 10, 2012

Vaccine Safety: www.cdc.gov/vaccinesafety/

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Immunization Schedules (2012):
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/spec-grps/hcp/conversations.htm

Before officially beginning the meeting, Dr. Baker called for a roll call 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.
- Dr. Cody Meissner: Payments are made to Tufts University Medical Center by Pfizer for participation in multi-center clinical trials.
- The remainder of the ACIP members declared no conflicts.

Dr. Baker indicated that this was a very difficult meeting for her. One of the reasons was that ACIP was losing three members who have become or already were very close friends. She indicated that Ms. Kristen Ehresmann is the Director of Infectious Disease Epidemiology, Prevention and Control (IDEPC) of the Minnesota Department of Health in St. Paul, Minnesota. One of Dr. Baker's favorite comments about Ms. Ehresmann's disclosure of conflict of interest was during a human papillomavirus (HPV) discussion when she disclosed that she had an adolescent son. As a member, she has chaired the Adult Immunization Working Group and the Immunization of Healthcare Personnel (HCP) Working Group, and also has been a member of four working groups: Harmonization of the Child / Adolescent Immunization Schedule, Meningococcal Vaccine, Hepatitis Vaccines, and Pertussis Vaccines. Dr. Baker expressed gratitude for Ms. Ehresmann's service and presented her with a certificate, as well as a gift of appreciation. Ms. Ehresmann indicated that this had been a wonderful experience for her, and that it was an honor to be able to participate on the ACIP. She said she had learned so much, and had enjoyed getting to know so many wonderful people. She said she would like to think that she would be remembered for contributions related to the state perspective and the immunization program perspective. However, she realized that one of the things she was most known for were the nuts and berries treats she brought. In light of that, and knowing that future members may not have that same propensity, she brought treats to share with everyone. She wished everyone the best and thanked them for the opportunity.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Baker then recognized Dr. Michael Marcy, who is a Clinical Professor of Pediatrics at the University of Southern California and the University of California at Los Angeles Schools of Medicine in Los Angeles. He has chaired the Pneumococcal Vaccine Working Group, and has been a member of the HPV Vaccine and Meningococcal Vaccine Working Groups. She said it seemed as though she had known Dr. Marcy since she was a young child, and he had never aged although she had gotten older. She thanked him for his service and presented him with a certificate, as well as a gift of appreciation. Dr. Marcy said that this was his last meeting, and he saw Dr. Schuchat trying to suppress a smile. Like so many who had gone before him, he felt that this had really been the high point of his medical career. The best part had been being able to work with persons not only at this table, but also CDC staff, liaison representatives, representatives of industry, representatives of academia, and private citizens, all of whom come together to try to reduce the suffering due to vaccine-preventable diseases. He said that being a member of this committee had been an honor and a privilege for which he was most grateful, and that he would miss it.

Dr. Baker then recognized Dr. Cody Meissner, who is a Professor of Pediatrics at the Tufts Medical Center in Boston. He has been Chair of the Meningococcal Vaccine Working Group and the Harmonized Child / Adolescent Immunization Schedule, and has participated in the Measles, Mumps, and Rubella (MMR) Vaccine Safety Working Group; the Japanese Encephalitis Vaccine Working Group; and the now retired Respiratory Syncytial Virus (RSV) Immunoprophylaxis Working Group. Dr. Baker said that Dr. Meissner had been a friend for a very long time, and that while she would miss seeing him at the ACIP meetings, she hoped to see him in other venues. She thanked him for his service and presented him with a certificate, as well as a gift of appreciation. Dr. Meissner said that it was hard to believe four years had passed so quickly, and to participate in the deliberations of ACIP over the past four years, and to witness the impact of these decisions on healthcare in the US had been a remarkable experience. He said that it had been a privilege to work with so many talented and dedicated individuals at CDC. He also acknowledged the energetic and selfless commitment of present and previous ACIP members, and that this experience had been quite inspiring for him. He expressed his hope that he had been able to contribute in some small measure to the accomplishments of the group.

Keynote Address

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

Dr. Frieden greeted everyone, thanked them for their commitment to public health and immunization, and added his gratitude to the four out-going members of ACIP. He thanked Dr. Baker for her stewardship and leadership, noting that she was completing her term as Chair and was the second ever female Chair. He also thanked Ms. Ehresmann and Drs. Marcy and Meissner for contributing their time and expertise to this very important work. In addition, Dr. Frieden welcomed those from Argentina and Japan, as well as those watching on the webcast. Traveling around the world, Dr. Frieden said he has been struck by the need for entities like ACIP in various countries. He believes that ACIP represents a best practice in public health, identifying key information, assessing scientifically and objectively what is available, deliberating openly and transparently, and coming to conclusions that are widely accepted by the medical community, insurers, providers, and policymakers. While they might not be right 100% of the

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

time, they could certainly be open 100% of the time and be based on data 100% of the time. He thinks that ACIP does its human best to do that.

Dr. Frieden noted that it was the 48th anniversary of ACIP's establishment. ACIP first met in 1964 in the recently departed Building 1, which many people still miss even though it was falling apart. During that meeting, ACIP covered 5 topics with 9 members. There were 3 invited participants and 10 CDC staff. ACIP has grown since then, but its essential efforts have not really changed. In fact, some of the topics have not changed as much as might be thought. He reviewed the minutes from that meeting earlier in the morning, and discussed a couple of excerpts from them. In 1964, ACIP discussed the vaccine schedule and how many different visits were needed in the first 16 years of a child's life and concluded that simplification was of practical importance. They commented that "the relative advantages and disadvantages of administration of these antigens at various intervals after birth, the spacing of doses, and the scientific and administrative decisions inherent in establishing practical immunization schedules are particularly important." So, the issue of balancing simplification, practicality, and science has been a challenge for close to 50 years. During the 1964 meeting, ACIP also discussed influenza vaccination. They said that "influenza vaccination has been shown to confer a substantial, if not a spectacular, order of protection against clinical illness" and they noted that "constant vigilance nationally and internationally is important if early detection of strains showing a marked antigenic shift is to be established." They further noted that "controlled field studies of vaccine efficacy among high risk groups are of vital importance."

In order not to be asking the same question in 10 to 20 years, it is important to ensure that practical studies and analysis are established that will help to achieve a simpler vaccine schedule, and will enable it to be targeted to people who will benefit the most and ensure that the highest risk groups benefit at least as much if not more than others. Other topics covered during that 1964 meeting included measles vaccination and rubella, for which there was not yet a widely accepted vaccine and which had seen a resurgence. At that time, ACIP also discussed the international implications of the smallpox effort. There had not yet been a decision to try to eradicate smallpox, but there was recognition that enormous successes were possible and that great progress was being made.

Disease eradication is really the ultimate goal in both sustainability and equity, because it is for everyone and for always. Smallpox has been eradicated, and polio is close to eradication. Currently, there is polio in fewer countries and fewer districts than ever before in recorded human history. Yet, there are enormous challenges in those remaining districts. It is encouraging to note that there is a tremendous commitment not only globally, but also in the leadership of countries, to polio eradication to protect children. Fundamentally, protecting children is what polio eradication is all about. CDC activated its Emergency Operations Center (EOC) in December 2012 and is doing everything within its power to support individuals and healthcare workers and to protect children, working with entities in countries to achieve polio eradication. Dr. Frieden is confident that polio will be eradicated in the near future.

In closing, Dr. Frieden again expressed his gratitude to all of the ACIP members. Ultimately, the wonder of ACIP is the reliance on objective data openly derived and the reliance on a decision-making process that is rational and openly engage in, with input from interested parties and the public and with a clear statement of what is known, what is unknown, and what will be done based on that knowledge.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Farewell to Dr. Carol Baker

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Pickering said that as many people knew, he has known Dr. Baker nearly his entire lifetime. When he was in high school, he admired her academic career and had followed her achievements since then. Dr. Baker was appointed as a member of ACIP on July 1, 2006 and has served as the ACIP Chair since September 1, 2009. The following photograph is Dr. Baker as she appeared at her first ACIP meeting:

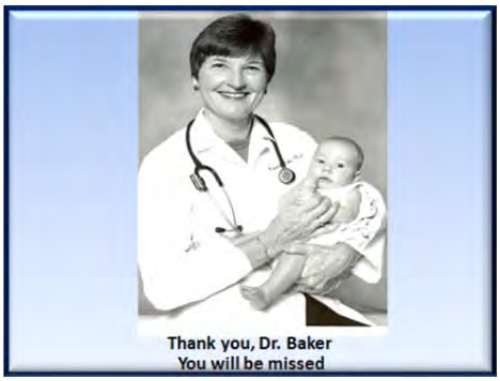
Dr. Pickering highlighted Dr. Baker's career as an ACIP member and subsequently as the ACIP Chair. There has been immense output by ACIP during Dr. Baker's tenure. In 2009 there were 12 publications (6 policy notes, 3 recommendations and reports, and 3 other); in 2010 there were 16 publications (6 policy notes, 7 recommendations and reports, and 3 other); in 2011 there were 15 publications (10 policy notes, 3 recommendations and reports, and 2 other); and in 2012 there have been 4 (1 policy notes and 3 other). ACIP recommendations are not official until Dr. Frieden approves them and they are published in the *Morbidity and Mortality Weekly Report* (*MMWR*). Dr. Frieden has approved all ACIP recommendations developed during Dr. Baker's tenure as ACIP chair. The *MMWR* publishes ACIP recommendations in several categories: policy notes, recommendations and reports, and other. The policy notes are short and are produced with a quick turnaround time; whereas, the recommendations and reports take a much longer period of time and are much lengthier and more detailed. The "other" category includes immunization schedules, notices to readers, and procedure updates. With Dr. Baker's support and urging, CDC is moving more toward policy notes, because as Dr. Baker has stated many times, it is important to get the information out to the public so that vaccines can be administered to people quickly.

At the working group level, Dr. Baker served as Chair of the Meningococcal Working Group from 2003 through 2009; as Chair of the Pregnancy Working Group from 2008 through 2009; Chair of the Yellow Fever Working Group from 2008 through 2010; and as a member of the Pertussis and Pneumococcal Working Groups from 2008 through 2009. This represents a phenomenal amount of work that has been undertaken. Select publications during Dr. Baker's tenure include Meningococcal Vaccine: Revaccination of People at Prolonged Risk; Yellow Fever Vaccine; Standardization of Pregnancy Recommendations; Vaccine Abbreviation

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Recommendations; GRADE Implementation; General Recommendations on Immunization; and Immunization of Health Care Personnel. While Dr. Baker was Chair of the Meningococcal Working Group, several recommendations were published, including an *MMWR* establishing recommendations for people at prolonged increased risk for meningococcal disease and the utilization of MCV4 [*MMWR*, September 25, 2009 / 58(37);1042-1043]. As Chair of the Yellow Fever Working Group, the 2002 recommendation document for use of yellow fever vaccine was updated in which the epidemiology of disease and vaccine safety issues were addressed [*MMWR*, July 30, 2010 / Vol. 59 / No. RR-7]. A major area of Dr. Baker's research has dealt with improving the health of pregnant women and infants. Dr. Baker provided guidance to ACIP on a process to formulate policy for vaccine recommendations for pregnant and breastfeeding women to ensure that recommendations on immunizations for pregnant women are developed using a consistent, rigorous process and are presented with clarity and uniformity. Dr. Baker's tireless effort in the area of prevention of perinatal Group B Streptococcal Disease has been monumental. Her work with Dr. Schuchat, members of the Division of Bacterial Diseases, and others in the National Center for Immunization and Respiratory Diseases (NCIRD) resulted in an *MMWR* publication titled "Prevention of Perinatal Group B Streptococcal Disease [*MMWR*, November 19, 2010 / Vol. 59 / No. RR-10]. Dr. Pickering emphasized that someday, ACIP will vote on a GBS vaccine.

In summary, the following recommendations were made by ACIP in 2011: Tdap (Updated Recommendations; Pregnant Women and Infant Contact); Influenza (Antiviral Agents; Annual Recommendations); General (General Recommendations on Immunization; Adult Schedule; Childhood Schedule; Health Care Personnel); MCV4 (Updated Recommendations; Booster Dose; Increased Risk); JEV (Booster Dose); Herpes Zoster (Update 50 through 59 Years of Age); HPV (Males); and HBV (Diabetes Mellitus). As thought is given to the variety of these recommendations, Dr. Baker's imprint can be recognized either directly or indirectly on all of the recommendations listed. In each of these areas, everyone will remember Dr. Baker's input, thoughtfulness, and guidance as ACIP moves forward. Dr. Pickering presented Dr. Baker with a certificate, plaque, and a framed Dr. Seuss poster. Many years ago, the Department of Health and Human Services (HHS) partnered with Dr. Seuss's wife to develop immunization posters with the Dr. Seuss logo. He concluded with the following photograph of Dr. Baker:

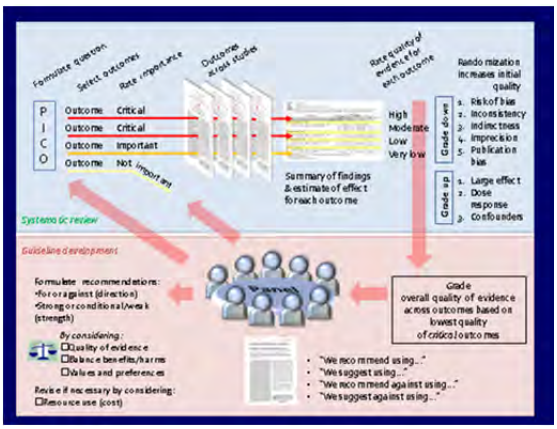


Dr. Baker read the first sentence of the Dr. Seuss poster, "Attention one and all. Please lend me your ear. Immunizations have changed. It's been quite a year." She thanked Dr. Pickering and said she was really worried about what he was going to say and which pictures he would show. The first photograph was when she was a post-Doctoral fellow. She said that one of the things she had learned as ACIP Chair was to learn from former Chairs. She also highlighted moments from her ACIP tenure. When she became the ACIP Chair July 1, 2009, she

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

scheduled a 4-day summer vacation, during which she got to discuss pandemic influenza H1N1 with the committee because there were many issues. This was followed by the vote for influenza seasonal vaccine for everyone 6 months of age and older. Tdap vaccine already had been licensed and approved for routine use, but the interval was a barrier to immunization, so the interval was changed to address “elders” and pregnant women. Hopefully, this will result in an impact on reducing young infant deaths. Also during Dr. Baker’s tenure, ACIP recommendations for immunization of healthcare providers were updated; a meningococcal conjugate booster vaccine was recommended for adolescents / college students and MCV4 was recommended for high risk children 9 through 24 month olds; Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was adopted; and HPV vaccine was recommended for young males, although she was unable to attend the meeting due to her mother’s emergency hospitalization.

Dr. Baker recommended that those who did not understand GRADE should study the following illustration:



She emphasized that annual ACIP tasks are also important. In terms of seasonal influenza vaccine and antiviral recommendations, Dr. Baker expressed gratitude to Dr. Keitel, whose friendship she has enjoyed for decades, but she stressed that it was great to have Dr. Keitel on the committee with her knowledge of influenza. The adult and pediatric immunization harmonized schedules have been less of an issue than in some previous ACIP tenures. Safety is always an issue. There were concerns of febrile seizures with MMRV and the scare of the other GBS with MCV4. While there were supply issues (e.g., Zostavax®) during Dr. Baker’s tenure, they were not as challenging as in the past. VFC for new vaccines, as well as unanticipated issues, also must be dealt with annually.

Dr. Baker shared a quote that previously was shared by Dr. Morse, and said that she knew this when she first came to ACIP, “Statistics are people with their tears wiped dry” [Dr. Jules Richmond, Former Surgeon General]. She said that what she now knows better than she did before was reflected in the quote, “As there are persons who mend torn garments, so there are physicians who heal the sick; but your duty [speaking to ACIP and CDC] is far nobler and one befitting a just person – namely to keep people in health” [Xenophon in *Cryopaedia*, 400 BC]. She emphasized that this really should be their goal—to keep people, especially children, in good health.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Things Dr. Baker said she had learned as Chair:

- ❑ I'm never the smartest person in the room
- ❑ I'm not the only one who doesn't fully comprehend cost-effectiveness analyses
- ❑ Acronyms, acronyms, acronyms…
- ❑ Never debate about vaccine policy with someone from the UK
- ❑ Even if you have a seating chart with names, you still may get it wrong
- ❑ How to terminate discussion with tact
- ❑ How to love one branch of the federal government
- ❑ And last, how to ring the bell!

She also learned how to speed read, because one of things they never told her until she received the first set of minutes was that she had to read the 100 to 200 page document and sign her name. Because she worries about signing her name to something she had not read, she read them.

In terms of financial disclosures, Dr. Baker reported that she received from the tax payers economy airfare, 2 nights hotel expense, a daily stipend, and the right to buy lunch at the meetings without standing in line. The knowledge and friends she gained was an immense blessing, and was not subject to the OGA form or federal income tax.

There are many challenges ahead for ACIP. Dr. Baker said she would be thinking about and praying for the members as they deal with adequate CDC financing, appropriate ACIP members to inform policy, creation of improved vaccine infrastructure, more vaccines added into the schedules, improved immunization rates, and vaccine refusal. She stressed what an immense privilege it had been to know the members, the liaisons, and especially the wonderful people at CDC. If she were in charge of the budget, Dr. Baker would give them a big piece. She emphasized that they must remember the goal, which she illustrated with a number of photographs of pregnant and post-partum women, families, and children. Keeping children and adults healthy is the job of ACIP.

In conclusion, Dr. Baker said she that while she would miss this job, she would not fall apart. She and Rocky will be thinking of and praying for all of those who remain into the future. Rocky will guide her across the country on their road trip. They may stop at a winery or two in California, but Texas has wineries, too. She thanked everyone very much for their friendship, and said that she was a better person for having had this job, and she really would miss it.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Pneumococcal Vaccines

Introduction

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

Dr. Bennett began this session by offering gratitude to Dr. Baker for all that she has done for ACIP. She also thanked the working group for their very exciting discussions over the last few months.

She then reminded everyone that 13-valent pneumococcal conjugate vaccine (PCV13) for adults was licensed for use among adults ≥50 years old on December 30, 2011. FDA approved PCV13 under the Accelerated Approval Pathway, based on non-inferior immunogenicity compared to pneumococcal polysaccharide vaccine (PPSV23). The indications for PCV13 are prevention of pneumococcal disease, including pneumonia and invasive disease, in adults 50 years of age and older; and prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. A condition of licensure was a randomized controlled trial (RCT) to evaluate the efficacy of PCV13 against pneumococcal pneumonia among adults ≥65 years old that is being conducted in the Netherlands.

The terms of reference for the Pneumococcal Vaccines Working Group are to:

- ❑ Review data on immunogenicity, efficacy, and cost-effectiveness of pneumococcal conjugate vaccines in adults
- ❑ Determine whether data available to date on PCV13 immunogenicity and cost-effectiveness are sufficient to determine value of immunizing adults with PCV13
- ❑ Develop a revised statement on pneumococcal immunization if determined that a statement including PCV13 recommendations for adults is necessary

During the February 2012 ACIP meeting, the issue regarding whether all adults should receive PCV13 was presented. The working group reviewed with ACIP evidence for PCV13 use among adults ≥50 years of age. The recommendation was deferred based on the belief that there were critical data that were not available at that time, including efficacy against pneumonia that is being assessed in the Community Acquired Pneumonia Immunization Trial (CAPITA); and understanding the indirect (herd) effects of PCV13 use in children. There simply has not been ample time to observe PCV13 indirect effects in adults.

Also during the February 2012 ACIP meeting, a tentative timeline was presented. The expectation was that the issue of the use of this vaccine in immunocompromised adults, and an update on indirect effects from use of PCV13 in children would be presented during the June 2012 ACIP meeting. The hope is that a further update will be offered during the October 2012 ACIP meeting on the impact of the vaccine across the population, and that by the February 2013 ACIP meeting preliminary results may be available from the CAPITA trial. An update also will be presented at that time regarding the indirect effects from use of PCV13 in children.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Perhaps by the June 2013 ACIP meeting, a recommendation can be made on the use of this vaccine in all adults.

Dr. Bennett indicated that during this session, presentations would be delivered on the impact of PCV13 use in children; PPSV23 for adults with immunocompromising conditions; PCV13 for adults with immunocompromising conditions; cost-effectiveness of PCV13 for adults with immunocompromising conditions; and recommendations for PCV13 use among immunocompromised adults.

The objectives of this session were for the working group to propose adding a dose of PCV13 to the currently recommended regimen of PPSV23 for adults with immunocompromising conditions. Given that the evidence, data, and rationale behind this policy change are somewhat complicated, the working group requested that ACIP review the presented evidence and consider a vote on a proposed recommendation at the end of this session.

Impact of PCV13 Use in Children

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

Dr. Moore reiterated the importance of understanding the indirect effects of PCV13 on invasive pneumococcal disease (IPD) among adults. There was a substantial (>90%) reduction in PCV7-type IPD caused by the serotypes included in the 7-valent vaccine among adults observed within 7 to 8 years of PCV7 introduction for children in 2000. The expectation is that a similar reduction may be observed over time among adults following introduction of PCV-13 for children. In addition to the CAPITA trial, the working group wanted to provide an update on this trend in IPD among adults. This information comes from data on IPD from CDC's active, population-based surveillance program, which is conducted in 10 areas throughout the United States (US).

Cumulative cases of IPD caused by the 6 additional serotypes that are new to PCV13 that were not in PCV7 among children under the age of 2 years from 2006 through about the first quarter of 2012 were presented. In 2007, the cumulative cases of IPD increased rapidly during the first part of the year, flattened out during the summer months when the incidence of IPD typically declines, and accumulated more rapidly toward the end of the year. This is typical of pneumococcal disease epidemiology from year-to-year. After PCV13 was introduced for children, in 2010 there was a typical rapid increase at the beginning of the year, a flattening out over the summer, the beginning of an increase toward the end of the year, and then a flattening out again. In 2011, there was a dramatic reduction in the incidence of IPD caused by the additional serotypes among children under the age of 2. That trend has continued into the first quarter of 2012.

A very similar trend was observed in adults 50 through 64 years of age, and then suddenly during the fourth quarter of 2011, there was a flattening of the accumulation of cases. A continuation of that reduction was observed through the first quarter of 2012. For adults 65 years of age and older, again for the latter part of 2011 there was a slight flattening out, which became much more obvious during the first part of 2012. There were dramatic reductions in serotype 19A and 7F with each successive period of observation from 2006 through 2011. Surmised from this is that not only have the rates of IPD declined among adults, but also they declined primarily because of reductions in serotypes 19A and 7F.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Thus, there is clear evidence of reductions in IPD driven by the additional serotypes in PCV13. The first evidence of this among children under the age of 2 years was in the fourth quarter of 2010, about 6 to 9 months after the vaccine was introduced. The first evidence among adults over 50 years old was in the fourth quarter 2011, about a year later. This has been driven especially by serotypes 19A and 7F. This trend is consistent with what was observed with introduction of PCV7, with a reduction in the incidence of disease among children under the age of 2 years, followed by reductions among older adults about a year or so later. CDC will continue to monitor these trends, and will report back to ACIP during future meetings.

Discussion Points

Dr. Duchin observed that there seemed to be some natural variability from year-to-year. He noticed that some of the earlier years had lower rates of disease in adults and children than some of the later years. He wondered whether it was possible to model what would be expected based on the variability that has been observed in past years, and the reductions that have occurred over time.

Dr. Moore replied that such a model is being created that will project into the future what trends will occur if PCV13 performs identically to PCV7. The results can be reported to ACIP in the future.

Dr. Schuchat found the 2012 data to be very exciting, and she wondered whether there had been time to assess the non-13-valent type disease. Another issue pertaining to 2011-2012 is the very warm winter and the very mild influenza season.

Dr. Moore responded that the trends have been typical for non-13-valent type disease.

PPSV23 for Adults with Immunocompromising Conditions: Background, Review of Data, and GRADE

Tamara Pilishvili, MPH
Epidemiologist
Respiratory Diseases Branch
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Pilishvili reminded the group that ACIP currently recommends use of PPSV23 in all adults 65 years of age and older, as well as adults 19 through 64 years of age with the following conditions: immunocompetence (e.g., chronic heart disease, chronic lung disease, diabetes mellitus, CSF leaks, alcoholism, cigarette smoking, asthma); functional / anatomic asplenia (e.g., sickle-cell anemia and congenital or acquired asplenia); and immunocompromised (e.g., HIV, hematologic cancer, solid cancer, transplant).

Routine revaccination with PPSV23 is not recommended for most persons. A second dose of PPSV23 is recommended 5 years after the first dose for persons aged 19 through 64 years with functional or anatomic asplenia; immunocompromising conditions (congenital or acquired immunodeficiencies; HIV infection; chronic renal failure or nephrotic syndrome; leukemias, lymphomas, Hodgkin disease; generalized malignancy; diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy; solid organ transplantation; multiple myeloma). For the remainder of the session, this entire group was referred to as adults with immunocompromising conditions for simplicity.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The first reason this presentation and the remainder of this session was focused on adults aged 18 through 64 years with selected underlying conditions is because of the very high incidence of IPD in adults with immunocompromising conditions. Individuals with hematological cancer and HIV / AIDS have the highest risk for IPD, with over 20-fold increased rates of disease compared to persons without these conditions [Kyaw, JID 2005;192:377-86]. The second reason to focus on this group is that the data demonstrate high rates of disease for immunocompromised persons despite the indirect effects of PCV7. Rates of PCV7-type IPD in this population are several folds higher than those among immunocompetent persons. The rates of overall and PCV7-type IPD have declined dramatically in both groups since introduction of PCV7 in 2000. However, among HIV-infected adults, the incidence of PCV7-type IPD is still more than 8 times higher than the pre-vaccine incidence in HIV uninfected adults. In other words, although PCV7 has reduced IPD rates in adults with HIV infection and without HIV infection, a very large disparity in disease rates still remains [Cohen, AIDS 2010;24(14):2253-62].

With regard to Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) of the evidence for PPSV23 use among immunocompromised adults, PPSV23 currently is a recommended vaccine for adults with immunocompromised conditions. In February 2012, GRADE of evidence was presented for PCV13 use for this group, and the key question for GRADE compared PCV13 use to PPSV23 use. In order to make this comparison of the new vaccine, PCV13, to currently recommended vaccine, it became evident that the working group needed to systematically review and evaluate the quality of available data for PPSV23.

The working group applied the the GRADE system to the current PPSV23 recommendations for immunocompromised adults. The following steps were included in the process of evaluating a body of evidence and moving from evidence to recommendations:

1. Formulate specific policy question
2. Identify and rank relative importance of outcomes
3. Summarize relevant evidence for each outcome, including number needed to vaccinate (NNV) where possible
4. Assess quality of evidence for each outcome
5. Summarize quality of evidence across outcomes
6. Review health economic data
7. Assess the balance of risks and benefits
8. Determine the recommendation category

First, the working group formulated a specific question to be answered by a recommendation. The policy question of interest is, “Should PPSV23 be administered routinely to adults with immunocompromising conditions?” The question formulated for GRADE was, “Should PPSV23 be administered routinely to adults with HIV?”

In terms of the rationale for GRADE of PPSV use among persons with HIV, HIV was chosen as a representative immunocompromising condition because the majority of evidence from published studies was available for adults with HIV. The corresponding question for PCV13 use among immunocompromised adults was presented during the February 2012 ACIP meeting, and was subsequently GRADEd for adults with HIV. The risks associated with PPSV use are not expected to be higher among adults with other non-HIV immuocompromising conditions. However, the expected benefits may not be generalizable to all immunocompromised adults.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

After formulating the key policy question, the target population (e.g., adults 19 years of age or older with HIV infection), intervention (e.g., PPSV23 administered as a single dose injection), and the control (placebo) group were defined for this question. Also defined were relevant health outcomes, and the relative importance of each outcome, including both desirable and undesirable effects, were determined. The following outcomes were ranked as critical: IPD, pneumococcal pneumonia, hospitalizations, deaths, serious adverse events, or systemic adverse events. All critical outcomes were included in the evidence profile. Data were missing on the critical outcome of hospitalizations.

In the evidence profile for the critical outcome of IPD, one clinical trial was included. This was a double blind, randomized placebo controlled efficacy trial among HIV-infected adults in Uganda. IPD was defined as isolation of pneumococcus from a normally sterile site. The intervention was a single dose of PPSV23. The results of the initial trial and follow-up study that was conducted in the same cohort show that PPSV was ineffective against IPD in HIV-infected adults. Negative but not statistically significant vaccine efficacy estimates were reported. The study findings, however, may have limited generalizablity to the US HIV-infected population. Of note, almost half of the study participants had CD4 counts below 200 cells/uL at enrollment.

In the evidence profile for the critical outcome of IPD, 6 observational studies evaluating the effectiveness of PPSV against all IPD among HIV+ adults were also included. The studies differed by size of the population, geographic location, and the percentage of IPD caused by vaccine types, but were fairly similar in terms of the level of immunosuppression among the participants. The adjusted vaccine efficacy estimates ranged from 10% to 86%. The overall effectiveness was estimated at 49%, which corresponds to the odds ratio of 0.51 (0.39, 0.66) and the results of the test of heterogeneity suggest that the data were fairly homogeneous.

In order to calculate number needed to vaccinate, the overall effectiveness of PPSV23 obtained from observational studies was applied to the incidence of IPD in HIV-infected adults in the US. An estimated rate was applied of 155 IPD cases with HIV/100,000 persons with AIDS based on 2010 data. Assuming 49% effectiveness and 100% coverage, a rate of 79 cases per 100,000 in vaccinated HIV-infected people was estimated. Therefore, the estimated number needed to vaccinate to prevent one IPD case would be 1316. The main limitation of this analysis is that the number needed to vaccinate was estimated based on vaccine effectiveness data from observational studies rather than efficacy studies.

For the critical outcome of IPD, one RCT was included that was downgraded from evidence Type 1 to Type 3 due to very serious concerns about indirectness. As mentioned earlier, the study was conducted in HIV+ highly immunosuppressed adults in Uganda [French N, et.al. 2000]. For the 6 observational studies included for this critical outcome, the evidence type was downgraded from Type 3 to Type 4 due to concerns about the risk of bias inherent in observational studies.

In the evidence profile for the critical outcome of pneumonia, the same efficacy trial among HIV-infected adults in Uganda was included. Pneumonia was defined as acute respiratory illness with chest radiograph confirmation. The results of both the initial trial and the follow-up study show that all-cause pneumonia was significantly more frequent in the vaccine arm than in the placebo arm, although the mechanism of failure in this population is not understood and it is unclear whether we these results can be generalized to the US population of HIV-infected adults.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In the evidence profile for the critical outcome of pneumonia, 5 observational studies evaluating effectiveness of PPSV against all-cause pneumonia among HIV+ adults were included. The studies differed by size of the population and geographic location, but were fairly similar in terms of the level of immunosuppression among the participants. The adjusted estimates ranged from no effectiveness to 58% effectiveness. The overall effectiveness was estimated at 31%; however, results of the test of heterogeneity have a significant p-value, which suggests that the data were highly heterogeneous.

For the critical outcome of pneumonia, one RCT was included that was downgraded from Type 1 to Type 3 due to serious concerns about indirectness. The study was conducted in highly immunosuppressed HIV+ adults in Uganda. For the 5 observational studies included for this critical outcome, the evidence type was downgraded from Type 3 to Type 4 due to inconsistency and due to concerns about the risk of bias inherent to observational studies.

In the evidence profile for the critical outcome of death, the same efficacy trial among HIV-infected adults in Uganda was included. The results of the initial trial showed no efficacy against this outcome, but the follow-up study showed 16% efficacy against mortality. This survival advantage in the follow-up study could be a chance finding, given that the same study showed lack of efficacy for pneumococcal outcomes. The authors report no changes in other opportunistic infections or clinical visits, suggesting that changes in health seeking behaviors could not explain results.

For the critical outcome of death, one RCT was included that was downgraded from Type 1 to Type 3 due to indirectness and other considerations, such as inconsistent findings on the follow-up study.

For the critical outcome of serious and systemic adverse events, post-licensure surveillance data were included. Severe systemic adverse events were reported rarely following PPSV receipt. There were no reports of severe febrile or anaphylactic reactions, and no neurologic disorders (e.g., Guillain-Barré syndrome) or deaths were associated with PPSV. Moderate systemic reactions (e.g., fever and myalgias) and severe local reactions (e.g., local induration) are rare. The evidence quality was judged to be Type 3 because no serious concerns were noted due to biases, inconsistency, indirectness, or other considerations.

The overall evidence type is a combined evidence type across all outcomes considered critical for a recommendation. In this case, quality of overall evidence was Type 3 to Type 4 and was determined by evidence quality for IPD and all-cause pneumonia, both of which had the lowest quality of evidence of all critical outcomes.

After determining the overall quality of evidence, the cost-effectiveness data were reviewed. The review of health economic studies identified a single study that considered the potential herd effects of PCV use among children. The cost-effectiveness analysis showed that the current PPSV policy, which includes all adults 65 and older and adults 19 through 64 years of age with chronic and immuocompromising conditions, is cost-effective at $3300 per Quality-Adjusted Life Year (QALY) compared to no vaccination, and prevents IPD cases and deaths. The main limitation of this study is that the model relies on assumptions regarding PPSV efficacy and post-PCV serotype distribution. This analysis included all adults for whom PPSV is currently indicated, and it is not clear how these results could be extrapolated to immunocompromised adults only.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The answers to the following 4 questions were considered to determine the recommendation category, and the working group members reached a general consensus on the answers to each of these questions:

1) Is the quality of available evidence considered to be lower? The working group concluded that the evidence is of low quality due to limited data on efficacy against IPD (only one RCT in HIV+ Uganda), and inconsistent findings from observational studies against all-cause pneumonia.

2) Is there uncertainty about the balance of benefits versus harms? The working group concluded that there is greater uncertainty about the benefits, but the vaccine appears safe to use in these populations.

3) Is there high variability or uncertainty in relative importance assigned to outcomes? Working group consensus was reached on which outcomes are important to prevent.

4) Is there uncertainty about whether the net benefits are worth the costs? Cost-effectiveness in the general adult population is demonstrated; however, uncertainty remains with regard to the assumptions utilized in cost-effectiveness analyses.

Based on a review of the data and the answers to these questions, the working group determined this to be a Category B recommendation.

The conclusions of the Pneumococcal Working Group are that there is a high burden of disease among adults with immunocompromising conditions; PPSV23 includes serotypes accounting for greater than 70% of IPD in this group; PPSV23 is effective against IPD in adults with HIV; there is inconsistent evidence for effectiveness against non-bacteremic pneumonia; and vaccine is safe to use in these populations.

PPSV13 for Adults with Immunocompromising Conditions: Background, Review of Data, and GRADE

Kathleen Dooling, MD, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Dooling reminded everyone that the GRADE process was presented during the February 2012 ACIP meeting. At that time, all of the steps followed by the working group were reviewed. During this session, in the interests of time, Dr. Dooling reviewed the policy question and steps 5 through 8, which are as follows:

5) Summarize quality of evidence across outcomes
6) Review health economic data
7) Assess the balance of risks & benefits
8) Determine the recommendation category

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The policy question reviewed under the GRADE process was, "Should PCV13 be administered routinely to adults with immunocompromising conditions?" The population under consideration was adults 19 years of age and older with HIV, given that this population had a body of evidence sufficient for GRADE. The intervention the working group wanted to evaluate was PCV13 administered as a single dose, and the control or comparison group was PPSV23 recipients. The next step was to decide which disease outcomes should be considered, and the relative importance of preventing each of them.

Regarding the quality of evidence for each outcome of interest, for IPD there was one RCT among HIV-positive patients in Malawi that demonstrated a vaccine efficacy of 74% (95%CI 30-90). The quality of the evidence was downgraded to a 2/3 because of indirectness of the study population. There were no serious adverse events in the 6 RCTs studied, and significantly fewer systemic adverse events with PCV13. These studies were conducted in immunocompetent subjects. Likewise, immunogenicity for PCV13 was non-inferior or superior to PPSV23, but the evidence was downgraded because the study population was immunocompetent. Immunogenicity also was studied in 4 trials involving HIV-positive individuals, and demonstrated non-inferior or superior response for PCV7 compared to PPSV23. Therefore, the working group assessed the overall evidence type to be 2/3.

To address Step 6, a cost-effectiveness model was created using a subset of immunocompromising conditions for which prevalence and IPD incidence could be reasonably estimated. Even in this limited model, it is important to note that significant assumptions regarding vaccine effectiveness were made in three of these groups in the absence of experimental data. The details of this model were presented by Dr. Charles Stoecker following this presentation.

In order to determine the recommendation category, the working group considered and answered the following 4 questions:

1) Is the quality of available evidence considered to be lower? The working group thought that the very serious concerns with indirectness, as well as a lack of evidence for critical outcomes, meant that the overall level of evidence was low.

2) Is there uncertainty about the balance of benefits versus harms? The working group agreed that the very high burden of disease in immunocompromised adults, despite the indirect effects from PCV7, demonstrate the potential for a net benefit from direct PCV13 use in the immunocompromised population.

3) Is there high variability or uncertainty in the relative importance assigned to outcomes? The working group reached consensus regarding critical outcomes.

4) Is there uncertainty about whether the net benefits are worth the costs? There is still uncertainty regarding the cost-effectiveness of PCV13 in addition to PPSV23.

Ultimately, these considerations led the working group to propose a Category B recommendation, meaning that the desirable consequences probably outweigh the undesirable consequences.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The working group concluded that there remains an extremely high burden of pneumococcal disease amongst immuocompromised adults. The GRADE process led the working group to conclude that PCV13 is likely effective in this group, and that benefits likely outweigh harms. Unlike age-based recommendations, no additional data are expected to influence GRADE conclusions for the immunocompromised group. Based on the PCV7 experience, indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from the adult immunocompromised population.

Dr. Dooling then discussed specific vaccination considerations such as the combination, sequence, and interval between vaccines. In terms of the proportion of IPD caused by serotypes included in each vaccine, half of IPD in immunocompromised adults is caused by PCV13 serotypes. The serotypes in PPSV23 that are not found in PCV13 account for an additional 21% of IPD in immunocompromised adults. Therefore, there is an opportunity for broader serotype protection through use of both vaccines.

If both vaccines are to be given, consideration must be given to which should be administered first. Three immunogenicity studies in HIV-positive patients demonstrate that antibody response is non-inferior or superior when PCV is given prior to PPSV compared to the other way around. Moreover, Phase III studies in immunocompetent adults show that PCV13 + PPSV23 produced a significantly stronger antibody response than the reverse sequence for 11 of the 12 common serotypes tested. A single study in HIV-positive patients in Uganda designed to test the response to PCV following PPSV showed that polysaccharide vaccine 5 years prior did not affect antibody response to PCV. Similarly, in one study in HIV-positive patients in the US, there was no difference in immunogenicity between PCV and PPSV given 3 to 8 years after the initial dose of PPSV. Therefore, the working group felt that the data favor use of PCV13 followed by PPSV23.

Next, consideration was given to the optimal interval between vaccines. It is important to note that no studies have been designed to test the optimal interval between vaccines. Studies of immunogenicity with PCV followed by PPSV have been carried out at 1-, 2-, 6-, and 12-month intervals. All intervals studied showed increases in antibody above baseline as well as non-inferior to superior response compared to PPSV alone. For those who have received PPSV, even fewer studies have examined optimal intervals for immunocompromised individuals who received PCV13. Studies in immunocompetent adults suggest blunting of the immune response less than 5 years after PPSV; however, no evidence of reduced immunogenicity in HIV-positive patients was observed when PCV was given 5 years after PPSV.

Thus in summary, for pneumococcal vaccine-naïve adults, the optimal sequence is PCV13 followed by PPSV23 at an interval of at least 8 weeks between vaccines. For adults previously immunized with PPSV23, a dose of PCV13 at least 1 year after PPSV23 may be optimal, although there are no data in immunocompromised individuals at that interval.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Cost-Effectiveness of PCV13 for Adults with Immunocompromising Conditions

Dr. Charles Stoecker
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Stoecker indicated that the objective of this study was to evaluate the cost-effectiveness of adding a dose of PCV13 for selected groups with high incidence of pneumococcal disease, and push the first two doses of PPSV23 back by one year. A comparison was made of additional program costs to changes in disease, medical costs, and non-medical costs. This was a cohort model comprised of a subset of immunocompromised adults based on the 2009 US birth cohort. Events in this model occur after diagnosis with an immunocompromising condition, and consequences are counted over a lifetime. The Societal Perspective was utilized, which means that an examination was made of program, disease, and non-medical costs. The costs are in 2009 dollars, and the standard 3% discount was applied. A New Steady State was modeled, meaning that the program ramp-up period was not examined.

The effects of vaccination were examined on invasive and non-invasive disease. For invasive disease, meningitis and all other syndromes such as pneumococcal bacteremia were tracked. Invasive disease always incurs hospitalization and may result in subsequent fatality. For non-invasive disease, all-cause pneumonia was examined, which may incur hospitalization and subsequent fatality. The annual incidence of four immunocompromising populations (e.g., HIV/AIDS, hematological cancer, organ transplant, dialysis patients) was used to populate the model. Hematological cancer patients (N=119,142) and dialysis patients (N= 112,719) comprise 75% of the model population. Pneumococcal disease rates for these four populations are high, though there is substantial heterogeneity in disease and vaccine-to-serotype matches across the full population.

Regarding the assumptions on efficacy by vaccine population and outcome, the estimates for the efficacy of PCV13 in the HIV/AIDS population come from an RCT of PCV7 in Malawi. The lower bounds for the efficacy of PPSV23 come from an RCT in Uganda, and the upper bounds are from observational studies in the US. The assumption was made that the vaccines would perform no worse in dialysis patients due to studies conducted for hepatitis B vaccine. Vaccines were assumed to be approximately 1/3rd as effective for hematological cancer and organ transplant patients, given that their immune systems are iatrogenically suppressed. It was further assumed that vaccine efficacies for both vaccines would wane linearly to 0% after 5 years, and that revaccination with PPSV23 after PCV13 would reset any waned immunity for common serotypes. Herd effects for the 6 additional serotypes in PCV13 for children were assumed to be similar to those observed for the PCV7 program for children. For vaccine costs, the maximum allowable reimbursement under Medicare Part B was used of $55.02 per dose of PPSV23, $124.37 for PCV13, and $25.55 for vaccine administration. Also assumed was that coverage rates, disease costs, and QALY decrements for pneumococcal syndromes vary by immunocompromising condition.

In terms of the base case results, in total, adding a dose of conjugate vaccine prevented 45 cases of IPD, 600 hospitalizations for all-cause pneumonia, and 5000 cases of all-cause pneumonia treated in the out-patient setting. This resulted in a net cost-savings of $7 million. These results primarily were driven by the dialysis population, which was large and had relatively high coverage rates, relatively high vaccine efficacy, and relatively good matches between disease and PCV13 vaccine serotypes. It also was assumed that vaccine efficacy was high in the HIV/AIDS population, which is reflected in the relatively modest $3000 per QALY

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

gained cost-effectiveness ratio. It was assumed that the vaccine would be far less effective in the hematological and organ transplant populations. This is reflected in the cost-effectiveness ratios. For the hematological cancer population, adding a dose of PCV13 cost $7 million per QALY gained. The model also indicated that adding PCV13 for the organ transplant population was a dominated strategy, which means that it resulted in an increase in costs and a decrease in health, though the decrease in health was quite small.

Several sensitivity analyses were performed around the base case. The dialysis population drove the results. One of the assumptions was that the vaccines would perform similarly in the dialysis population and the HIV/AIDS population. That assumption was relaxed and it was assumed that the vaccines from the dialysis population performed like those in the organ transplant and hematological cancer populations. In this scenario, there were still gains in health, but the policy was no longer cost-saving. Again, since the dialysis population drove the results and coverage rates in the dialysis population were quite higher than the other populations, there was concern about what would happen if coverage rates increased in all four populations due to recommendation of a new vaccine. When coverage rates were increased to 100% for all four populations, the policy remained cost-saving and health outcomes increased. The annual model was not equipped to precisely model the “8 weeks or more” language in the proposed recommendation, but a sensitivity analysis was conducted in which the doses of conjugate and PPSV were administered in the same year. The results were quite similar to those in the base case. Substantial uncertainty surrounds the assumptions around vaccine efficacy, so ranges were used for each of the vaccines. When PCV efficacy is high or PPSV efficacy is low, the health gains and cost savings increase. However, if PCV efficacy is low or PPSV efficacy is high, the policy was dominated. Again, that means that costs increased and health outcomes decreased.

One of the major limitations of the study is that the majority of data on vaccine efficacy is based on expert opinion, and published data were available only for HIV. Also, the substantial heterogeneity among the populations examined also raises an important concern about the validity of extrapolating these results to the recommendation. Data are lacking on excluded groups, particularly those on immunosuppressives, which could substantially change the cost-effectiveness estimates.

In conclusion, in aggregate, the cost-effectiveness analysis indicates that PCV immunization is cost-saving for four selected sub-populations. Each of the four groups modeled responds differently to the vaccine due to the heterogeneity of serotype coverage and vaccine efficacy.

Discussion Points

Dr. Vazquez inquired as to why the interval for PPSV followed by PCV13 was 12 months.

Dr. Dooling replied that there are limited data upon which to base the interval, especially in the circumstance of polysaccharide vaccine followed by conjugate vaccine in immunocompromised populations. Studies that are taken from 3 to 5 to 8 years do not seem to indicate any blunting of response of hypo-responsiveness, and the period of one year was in part based on programmatic considerations. That would be an interval that would not be so long that there would be a reduction of vaccine effect before the second vaccine, but not too short to potentially encounter hypo-responsiveness.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Regarding the flattening out of the curve of IPD among adults less than or greater than 64 years of age, Dr. Marcy noted that the early months are the influenza season. He was concerned that everyone was looking to the CAPITA trial, which is being conducted in a country the size of Maryland with a population of 16 million, a national health service, and high compliance. He wondered whether those data could be extrapolated to the US population, which is much more diverse and has no universal healthcare. If that curve continues to be flat for IPD, he wondered whether that would trump the CAPITA trial. That is, why is CAPITA needed?

Dr. Matt Moore responded that the issue is the distinction between IPD and pneumococcal pneumonia, which is not always invasive. He hoped one thing that would be learned from the CAPITA trial would be how well PCV13 works against non-invasive or non-bacteremic pneumococcal pneumonia, because the burden of that disease is much greater than the burden of invasive pneumococcal disease. Even if the invasive disease line flattens out, if there is a very robust answer from CAPITA that indicates that the vaccine has a tremendous effect against non-invasive or non-bacteremic pneumococcal pneumonia, it may still be a very strong policy to adopt.

Dr. Marcy emphasized that his concern was if it did not show that.

Dr. Matt Moore stressed that they would have to wait to see what it does show.

Dr. Sawyer requested clarity about whether he understood that the vaccine efficacies were both projected to wane over 5 years. If so, he wondered why that was chosen since his understanding of conjugate vaccines is that in general, they should last longer. If that was not assumed, he wondered whether this would impact cost-effectiveness.

Dr. Matt Moore (SME) responded that there are many assumptions in the model. It was very difficult to find the data to support every assumption that needed to be made. The assumption regarding the 5-year waning of immunity came from polysaccharide vaccine data that have shown decline of antibodies and, more importantly, decline of effectiveness over roughly a 5-year period. It is unknown whether this will occur with conjugate vaccines in adults. This is an expert opinion assumption rather than a well evidence-based assumption.

Dr. Sawyer asked whether a sensitivity analysis could be done to determine whether, if conjugate vaccine was assumed to last longer, it would substantially change anything in the cost-analysis.

Dr. Stoecker replied that the life expectancies in these populations are not as long as in the general population, so this assumption may change the results, but it is unclear what the effect would be exactly.

Within the GRADE approach, Dr. Temte noted that there were a couple of times Ms. Pilishvili mentioned that observational studies were downgraded because of the inherent bias. He thought GRADE accounted for the inherent bias by entering the cohort studies at a lower level. He wondered whether there were any specific biases that led to downgrading those.

In addition to inherent biases, Ms. Pilishvili clarified that the point estimates ranged from study-to-study, the studies were combined from different sized populations, effectiveness was estimated against all IPD, and the proportion of IPD by serotypes was different from study-to-study. For some of the studies, there was concern that there might be an over-estimate of

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

vaccine effectiveness that would be expected for the overall effect on all IPD. So, there were multiple reasons to downgrade the evidence type from the observational studies.

Dr. Temte recently had a long-term patient on dialysis who experienced a very tragic death from pneumococcal pneumonia and IPD. Not only was it tragic, but also it was an incredibly expensive three-week hospitalization. He thought the rate at which people are going on dialysis is increasing in the US at an alarming rate. In addition, increasingly younger people are going on dialysis for longer periods of time. The question regards whether that affects the cost-effectiveness estimates, or was more in terms of total cost the country would realize.

Dr. Stoecker thought that would certainly affect the cost-effectiveness ratio. The data on the size of the dialysis population was based on the most recent evidence from the US Renal Data System. If that trend changes, then a larger share of the immunocompromised population will be on dialysis, and vaccination has been shown to be quite cost-effective for that population.

Ms. Rosenbaum requested that someone from Centers for Medicare and Medicaid Services (CMS) elaborate on the obligations of dialysis centers to assess immunization status, and assure that preventive measures are adopted and in place in the event that coverage is expanded. It would greatly increase the effectiveness of the recommendations ACIP makes.

Dr. Pickering indicated that this question could be e-mailed to the CMS representative, given the technical difficulties with the teleconference line.

Regarding the limitations of the vaccine system for adults, Dr. Jenkins requested input regarding whether the system worked any better for the unique population of adults with immunocompromising conditions with regard to what could be expected in terms of uptake rates of vaccination.

Dr. Matt Moore (SME) responded that the HIV community is very good at delivering preventive services for their patients. Some studies have assessed coverage with polysaccharide vaccine among HIV-infected adults, with some rates found to be at approximately the 70% to 80% range. There is some reason to expect that coverage may be better in some of these groups than what is observed in the general adult population who have indications for polysaccharide vaccine.

Dr. Coyne-Beasley noted that a significant amount of time had been spent focusing on adults, defined as people who are greater than 19 years of age, and certainly adolescent HIV has been decreased through the advent of antiretrovirals during pregnancy, but she was still curious about the implications of the pneumococcal vaccine for the adolescent population less than 19 years of age.

Ms. Pilishvili replied that the adolescent recommendations for PCV13 became covered when the vaccine was recommended for children. For children 6 through 18 years of age, an additional dose of PCV13 was recommended when PCV13 replaced the 7-valent vaccine formulation. The conditions for which that additional dose was recommended for children 6 through 18 years of age will be harmonized with the set of conditions that are considered for PCV13 use among adults.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Referring to slide 7 of Dr. Dooling's presentation, Dr. Sawyer requested a reminder of the determination of a recommendation category within GRADE. Of the four questions, there were two "yes" and two "no" responses. The final conclusion was that this led to a Category B. He wondered what the decision would be if there were three "no" and two "yes" responses, and how the answers to those questions are translated into the category level.

Ms. Pilishvili responded that the guidance for GRADE does not really have a mathematical formula to determine an evidence category. Frequent "yes" answers increase the likelihood of Category B recommendation.

If he understood GRADE and how that is applied to the language of a recommendation, Dr. Sawyer thought this came out as something short of "should" do something. He was struggling with how objective or subjective the determinations are and how that will be converted to language.

Dr. Temte reminded everyone that with GRADE, there is no hard and fast rule for the level of evidence and the type of recommendation. There can be a very strong recommendation based on very low quality evidence, which is fine. The guidance document tried to help people through the process, but there are no exact rules and no mathematical formula. Essentially, it would be fine to have a "should" recommendation with a remark indicating that there are limitations in the data.

Dr. Coyne-Beasley asked whether there should be at least one "no" response to the four questions in order to select a higher category, because there should not be variability or uncertainly in what is important. She thought the aim should be for the answer to be "no."

Dr. Dooling clarified that she misspoke. In the table as it is currently worded, "no" means strengths.

Ms. Ehresmann noted that the third slide coming up in the next presentation does a good job of identifying the categories and what it means for recommendations.

Dr. Schuchat appreciated everyone who has been working on GRADE and the specific vaccine recommendations, given that they are in a learning mode in terms of implementing the system. She thought important to remember was that ACIP adopted the GRADE process to make extremely transparent and explicit the quality of evidence available before decisions were made. There is a sense when members recognize explicitly how strong or weak the evidence is, it may influence the direction to take with the recommendations. However, this committee always has the practical need of the provider and the programs to receive clear advice. This is all about transparency, explicit review of the data, opening the gaps in the data for potential future evaluation, and the responsibility to make practical, implementable recommendations.

For the benefit of the non-working group members, Dr. Duchin thought it would be accurate to view the recommendation category as a summary of the evidence that was used by the working to develop the recommendation.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Recommendations for PCV13 use Among Immunocompromised Adults

Tamara Pilishvili, MPH
Epidemiologist
Respiratory Diseases Branch
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Pilishvili began with a summary of the main conclusions by the working group. Based on the data that were presented beginning with the February 2012 ACIP meeting, she noted that the full committee had now heard the evidence and the GRADE for the currently recommended PPSV vaccine, the GRADE and evidence for the newly licensed PCV13 vaccine, and the rationale and evidence for the combined use of both vaccines in the immunecompromised high risk adult populations.

The working group concluded that there remains an extremely high burden of pneumococcal disease among immunocompromised adults. Indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from the adult immunocompromised population. The GRADE process led the working group to conclude that PCV13 is effective in this group and that benefits likely outweigh harms. However, PCV alone may not provide an adequate coverage of disease-causing serotypes. Therefore, a combined PCV and PPSV regimen may be more optimal than either vaccine alone. The working group decided that benefits likely outweigh harms, and both PCV13 and PPSV23 should be recommended for adults with immunocompromising conditions.

Categories of immunocompromised adults to consider for PCV13 recommendation language include vaccine-naïve adults 19 years of age or older with immunocompromising conditions who previously have not received PPSV23; and PPSV-immunized adults 19 years of age or older with immunocompromising conditions who received 1 or more doses of PPSV for any of the current indication.

The working group proposed to include the following conditions as indications for PCV13 for adults 19 years of age or older:

- Functional or anatomic asplenia

- Immunocompromising conditions:
  - Congenital or acquired immunodeficiencies
  - HIV infection
  - Chronic renal failure or nephrotic syndrome
  - Leukemia, lymphoma, Hodgkin disease
  - Generalized malignancy
  - Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy
  - Solid organ transplantation
  - Multiple myeloma

- CSF leaks and cochlear implants

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

All of these, with the exception of CSF leaks and cochlear implants, are indications for an additional dose of PPSV among adults. All of these conditions are indications for PCV13 among older children and adolescents. The working group proposed to include CSF leaks and cochlear implants as indications for PCV13 use among adults 19 years of age or older. Although these 2 conditions are not indications for an additional dose of PPSV, they were included as indications for PCV13 among children 6 through 18 years of age.

Regarding the recommendation for PCV13 and PPSV23, for vaccine naïve adults, a PCV13 dose is recommended to be given before PPSV23 whenever possible. PPSV23 should be given at least 8 weeks after a dose of PCV13. The recommendations for a second dose of PPSV and a dose of PPSV at age 65 years or older would remain unchanged. For adults previously immunized with PPSV, a dose of PCV13 is recommended to be given to adults with immunocompromising conditions who received one or more doses of PPSV23 one or more years after the last PPSV23 dose. The total number and interval between PPSV23 doses would remain unchanged from the current recommendations.

For prevention of pneumococcal disease among adults with immunocompromising conditions, it is recommend that adults 19 years of age or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who previously have not received PCV13 or PPSV23 receive a dose of PCV13 first followed by currently recommended doses of PPSV23. The proposed minimum interval for PPSV to be given after PCV is 8 weeks. The recommendations for the second PPSV dose and a dose at age 65 or later remain unchanged.

For PPSV-naïve adults the working group proposed the following recommendation for a vote:

> *“* Adults 19 years of age or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks or cochlear implants, and who previously have not received PCV13 or PPSV23 receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later*.”*

The current recommendations for PPSV23 for adults 19 years of age or older with immunocompromising conditions would remain unchanged:

> *“*A second dose of PPSV23 is recommended 5 years after the first dose for persons aged 19through 64 years with functional or anatomic asplenia and for persons with immunocompromising conditions*.”*
>
> *“*Those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have passed since their previous dose. Those who receive PPSV23 at or after age 65 years should receive only a single dose of PPSV23*.”*

The following transition recommendation was proposed for adults 19 years of age or older previously vaccinated with PPSV 23:

> “Adults 19 years of age or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who previously have received one or more doses of PPSV23 are recommended to receive a dose of PCV13 one or more years following the most recent dose of PPSV23.”

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

On the basis of the presented information, the working group proposed the following recommendation for a vote:

> **"**Adults 19 years of age or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks or cochlear implants, and who previously have received one or more doses of PPSV23 receive a dose of PCV13 one or more years after the last PPSV 23 dose was received.
>
> For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years since the most recent dose of PPSV23."

Discussion Points

Dr. Baker indicated that she would like to address this as one vote rather than two votes, and requested that the discussion be centered on polysaccharide naïve individuals and those previously vaccinated.

Dr. Sawyer requested further clarification on the one-year interval for those who receive PPSV first in terms of why it is one year.

Ms. Pilishvili replied that none of the studies reviewed were designed to evaluate the optimal interval for receipt of PCV following a dose of PPSV23. There are studies that show that there may be concerns regarding hypo-responsiveness for immunocompetent adults to whom two doses of polysaccharide are given less than 5 years apart, or if conjugate is given less than 5 years after PPSV23. There is no evidence for a one-year interval as recommended. However, based on the expert opinion, there may be less concern for hypo-responsiveness among immunocompromised adults compared to immunocompetent adults. There is also a balance between waiting too long by delaying a dose of PCV13 and leaving these adults unprotected.

Dr. Keitel inquired as to whether it was reflected in the written materials that this is a Grade A recommendation with some comment about the strength of the evidence.

Ms. Pilishvili responded that as of that morning, they consulted with Dr. Temte to seek his guidance on how to proceed. Most of the working group members felt uncomfortable with permissive language or use of the word "may." Most felt that ACIP "should" recommend both vaccines to this group. In terms of how the recommendation language is presented, the working group will be very transparent that the evidence type is 2 to 3 for the conjugate vaccine and 3 to 4 for the polysaccharide vaccine. While the evidence is moderate to weak, the recommendation will be deferred to GRADE experts in terms of the category of the recommendation.

Dr. Temte added that from the discussion during the morning, everyone was hesitant to put the strong recommendation in going through the process, but the level of evidence can be uncoupled from the recommendation. From a practitioner's standpoint, using the word "should" does more than "may."

Dr. Keitel clarified that this meant the recommendation would be a Category A, but based on weak evidence. She suggested "≥ 8 weeks" should be removed from the first line because that is a different scenario from a vaccine naïve person. It should be "5 years between the two polysaccharides," and 8 weeks should not be there.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Pilishvili responded that the reason this interval was kept consistent was because of what was believed should be the recommended order of the vaccines, and whether any benefits are being achieved giving the conjugate first, followed by a dose of polysaccharide vaccine. By expanding the window, if adults are not protected by the additional serotypes, it would be the same argument of extending that window and not giving an additional dose of polysaccharide.

Dr. Temte noted that this is a fairly complicated recommendation in terms of the timing intervals. However, this can be placed into a vaccine registry pretty simply. The question regards whether there are resources or interest in trying to provide health systems with the potpourri of ICD-9 codes for the immunocompromising conditions to allow groups to integrate this into their EMRs. A lot of EMRs will support registries, and integration with registries is increasing. One of the biggest problems is with the timing versus the conditions, with the registries having the timing and the EMRs having the conditions.

Dr. Schuchat replied that CDC is actively involved in trying to improve the interoperability between immunization information systems or registries and EMRs, working toward bidirectional flow and decision support, and having ACIP recommendations programmed into the software. Certainly, the EMRs with medical conditions and standard codes are prime territory for that. If this has not been done, it would be very good to do.

Dr. Marcy pointed out that they were having a long discussion on “yeses” and “Nos” and GRADE A, B, and C and ones, and twos, and threes, and then made a completely arbitrary decision that there is a one-year interval between PPSV and PCV. There are no data and if the interval is a year as opposed to six months, the susceptibility period is being extended for these people. He did not understand why they were recommending this. He suggested adding, “Although shorter intervals may be used, there are no data.”

Dr. Cindy Whitney (SME) worried that the one-year recommendation was on the short side. Reviewing the data on how well the conjugate response is for people who have received polysaccharide, in immunocompetent hosts one year would be too short. The wait really should be several years. In immunocompromised individuals, a shorter window could be used, but she would hesitate to go below one year. She did not think six months would be a good idea.

Dr. Marcy said he understood that less than five years could perhaps result in hypo-responsiveness, but he did not perceive a major difference between 12 months and 6 months.

Dr. Whitney (SME) replied that there is known to be a fair amount of antibody decay over the first year, so at least immunization would not be given when antibodies are higher. While it was unknown how this would work in the immunocompromised, she thought a year was better than six months.

Dr. Duchin pointed out that the working group came to this decision through consensus and expert opinion in the absence of data, but was certainly open to another suggestion about what the optimal interval should be, given that there must be something in the recommendation.

Dr. Sawyer requested clarification on whether the current recommendations for use of polysaccharide vaccines indicating a second dose in five years, and perhaps even a third dose after age 65, apply to those with CFS leaks and cochlear implants, or if those groups were being added with the proposed recommendation.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Pilishvili responded that there had not been any discussions about adding anything to the current recommended indications for PPSV where CFS leaks and cochlear implants are not included. She indicated that the language of publication would be reviewed to ensure clarity.

It seemed to Dr. Campos-Outcalt that the GRADE process in this instance did exactly what ACIP hoped it would, which was to help the committee assess the quality of the data, which was then separate from the strength of the recommendation. An A recommendation should be made on low quality evidence with hesitation, which is exactly what they were doing. Level 3 and 4 evidence is also likely to change with time. To him, they were doing exactly what they needed to in a transparent fashion, with the knowledge that in the future this needs to be followed.

Referring to Slide 9, Dr. Bocchini noted that for the third group of individuals who had two doses of polysaccharide vaccine and were recommended at age 65 to be given the polysaccharide first and the conjugate at a one-year interval, it seemed that it would be better to reverse that (e.g., the conjugate followed by polysaccharide 8 weeks later).

Ms. Pilishvili replied that the polysaccharide doses shown on that slide were all for adults who already had received one or more doses of the polysaccharide vaccine. The third schematic of a schedule on the same slide would be for adults who had received up to three doses of polysaccharide, for whom a dose of conjugate vaccine would be recommended.

Dr. Vazquez requested clarity regarding the transition from being a child to being an adult in terms of “PCV13 naïve” and whether this was saying regardless of how many years before they received PCV13 they turned 19, if they had it at any point in their lives and now had cancer, that counted as naïve.

Ms. Pilishvili responded that there is an aging cohort of children and adolescents who may have received PCV13. The working group has not addressed this group, and was recommending the proposed regimen for adults who are vaccine naïve for both vaccines. As the cohort of adolescents ages, at the same time, the working group will be addressing a question of potential revaccination with the conjugate vaccine. The aging cohort of children who may have received one or more doses of the conjugate vaccine will be covered by those discussions. There are on-going studies that assessed the sequential doses of PCV. As these studies become available and more is learned about the benefits of more than one dose of PCV, the working group will address the question of adolescents and children.

Dr. Baker stressed that on-going work was needed to answer the numerous questions that had arisen, and it was certain that there would be additional data perhaps to modify these recommendations and to deal with aging children, young adults who develop an immunocompromising conditions, and healthy adults 65 years of age and older.

Dr. Duchin made a motion that the proposed recommendation language for both PPSV naïve adults and previously vaccinated adults be accepted as written. Ms. Ehresmann seconded the motion.

Ms. Brewer (ANA) wondered whether the working group discussed adults whom vaccine type cannot be determined.

Ms. Pilishvili replied that if they were immunized in adulthood, it would be fairly easy to determine early during the transition to new recommendations.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Brewer (ANA) pointed out that that would be for now, but she was thinking for next year that would be a different question because this recommendation, if passed, people will be vaccinated with one or the other and may not remember what type of vaccine they received.

Ms. Pilishvili did not think she could address the question regarding how that would be determined. The same issue has occurred at the end of research studies being conducted and the transition between PCV7 and PCV13, and trying to determine whether children had one or the other. To her knowledge, it had been challenging during transition periods to determine the type of vaccine. She invited suggestions on how that could be done.

Dr. Sawyer thought this was an important question, and that in the language of the recommendation it needed to be addressed in some way. Since there is a licensed product for adults over the age of 50, people are beginning to use this vaccine on their own, so this will occur.

Dr. Duchin proposed that this not be included in the language of the recommendation, but that it be included in the annotated text instead.

Dr. Sawyer clarified that inclusion in the supporting documentation was what he meant.

Dr. Loehr (AAFP) asked Dr. Campos-Outcalt to discuss his thinking regarding why he would use “should” rather than “may” in the recommendation, given that clinical decision-making is important.

Dr. Campos-Outcalt replied that he was more or less reflecting what he sensed to be the consensus of the group in terms of discomfort with ambiguous language in a group with high morbidity and mortality from the disease. He thought it was appropriate to go to an A, which appeared to be where the group was headed, and he did not see this as optional.

Dr. Loehr (AAFP) inquired as to whether the working group had considered removing people with hematological cancers and organ transplants from the recommendations since those seem to not be as cost-effective.

Ms. Pilishvili responded that this was not part of the discussion. A major part of the discussion focused on harmonizing the recommendations with the existing recommendations. All of those groups are at high risk for pneumococcal infections. Because of the high burden of disease and increased risk of pneumococcal disease, the working group felt that it was as important to protect those listed. There are no data on the burden of disease for other conditions listed under the category of immunocompromised, as well as for persons with cochlear implants and CSF leaks. They were not able to estimate the cost-effectiveness for these groups as well, but based on the burden of disease data, the working group believes those adults also should be protected with these recommendations.

Dr. Bennett reported that the working group struggled quite a bit with the language of “should” versus “may” and whether to make the recommendation strong or permissive. The members felt that a strong recommendation was more in keeping with the guidance they wanted to send to physicians. However, the wording now states “we recommend” rather than “should.” The reason for that is to allow for some clinical decision-making, and to make the recommendation more open to interpretation by physicians. They did not want to put physicians in a position that makes them feel they are not providing adequate care because they decide that the support for

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

this recommendation is not as strong as they would prefer for their individual patients. However, the working group did want to recommend this vaccine.

Dr. Turner (ACHA) said that as he read the recommendation, if he had a 19-year old student who was immunocompromised, they would be given conjugate at age 19, polysaccharide 8 weeks later, a second dose of polysaccharide at age 24, and then would not receive another dose until they turned 65 years of age. He requested a reminder regarding why the polysaccharide was not being recommended every 5 years for the next 40 years of their life.

Ms. Pilishvili responded that this was due to the lack of evidence for multiple revaccinations with the polysaccharide vaccine. There are limited data on efficacy and safety of multiple doses of polysaccharide vaccine.

Vote: Recommendations for Pneumococcal Vaccine use among Immunocompromised Adults

Dr. Duchin made a motion that the proposed language for both PPSV and PPSV naïve be accepted as written. Ms. Ehresmann seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

15 Favored:	Baker, Bennett, Bocchini, Coyne-Beasley, Duchin, Campos-Outcalt, Ehresmann, Jenkins, Keitel, Marcy, Rosenbaum, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
1 Abstained:	Meissner

Influenza

Introduction

Wendy A. Keitel, MD
Chair, Influenza Working Group

Dr. Keitel joined in thanking Dr. Baker for her wisdom, commitment, and leadership over the years. She also bid farewell to Ms. Ehresmann, Dr. Marcy, and Dr. Meissner and said that it had been a great pleasure to work with them. In addition, Dr. Keitel thanked the busy Influenza Working Group, reporting that their activities over the last few months included discussion of vaccine products currently under development; discussion of vaccine safety monitoring and preliminary 2011-2012 vaccine effectiveness estimates; development and discussion of dose algorithms for children aged 6 months through 8 years; and review of evidence base for TIV and LAIV in healthy children using GRADE, including discussion of inclusion / exclusion criteria and weighting of relevant outcomes and final analyses to be presented in October.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Influenza Activity / Surveillance Update

Lyn Finelli, DrPH, MS
Lead, Influenza Surveillance and Outbreak Response Team
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Finelli reported on data from 2010-2011 and 2011-2012 seasons from the Work Health Organization / National Respiratory and Enteric Virus Surveillance System (WHO / NREVSS) collaborating laboratories, which describe national virologic surveillance. Even though the percent positive remained about the same from year to year, there were many fewer influenza viruses. That reflects far less influenza activity and influenza-like illness (ILI) in the community. H3N2 prevailed this year as the predominant virus, but B viruses were observed in March and were predominant during the last half of the season. A low amount of influenza activity was also observed in the US outpatient Influenza-Like Illness Surveillance Network (ILINet). Baseline was reached for only one week. Normally during an influenza seasons, baseline is exceeded for 8 to 20 weeks, with an average of 13 weeks. There was not a normal peak in March as is observed in a typical influenza season. The 2011-2012 season began slowly, increased somewhat in January, peaked for one week only in March, and then returned to below baseline.

Based on hospitalization data from the Emerging Infections Network, laboratory-confirmed hospitalization rates this year for almost all age groups are about half of what they were last season; however, rates for the 0 to 4 year old age group are about one quarter of what they were last season. Based on data from the 122 Cities, pneumonia and influenza mortality were below the threshold and seasonal baseline for most of this year. There were 26 influenza-associated pediatric deaths this year. With the exception of the pandemic when there were 282 pediatric deaths, there have been approximately 100 deaths per year.

Dr. Finelli then explained that novel influenza A virus infections are those infections by viruses that do not normally circulate in humans and are animal in origin. This year, there have been 13 cases of human infection with novel influenza A (H3N2) variant (H3N2v). All of these H2N2v viruses were of swine origin and have been reported since August 2011. About half of these were associated with exposure at agricultural events or on family farms, and about half were human-to-human transmission. All of these H3N2v viruses have the M gene from the pH1N1 virus. This gene in animal models is thought to confer increased transmissibility. Of the cases, 1 was in an adult and 12 occurred in children. This reflects the immunity or susceptibility profile in adults and children. Of the 13 cases, 6 were in persons who reported no recent exposure to swine, so they were person-to-person transmissions. There were two (1 H1N1v and 1 H1N2v) virus infections identified during the 2011–2012 season, both of which occurred in children.

From October 2011 through May 2012, CDC antigenically characterized 1887 influenza viruses submitted by laboratories in the US. Of the pH1N1 viruses tested, 503/527 (95%) were characterized as A/California/7/2009-like and were similar to the pH1N1 component of the 2011–2012 influenza vaccine. Of the influenza A (H3N2) viruses tested, 864/1,058 (82%) were characterized as A/Perth/16/2009-like and also were similar to the influenza A (H3N2) component of the 2011–2012 influenza vaccine for the Northern Hemisphere. Of the influenza B viruses tested, 147/302 (49%) belonged to the B/Victoria lineage and 95% of these were characterized as B/Brisbane/60/2008-like, the influenza B component for the 2011–2012 Northern Hemisphere influenza vaccine.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

From October 2011 through May 2012, a total of 2756 influenza virus specimens were tested for antiviral resistance. None of the 317 influenza B viruses and none of the 1275 influenza A (H3N2) tested was resistant to oseltamivir and zanamivir. Among the pH1N1 viruses tested, 16 of 1164 (1.4%) were resistant to oseltamivir and none were resistant to zanamivir. High levels of resistance to the adamantanes (amantadine and rimantadine) persist among pH1N1 and influenza A (H3N2) viruses currently circulating globally. These drugs are not recommended for treatment.

In summary, influenza activity in the US during the 2011–2012 season occurred at low levels overall. Activity increased in January and February and peaked in mid-March for a very brief period. This season set record for the lowest and shortest peak since surveillance began in the 1997-1998 season. Influenza A (H3N2) viruses predominated overall, but influenza A (H1N1)pdm09 (pH1N1) and influenza B viruses also circulated widely, especially at the end of the season. This influenza season was mild compared with recent years, with a lower percentage of outpatient visits for ILI, lower rates of hospitalizations, and fewer deaths attributed to pneumonia and influenza.

In terms of why the 2011-2012 influenza season been mild, this is the third consecutive season of H1N1 A/California/7/2009-like virus circulation, the second consecutive season of H3N2 A/Perth/16/2009-like virus circulation, and the second consecutive season of B/Brisbane/60/2008-like virus circulation. There has been a good vaccine / virus match over all of these years. There was estimated vaccine coverage of 27% during the 2009-2010 (2009 H1N1 monovalent) season, 43% in 2010-2011, and 46% (preliminary estimates) in 2011-2012 with higher coverage in children. Vaccination coverage combined with immunity from natural infection has resulted in high levels of immunity in the population.

Vaccine Effectiveness

Dr. David Shay
Epidemiology and Prevention Branch, **Influenza Division**
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Shay explained that the US Flu Vaccine Effectiveness (VE) Network is designed to provide estimates of clinical effectiveness of licensed vaccines by age group and by influenza type and subtype. The network currently consists of 5 study sites spread across the US. As previously noted, it has been a relatively late and mild influenza season. In this network, surveillance for influenza began in November 2011 at the 5 participating VE sites, but enrollment did not begin until January 2012 and continued through end of April in some sites.

The outcome that is assessed in the network is Reverse Transcription Polymerase Chain Reaction (RT-PCR) confirmed influenza infection that results in an outpatient visit. The 5 study communities include Marshfield, Wisconsin; Southeast Michigan; Seattle, Washington; Pittsburgh, Pennsylvania; and Temple, Texas. Enrollees include patients evaluated for acute respiratory symptoms in outpatient settings who were prospectively enrolled and tested for influenza by the CDC real-time RT-PCR. The laboratory component of this is tested each season. There is a proficiency panel for virus detection with PCR and for virus culture that each site has to pass. During this session, Dr. Shay presented data for the interim study period from January 2012 through March 2012. This is a case-control study in which the cases are those who test positive for influenza, and the controls are those who test negative for influenza.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Vaccination status is determined by self-report followed eventually by confirmation through record review. The data presented during this session were based on self-report of vaccine status. Immunization was defined as the receipt of at least one dose of vaccine 14 or more days before onset of respiratory symptoms. The analysis has been done in a consistent manner*:* VE = (1-adjusted OR) x 100%, estimated with logistic regression models, with assessment for potential confounding by age, sex, race, ethnicity; date of symptom onset and days between onset and testing; insurance status; self-report of asthma; self-report of usual health status as validated by a CDC 5-point scale (Excellent, Very Good, Good, Fair, Poor); and self-report of current health status defined on a 0-100 scale taken from a valid instrument (EQ-5D).

In terms of enrollment status by week and study site, two of the sites (e.g., Marshfield and Michigan) had a relatively short typical influenza peak. The other three sites, particularly University of Pittsburgh, had very low levels of activity throughout the season. People continued enrolling past the March 25, 2012, and quite a few B viruses were observed in Seattle in April 2012. With regard to the characteristics of the cases and controls, there were 329 influenza cases and more than 3000 influenza negative controls. The distribution in terms of enrollment of cases and controls is fairly consistent by study site, and the remaining characteristics of cases and controls are very similar to what they have been in past seasons. There is a tendency to enroll more females than males; a tendency to enroll more people who are 18 years of age and less; and difficulty in enrolling older individuals, particularly those who are 65 years of age and above despite significant efforts, including outreach to geriatric health clinics. There is obviously an interest in the US in influenza vaccine effectiveness in those 65 years of age and older. The characteristics of vaccinated and unvaccinated enrollees are also very similar to what they have been in the past. Overall, 7% of the vaccinated participants had a positive test for influenza versus 14% of the unvaccinated participants.
The interim vaccine effectiveness estimate, when adjusting only for age group and study site, is 54% (95% CI 40% to 63%). When adjusting for age, site, race / ethnicity, days between onset and testing, and health status, the vaccine effectiveness estimate is 52% (95% CI 39% to 63%). Little evidence of confounding was observed. By age group, vaccine effectiveness was very similar in this season as opposed to some past seasons:

By Age Group	Vaccine Effectiveness
6 months to 8 years	55% (95% CI 30% to 71%)
9 to 18 years	45% (95% CI -3% to 71%)
19 to 49 years	51% (95% CI 21% to 70%)
50+ years	54% (95% CI 19% to 74%)

An insufficient number of individuals 65 years of age and older are enrolled at this time to make a separate estimate for that age group.

Vaccine effectiveness type and subtype was as follows:

Type / Subtype	Vaccine Effectiveness
A	47% (95% CI 32% to 59%)
H3N2	41% (95% CI 21% to 56%)
H1N1	76% (95% CI 50% to 88%)
B	83% (95% CI 46% to 94%)

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In terms of preliminary impressions and next steps, from January 2012 through March 2012, the Vaccine Effectiveness Network enrolled 329 influenza cases and 3071 influenza-negative controls. Interim vaccine effectiveness was approximately 50%, with little evidence of confounding and stable vaccine effectiveness by age group. Evidence of lower vaccine effectiveness has been observed for H3N2 in interim estimates, which is similar to what has been observed in Europe and Canada. Enrollment continued through the end of April. Final vaccine effectiveness data will include over 700 cases and 5000 controls and was due the week of this ACIP meeting. Pending are vaccine receipt and date confirmed by record review, pre-existing health conditions from electronic medical records (ICD-9-CM codes), and 30-day follow-up. The CDC laboratory will antigenically characterize and sequence HA and NA for 30 to 40 viruses sampled throughout the season from each of the study sites.

Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

With regard to febrile seizures for the 2010-2011 season, Dr. Shimabukuro recapped that the FDA Vaccine Adverse Event Reporting System (VAERS) data mining signaled for Fluzone® and febrile seizure. This resulted in a Vaccine Safety Datalink (VSD) investigation. Increased risk for febrile seizures was highest in 12- to 23-month olds, peaking at approximately 16 months with a risk difference of 45 per 100,000 doses concomitant trivalent inactivated influenza vaccines (TIV) and PCV13 doses. No policy change was recommended for TIV or pneumococcal conjugate vaccine (PCV13) for 2011-2012. Further investigation is underway to determine whether other childhood vaccines may be contributing to the febrile seizures. Disproportionate reporting continues to be observed for febrile seizures in young children following Fluzone® in VAERS data mining for 2011-2012. This was not unexpected, given that there was no formulation change for 2011-2012 and due to the possibility of stimulated reporting for the past season based on increased awareness of this issue from the prior seasons. An elevated relative risk was observed for seizures following TIV in children age 6 through 23 months in VSD surveillance of automated data for 2011-2012. The magnitude of risk is consistent with the risk observed in 2010-2011. No increased risk was observed in children 24 through 59 months of age.

Guillain–Barré Syndrome (GBS) cases following influenza vaccination have been observed and reported. Gastrointestinal and upper respiratory infections are known risk factors. There was no disproportionate reporting for GBS following TIV or live attenuated influenza vaccine (LAIV) in VAERS data mining for 2011-2012. This was also true for 2010-2011. There was no elevated risk for GBS following TIV or LAIV in VSD surveillance of automated data for 2011-2012, which was the same for 2010-2011.

Regarding 2009 H1N1 vaccine and GBS, in the past several months a series of papers have been published on line focused on the risk of GBS following H1N1 vaccine. The end of season analyses for GBS following 2009 H1N1 inactivated monovalent vaccine, a small statistically significant increased risk was observed in some surveillance systems. There have been variable results across surveillance systems and when using different study methodologies. When the sample size was large enough to detect a small increased risk, the risk for GBS following 2009 H1N1 inactivated monovalent vaccine was similar to risk observed for US seasonal TIV in some past seasons [Lasky et al. The Guillain-Barré syndrome and the 1992-

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

1993 and 1993-1994 influenza vaccines. N Engl J Med. 1998;339:1797-802], but was substantially lower than the risk observed following 1976 swine influenza vaccine.

Dr. Shimabukuro shared an updated table that was shown during previous ACIP meetings that summarized GBS results from US 2009 H1N1 vaccine safety surveillance systems, including Emerging Infections Program (EIP) GBS surveillance, VSD, Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Centers for Medicare and Medicaid Services (CMS), Department of Defense (DoD), and Department of Veterans Affairs (VA) data. The study designs were primarily self-control and case-centered. For the final analyses, the cases in these systems were chart-confirmed. The statistically significant increased risks ranged from 1.57 (1.02, 2.21) to 4.4 (1.3, 14.2).

In terms of allergy and anaphylaxis, the recommendations for egg allergic patients were updated for 2011-2012. This is the first season for which those recommendations were in effect, which is why the decision was made to offer a quick review of allergy and anaphylaxis. As a general reminder of the recommendations, if a person could eat eggs they could be vaccinated with either TIV or LAIV. If someone could eat eggs or egg-containing food and experienced hives only, the recommendation is to vaccinate with TIV and observe for 30 minutes. For those who have eaten eggs and experienced symptoms of anaphylaxis, the recommendation is to refer to a physician with expertise in management of allergic reactions for further evaluation. There was no disproportionate reporting for allergy or anaphylaxis following TIV or LAIV in VAERS data mining for 2011-2012. LAIV was included because there is always a possibility that these recommendations could have been inadvertently applied to LAIV. Allergy and anaphylaxis reports in VAERS following influenza vaccination in egg allergic patients during 2010-2011 included 15 non-anaphylactic allergic TIV and no LAIV reactions, and 3 TIV and no LAIV anaphylaxis reactions. During 2011-2012, there were 15 non-anaphylactic allergic TIV reactions and 1 LAIV reaction, and no TIV and 1 LAIV anaphylaxis reaction. The anaphylaxis reaction was a complicated case of a patient with a known egg allergy who was involved in desensitization with an allergist. This is more of an outlier and is not consistent with someone who received LAIV possibly because the TIV recommendations were confused with the LAIV recommendations.

This is the second season of use of high-dose TIV. There were 600 VAERS reports after high-dose TIV, 88% of which were non-serious. This compares to the previous season in which there were 672 reports after high-dose TIV, of which 91% were non-serious. No new safety concerns have been identified. This is the first season of use of intradermal TIV. There have been 51 VAERS reports after intradermal TIV, of which 96% were non-serious. No safety concerns have been identified.

Discussion Points

Regarding influenza vaccine effectiveness, Ms. Rosenbaum noted that no data were presented on Latino populations. She wondered whether those data were available.

Dr. Shay replied that data are available on Latino populations, but he did not have room on the table presented to include that information. Self-reported ethnicity was collected as part of this study.

In anticipation of the upcoming season, Dr. Schaffner (NFID) wondered whether any information was available about circulating strains and the extent of illness in the Southern Hemisphere thus far.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Finelli responded that ILI is increasing in the Southern Hemisphere, but no information was available about severity or extent of that illness. She did not believe the season had peaked there yet.

Dr. Meissner requested clarification of an issue regarding GBS. The statement was made that when the sample size was large enough to detect a small increase in risk, it was similar to that observed for the US seasonal TIV vaccine. He thought it could not definitely be stated that there is an increased risk of GBS after TIV, given that the numbers are simply not adequate to confirm this.

Dr. Shimabukuro indicated that the EIP surveillance system covers 45 million individuals and VSD covers about 9.5 million individuals. In both of those systems, there was a small statistically significant increase detected. The VA reinforces that their surveillance is a pilot system at this time that has very small numbers and does not have the power of the EIP or VSD. PRISM covers a substantial number of people as well. Dr. Shimabukuro reiterated that there was a small statistically significant increased risk observed in some surveillance systems, and it was variable across systems and across methodologies. This is consistent with the risk observed in some previous seasons, but much less than in 1976.

Ms. Stinchfield (NAPNAP) requested more information about the character of the intradermal TIV VAERS reports besides the fact that most of them were non-serious.

Dr. Shimabukuro replied that 96% were non-serious, and he believed most of those were local reactions, which would be expected based on the clinical trials. This was reassuring, and he indicated that he could acquire more specific information about the breakdown.

Dr. Keitel requested further information about the season before the US season in the Southern Hemisphere in terms of whether there was likewise a very mild season. She also wondered about the nature of the low attack rate in terms of trying to determine vaccine efficacy using Dr. Shay's study design.

Dr. Finelli replied that the Southern Hemisphere did not experience a very mild season like the US had this year. Vaccine coverage in that population is also much lower than in the US.

Dr. Shay responded that last year they had 4 study sties and enrolled over 1000 influenza cases. This year with 5 study sites they expect to enroll 700 influenza cases. That reflects two things. Not only was it a mild year, but also there were more sites and broader geographic representation across the US. For example, a peak of H3N2 was observed in the mid-West as well as a peak of B in the latter part of the seasons. Because this is a case-control study, power is defined by the number of vaccinated cases, and there will be enough vaccinated cases this year to make age group and type-specific estimates of vaccine efficacy as in previous years. It was a very difficult season for cohort studies, which did not work out this year.

Dr. Temte noted that data also were collected on the self-reported pre-health status, and was curious whether differences were found in terms of severity of illness between vaccinees and non-vaccinees.

Dr. Shay replied that whole datasets are not yet available. In the preliminary assessments of 300 cases thus far, no difference has been observed in acute severity of illness by vaccine status. However, those with influenza do tend to be more significantly ill than those without

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

influenza. This is similar to what has been observed in past studies that have used more measures.

Dr. Duchin requested further insight into H3N2 and the modest vaccine efficacy. He has received a number of questions locally because there have been more than the usual number of anecdotal reports of immunized persons presenting with influenza A toward the end of the season, particularly from healthcare facilities. He was curious about waning immunity due to the late season, and any changes in the H3N2 virus that might be related to the estimate being what it is.

Dr. Shay responded that dataset is relatively limited, and can be better assessed once information is acquired on 700 cases. A decrease has been observed in vaccine effectiveness in terms of the early versus the late season. There are not enough data yet to determine whether this is likely due to an H3 only effect, or an effect due to increased time since vaccination. There has not been a season that has been quite this late previously, but datasets are being collected for all previous seasons for which there are vaccine effectiveness data to specifically assess whether there is any evidence of decrease in effect with an increasing time since vaccination. More information about this will be available in a few months.

Dr. Warshawsky (NACI) wondered about vaccine effectiveness for influenza B, given that half of the B lineages were of the opposite lineage. She was surprised to it that high.

Dr. Shay agreed that this was somewhat surprising, but indicated that this effect has been observed previously in the US and in some other countries that are conducting more studies. Europe and Canada have similar networks of vaccine effectiveness sites. While there is not a great explanation for it, it is an effect that has been observed in the past. Particularly in adults, there may be some cross-lineage protection.

Dr. Bennett has also been questioned about waning immunity, particularly in the elderly. She wondered whether there were plans to increase enrollment of elderly patients in these studies in order to assess this critical question.

Dr. Shay reiterated that an effort was made this year to increase enrollment of elderly patients. Based on information from three of the study sites, one of the issues that has arisen is that often older individuals who are ill do not present to the office unless they are very ill. There is no problem enrolling children and young adults who tend to present in a doctor's office quicker with an acute respiratory illness. Even working with geriatric health clinics, it has been difficult to enroll elderly patients. This will be discussed during the next network meeting at CDC in August to determine whether there are other action that can be taken, including having the call nurses at the University of Pittsburgh encouraging older individuals to participate who call in with an acute respiratory illness who seem to meet the inclusion criteria. This has not been done in the past. The existing health system has been used to enroll cases and controls, but that has resulted in the difficulty enrolling older individuals.

Dr. Sun (FDA) noticed that effectiveness is 54% for those 6 months to 8 years of age. He wondered whether some of that was due to receipt of LIAV versus TIV.

Dr. Shay replied that there were not enough cases of cases and controls who receive LIAV to make a separate estimate. Usage patterns of LIAV vary considerably across the US, so there is not as much penetration in the study sites now as there was in the past. It is anticipated that LIAV versus TIV will be able to be assessed at some point.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Marcy noted that relative risk is of interest to epidemiologists and the anti-immunization community. However, they are not ACIP's primary audience. Its primary audience is the clinicians who administer the vaccinations. He would hope that attributable risk could be determined for all of these graphs. For instance, on the curve for febrile seizures with the combination of the third subheading that stated "represents one addition seizure for every 3000 doses." For GBS, instead of odds ratios between 2 and 4, indicating how many additional cases this represents for X number of doses is what clinicians want to know. Giving 300 influenza immunizations in a year, it would take 10 years to observe one additional febrile seizure. He hoped they would use attributable risk far more often than relative risk.

Dr. Shimabukuro agreed that this was easier to digest. The published papers have relative risks as well as attributable risks. For some of the work in progress, only relative risk was available. The EIP and VSD papers do report attributable risk, so risk differences as well.

For the record, Dr. Schuchat indicated that the GBS syndrome during the pandemic in the EIP data and meta-analysis is estimate to be 1 excess GBS syndrome case per million doses vaccinated; whereas, during 1976 it was approximately 1 to 2 excess cases per hundred thousand people vaccinated. The excess of 1 or 2 per million is similar to the 1992-1993 influenza season and not to other seasons that have been assessed.

For vaccine efficacy in terms of the formula being the same for the last two seasons, Dr. Brady wondered whether people in the not vaccinated group could have received the vaccine the year before and whether that could potentially have impacted the rates.

Dr. Shay responded that there is information on receipt of previous vaccines, but only from the record reviews. While that information is not yet completed, that potential effect will eventually be assessed.

In preparing for this meeting, Dr. Moore (AIM) indicated that a question arose about differences in understanding about whether egg allergy with hives only is really considered by the committee to be a precaution to immunization. The reason this technicality about the word choice arises is because of immunization registries. Different states interpret this differently for that purpose. It is known that it is only necessary to wait an extra 30 minutes after administering the vaccine. She wondered whether this was considered to be a precaution by ACIP. The issue pertains to the perception of the word "precaution." When someone hears this, it may make them hesitate to administer the vaccine; whereas, others may not perceive it as a precaution if only an extra step is recommended to be taken.

Dr. Grohskopf responded that to her knowledge, this is not listed as a precaution on the package insert. The language used in last year's guidance notes that the vaccine may be given to those who have only hives as their reaction to eggs "with the following precautions," which does not quite have the same meaning. There was discussion about being more formal with the use of the "precaution" last year when the document was drafted, but there was advice against that because it is not listed as such in the package insert. There has been additional discussion over the past few weeks about whether this should be expressed in a more crystalline manner in the guidance.

Dr. Baker reported that the 2012 Red Book has been published, and is very clear that this is not a precaution.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Proposed Recommendations

Lisa Grohskopf, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Epidemiology and Prevention Branch, **Influenza Division**
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf summarized the proposed recommendations for use of influenza vaccines in the US for the 2012-2013 US season. The ACIP influenza vaccine statement for 2012-2013 will include relevant updates on several topics. A draft of this document was distributed with the ACIP background materials. The updates include the following:

- The influenza vaccine virus strains for the 2012-2013 season
- Reiteration of the recommendation for routine annual vaccination for all persons age 6 months and older
- Dose recommendations for children 6 months through 8 years of age
- A brief summary of the investigation of febrile seizures associated with use of TIV and PCV-13 in very young children, which has been discussed at previous ACIP meetings and also briefly during this meeting

The document also acknowledges the recent approval by the FDA of quadrivalent LAIV, and notes that this vaccine is anticipated to be available for the 2013-2014 season; that is, not the coming season but the one following. Trivalent LAIV will remain available for the 2012-2013 season.

Regarding vaccine strains for the 2012-2013 season, strain recommendations for the Northern Hemisphere vaccines were made by the World Health Organization (WHO) in late February 2012, at about the time of the last ACIP meeting. These strains were adopted by FDA at the meeting of the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) on February 29, 2012. For the 2012-2013 season, there will be changes to the A (H3N2) and B strains as compared with the previous season's vaccine. The strains for 2012-2013 will be as follows:

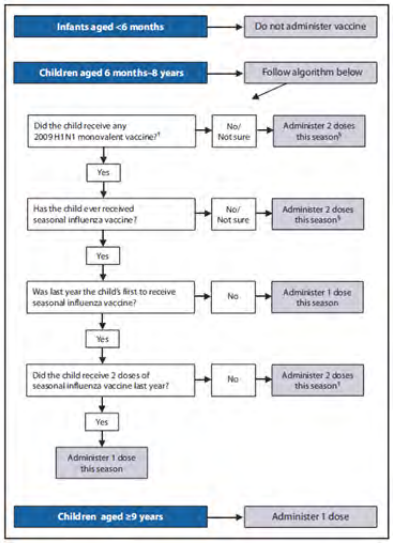
- A/California/7/2009 (H1N1)pdm09, which was contained in the 2009 monovalent and seasonal vaccines in the 2010-2011 and 2011-2012 seasons

- A/Victoria/361/2011 (H3N2), which is different for this year

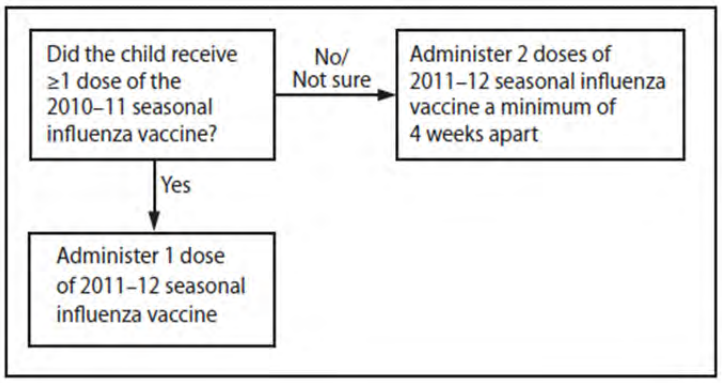
- B/Wisconsin/1/2010, which is a Yamagata lineage virus that replaces the previous Victoria lineage virus

The following illustration shows the algorithm published in the 2010-2011 season ACIP influenza statement for children 6 months through 8 years of age, which depicts the various elements that went into decision making, including consideration of whether monovalent 2009 H1N1 vaccine had been received; whether and how many doses of season vaccine were received; whether and how many doses of seasonal vaccine were received previously; and whether the previous season had been the child's first season, and if so, whether two doses were received:

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf



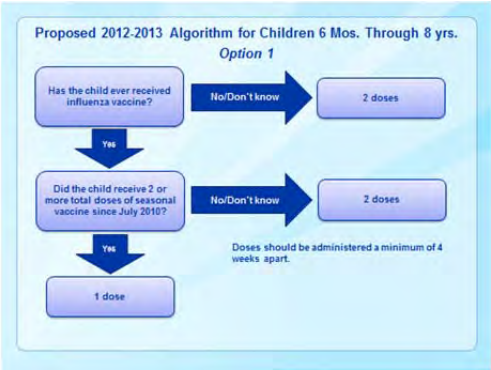
Children in the children 6 months through 8 years of age require 2 doses a minimum of 4 weeks apart during the first season that they receive influenza vaccine. The instructions and guidance for this were relatively easy to verbalize until the pandemic when the antigenic novelty of the pandemic strain necessitated consideration of additional antigen, given that the previous doses of the seasonal vaccine a child may have received could not be assumed to adequately prime for the novel antigen. This created some complications in the instructions and guidance regarding how to determine who would need one versus two doses. Because there was no change in the vaccine strains in the 2011-2012 season from the 2010-2011, and an additional measure permitted simplification of the algorithm somewhat for the past season. The algorithm as published is shown here:

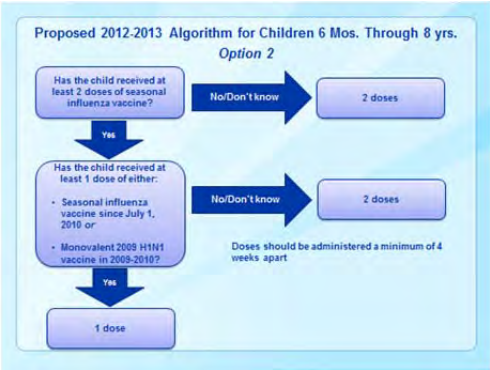


According to this algorithm, children who received at least one dose of 2010-2011 seasonal vaccine needed only one dose in 2011-2012, and those who did not needed 2 doses in 2011-2012. Of note, this algorithm did not consider history prior to the 2010-2011 season, and did not consider receipt of 2009 monovalent vaccine. As a result, somewhat more children would be recommended to receive two doses than would otherwise be the case. This somewhat simplified the recommendations, and also was harmonized with the recommendation of the American Academy of Pediatrics (AAP).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

For 2012-2013, there will be changes in 2 of the 3 vaccine strains, so some slight changes are needed. Two algorithms were considered by the working group, both of which take the strain changes into consideration. They differ essentially in whether a child's vaccination history prior to the 2010-2011 season is considered. The working group was split with regard to these two algorithms, so both options were presented and are shown as follows:





One similarity between the two options is that both are thought to adequately capture who needs two doses, which is obviously important to consider. The difference between the two is whether the vaccination history of the child is considered prior to the 2010-2011 season.

The first box in Option 1 asks whether the child ever received vaccine. If not, 2 doses are needed. If yes, the next question regards whether 2 or more total doses were received since July 2010. If no, 2 doses are needed. If yes, only one dose is needed. This algorithm is similar to last year's in that history prior to the 2010-2011season is not considered. It has as advantages consistent with last season's approach, and is relatively simple. Also, it is the approach which currently is favored by the American Academy of Pediatrics (AAP). Its chief disadvantage is that in disregarding vaccination history prior to July 2010, some children who may need only one dose will be recommended to receive two (e.g., a child who was previously fully vaccinated with seasonal and monovalent pandemic vaccines, but who did not receive vaccine in the 2010-2011 and 2011-12 seasons).

Option 2 does consider receipt of vaccine prior to the 2010-2011 season. It asks first whether the child received at least 2 doses total of seasonal influenza vaccine. If not, 2 doses are needed. If yes, it asks whether either at least one dose of seasonal vaccine since July 2010 or at least one dose of monovalent 2009 H1N1 vaccine was received. If not, again, 2 doses are needed. If yes, only one dose is needed. The advantages of this approach are that it is still somewhat simple, and that because it considers receipt of both seasonal and pandemic vaccine prior to July 2010, it is less likely to lead to some children who need only 1 dose being recommended to receive 2. If this earlier vaccination history is not known, it reverts to an approach similar to that of Option 1. A disadvantage is that some felt this approach to be sufficiently more complicated to make it difficult to execute in busy practice settings. Adoption of this approach could also lead to a recommendation that differs slightly from that of AAP, if AAP adopts Option 1.

In addition to the two algorithms, the working group also considered some additional language for possible inclusion in the text of the document should Option 1 be selected. This language reflects the additional information included in Option 2, and would give clinicians who are able to ascertain earlier vaccination history the option to consider recommending 1 dose when appropriate:

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

"For simplicity, this algorithm takes into consideration only doses of seasonal influenza vaccine received since July 2010. However, providers may consider on a case-by-case basis administering one dose rather than two to children who are known to have received either:

1) ≥2 doses of seasonal influenza vaccine previously, including at ≥1 dose of seasonal influenza vaccine since July 1, 2010, or

2) ≥2 doses of seasonal influenza vaccine previously plus monovalent 2009 H1N1 vaccine in 2009-2010."

Discussion Points

Dr. Keitel commented that Option 2 includes the history of immunization since the age of 6 months, not just the 2009-2010 season. A child born in 2003 who may have received multiple doses of seasonal vaccine in the first 7 or 8 years of life, may be told they need two doses. They would if they had not any monovalent H1N1 antigen in some fashion.

Dr. Baker reminded everyone that the February 2012 ACIP meeting was unique in that there was no discussion about the influenza strains in the vaccine because that information had not been cleared by VRBPAC. She clarified that the reason AAP proposed an algorithm was because their meetings are in April and October. It was a fluke of scheduling that AAP forced them into developing an algorithm before the ACIP consideration. She thought this was a one-time situation. Typically, AAP works closely with ACIP to develop a harmonized algorithm.

Dr. Duchin endorsed Option 2. As a parent, he would like his child's physician to ascertain all of the available information to determine whether his child needs an additional vaccination or he needs to take time off to take his child back for an extra visit for a vaccine that they might not need at all. If it is unknown, the algorithm defaults to the same position anyway. He thought this was a good option, and he motioned to propose that ACIP accept Option 2. Dr. Keitel seconded the motion.

Dr. Sawyer requested clarification regarding whether they were saying if a child received a vaccine in the distant past and received a vaccine that included pandemic H1N1, the child would only need one dose.

Dr. Keitel responded that they were saying two doses of trivalent vaccine in the past, at least one of which contained an H1N1.

Dr. Sawyer made the observation that this language was more similar to the language prior to H1N1, and he would support that. Option 1 would be another approach to this algorithm, which is very difficult for clinicians to keep straight.

Dr. Marcy argued against this. Two recommendations not harmonized from AAP and ACIP are likely to cause more confusion. He did not think this was a good idea at all, because it implied that one or the other does not have all of the facts or is not making the appropriate recommendation. While he had no preference for Option 1 or 2, he did prefer to harmonize with AAP and American Academy of Family Physicians (AAFP).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Kimberlin (AAP) concurred that it would be AAP's preference to have harmony between ACIP and the AAP's position on this as well as other recommendations related to vaccines.

Dr. Brady (AAP) indicated that when AAP assessed this, they tried to consider which would offer the simplest opportunity to address the situation of administering vaccine. While he understood the interest in trying to avoid having parents leave work for a return visit, it was also important to recognize that as many as 35% of the influenza vaccines are not administered in pediatricians' offices. In order to make the information more clear, AAP thought it would be more important to simplify the algorithm and ask people about vaccine history for the previous two years compared to trying to depend upon recall of longer timeframes.

Ms. Ehresmann emphasized the value of stronger immunization information systems and more providers participating in terms of addressing vaccine history and simplicity.

Dr. Temte reported that he recently had the opportunity to attend the North Dakota State Immunization Conference, which was attended by approximately 275 people. Interesting was that the participants were comprised primarily of those who implement policy. Dr. Andrew Kroger was there and discussed influenza recommendations, and the topic of pediatrics arose. The plea was to keep it as simple as possible. With that in mind, Dr. Temte was curious about the future in terms of when H1N1 would no longer be considered a benchmark from which to work.

Dr. Campos-Outcalt said he had always been confused by this topic and why some children need two doses and some need one, and why a dose from years ago matters at all now that the antigens have changed. Based on this, it seemed like every time the antigens changed, two doses would be needed to be fully immunized. He would tend to support the easiest option as well in terms of simplicity.

Dr. Keitel responded that the general concept is for the child to be primed against the subtype, and it is considered a 2-dose prime. Option 2 reflects the fact that a child has had two doses of an H3 and two doses of an H1, making sure that they at least had one dose before and would receive one dose this fall, and that they had two doses of the B.

Dr. Baker acknowledged that the focus on H1N1 was that it was new strain. A positive aspect of the pandemic is that older people already had protection to a large degree in that they were not vaccinated.

Regarding simplicity, Dr. Duchin did not feel that the algorithm that offered the option to determine whether a child needs a second vaccination was more complex. While it does required that an attempt be made to determine whether two doses have been given, a physician could easily go to the 2-dose arm if this information is unknown. It is in the best interest of those who have already received the adequate number of vaccinations not to have another one if that is an option.

Dr. Meissner requested clarity about whether a child could be primed by a subtype that is not the same as in the current vaccine.

Dr. Keitel confirmed that this was correct. This algorithm would mean that this would be the third dose of an H3N2-containing vaccine.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Bocchini noted that Option 2 created the possibility that if a child had received the monovalent vaccine, they could receive a single dose, but would have only had one dose of B; whereas, Option 1 enables the child to have at least one dose of B, which would fulfill the requirement of the prime and the boost for the second dose. That is why he favored the simplicity of Option 1.

Dr. Keitel clarified that Option 2 begins with a history of two prior doses, which would be two B and two H3.

Ms. Rosenbaum pointed out that many children do not have a continuous relationship with a single physician, and millions of children do not have an electronic health record (EHR). She wondered what the protocol would be if both options were too complex, and if no information was available. If the default was that 2 doses should be given if vaccine history is unknown, the question regarded whether to try to obtain the best evidence, or if considerations of safety and effectiveness were such that the algorithm that is easier to use should be selected.

Dr. Sawyer thought that a discrepant recommendation would be a problem, and he requested clarification regarding whether the AAP algorithm had already been published and could be modified.

Dr. Brady (AAP) replied that the AAP algorithm had not yet been published. It is in the final stages to be reviewed by the board.

Dr. Baker added that this meant that there was still a possibility for change, given that it had not been reviewed by the board, which sometimes makes changes.

Ms. Ehresmann noted that Option 2 specifies 2 doses of seasonal vaccine in the first box. That would mean that the monovalent would have to be in addition to that. While she understood that because of the novel aspect of the pandemic strain it was important to ensure that children were primed with two doses, she also wondered at what point a determination would be made that the novel strain had been in circulation long enough that this would not be necessary.

Dr. Keitel responded that a few more years would be necessary. Eventually this will be a moot point, but the fact is that children have been exposed to the virus and many have been vaccinated as well.

Dr. Brewer (ANA) spoke in favor of Option 1 and expressed confusion about Option 2 because it states “if the child has received at least 2 doses of seasonal influenza vaccine,” which would answer affirmatively to the first question in the second box. The point is whether the child had the monovalent pandemic vaccine, which would force them to receive 2 doses even if they had received 2 doses of H1N1 vaccine in their seasonal vaccines. She was confounded about the importance of the monovalent vaccine being the determining factor.

Dr. Keitel clarified that the second box addresses whether the child has been exposed at any time to the 2009 H1N1 antigen. That could have been by means of receiving a vaccine dose since 2010 or a monovalent dose. That could be included in one of their seasonal doses, but they have to had one because the antigen is still the same, and they will receive a second dose this year.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Brewer (ANA) pointed out that the other factor is that there may children who are 2.5 years of age who were not even alive in 2009, but had 2 doses of seasonal influenza since 2010 and are now going to have to have another second dose season. This is adding people who do not need to receive 2 doses.

Dr. Keitel clarified that if they received 2 doses of seasonal and both contained H1N1, they would only need 1 dose.

Dr. Brewer (ANA) said the language would then need to be modified to ask, “Has the child received at least 1 dose of either?” It currently read to her as if they would had to have had both.

Dr. Keitel indicated that the original language read, “Has the child received any vaccine that contained 2009 H1N1 antigen?”

Dr. Lewin (BIO) clarified that walking through the algorithm, if a child had received 2 doses of vaccine in 2011-2012, the answer to the first box would be “yes.” This would move to the question, “Has the child received at least 1 dose of either?” makes this somewhat confusing. He suggested working through a series of scenarios, because it was not clear to many people—not the concept, but the way the flow chart works. Essentially it is saying that if a child has received 2 doses of seasonal vaccine, they should receive 1 dose. However, there is an in-between step that is difficult to understand.

Dr. Meissner thought that harmonizing the recommendations between ACIP and AAP was critical. He requested further information about changing what had been submitted to the board.

Dr. Brady (AAP) responded that changes could be made, but the vote was 10 to 0 in favor of the simplified version. He thought the discussion they were hearing about Option 2 illustrated how people would arrive at confusing responses, which was what the AAP wanted to avoid.

Dr. Pickering thought it was interesting that they wanted a simplistic algorithm, but ACIP members and others had confusion about it. Many who deliver presentations to various pediatrician, family physician, and nurse practitioner groups are asked to keep things simple. There are other preventive services with which these practitioners deal other than vaccines. Moreover, there are 15 vaccines on the immunization table. If this recommendation is too confusing, it will be detrimental to the health of children because they will not receive appropriate vaccines.

Given that one type but not the exact type was needed, Dr. Campos-Outcalt wondered why the algorithm from last year would not work this year, since basically the same three types are included in the vaccine this year as last year.

Dr. Keitel clarified that there are two new strains.

Dr. Campos-Outcalt pointed out that they are H3N2s and a B. He requested clarity regarding whether any H3N2 and any B would prime the child for the next.

Dr. Keitel responded that the only study that would inform this was conducted by Dr. Janet Englund in 6 month old through 24 month old children. They showed that if these children received 1 dose 1 year and then the antigen changed and they received the second dose the following season, the immune responses were inferior to those than if they received 2 doses of

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

the same antigen. The difference is that Option 2 pertains to children who already received 2 H3 and are receiving a third. That is a different situation.

Dr. Zahn (NACCHO) pointed out that the second box in Option 1 answers the first question. In order to really simplify this, the first box could be eliminated.

Dr. Grohskopf replied that this was raised in the working group. She requested that Dr. Bernstein comment on this.

Dr. Bernstein (AAP) replied that the first box was included because of the millions of children who need vaccines. When a child presents to a physician's office, the first box would allow someone other than a nurse or physician to ask the question without having to interpret the dates on their immunization record in order to establish whether they need 2 doses from the outset.

It seemed to Dr. Zahn (NACCHO) that the person who asked the first question would have to be knowledgeable enough to ask the second question as well.

Dr. Bernstein (AAP) replied that they have to be able to ask the second question, but they do not have to be able to answer it. They can answer the first question rather easily when they are trying to get through 1500 to 2000 patients per doctor in a given practice.

Dr. Marcy said it was a matter of syntax and should be "a total of 2 or more doses" rather than "2 or more total doses," which means 0.5mL.

Ms. Ehresmann thought that some of the practice acts in some states would suggest that an assessment would not be made by someone at a low level, who may be the appropriate person to administer the vaccine but not to make the assessment. If that was the only reason for that box, it should be considered in the decision-making process.

Dr. Baker thanked everyone for their thoughtful questions and comments, acknowledging that this clearly is an interesting issue. Like influenza, there is nothing predictable about the discussion each year.

Dr. Zucker (New York City Department of Health) reminded everyone that a tremendous investment has been made in immunization information systems. New York City has 90% participation by providers, and over 90% of the vaccines administered are reported to the registry. New York City will program its registry with the information from the recommendation made by ACIP to offer immediate decision support for providers. A lot of the complexity can be made much easier for the provider. Regardless of the recommendation made, clear language that will allow prior vaccination history to be taking into account needs to be included. If the information available is not used, it was unclear to her why the investment was made in immunization registries across the country. She thought locations should build upon current capacity. Responding to an inquiry by Dr. Baker regarding whether pharmacists could access the registry and administer vaccinations, Dr. Zucker responded that in New York State pharmacists do not vaccinate anyone under 18 years of age, but they do have access to the registry.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Vote: Recommendation for 2012-2013 Influenza Vaccine Algorithm Option 2

Dr. Duchin made a motion to support Option 2 as written, with clarifications to the text based upon the discussion to make it easier to implement. Dr. Keitel seconded the motion. The motion did not carry with 4 affirmative votes, 11 negative votes, and 0 abstentions. The disposition of the vote was as follows:

4 Favored:	Duchin, Campos-Outcalt, Ehresmann, and Keitel
11 Opposed:	Baker, Bennett, Bocchini, Coyne-Beasley, Jenkins, Marcy, Meissner, Rosenbaum, Sawyer, Temte, and Vazquez
0 Abstained:	N/A

Discussion Points

Given that the motion did not carry, Dr. Baker requested another motion.

Dr. Marcy made a motion to support Option 1 as written, which Dr. Sawyer seconded.

Dr. Duchin requested that the annotated text reflect that physicians who are able to ascertain the accurate immunization history of their patient can avoid administering an unnecessary vaccine.

Dr. Baker thought that was obvious from the discussion and those who voted one way or another.

Dr. Temte added that the recommendation should read very clearly so that programmers could logically place it in immunization registry systems.

Vote: Recommendation for 2012-2013 Influenza Vaccine Algorithm Option 1

Dr. Marcy made a motion to support Option 1 as written. Dr. Sawyer 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:	Baker, Bennett, Bocchini, Coyne-Beasley, Duchin, Campos-Outcalt, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Vaccines for Children

Jeanne M. Santoli (jsantoli@cdc.gov)
Immunization Services Division
National Center for Immunization and Respiratory Diseases

Dr. Santoli noted that the additional language would not be reflected in her presentation, but would be amended in the final Vaccines for Children (VFC) recommendation. She indicated that the purpose of this resolution was to update the recommendations for the second dose of influenza vaccine in children 6 months through 8 years of age.

The current wording for TIV for eligible children will not change from "All children aged 6 months through 18 years." Also unchanged in the TIV component would be the recommended schedule of "6 months through 8 years: 1 or 2* doses" and "9 through 18 years: 1 dose." The proposed changes for the revised TIV footnote included two options:

> Option #1
> *All children ages 6 months through 8 years who receive a seasonal influenza vaccine for the first time should receive 2 doses at least one month apart. Children who have received seasonal influenza vaccine previously, but who have not received 2 or more total doses since July 2010 should also receive 2 doses. Children who have received 2 or more total doses of seasonal vaccine since July 2010 should receive 1 dose.
>
> Option #2
> * All children ages 6 months through 8 years who have not received at least 2 doses of seasonal influenza vaccine in the past should receive 2 doses at least one month apart. Children who have received at least 2 doses of influenza vaccine previously, but who have not received at least one doses of either 1) seasonal influenza vaccine since July 1, 2010 or 2) monovalent 2009 H1N1 vaccine in 2009-2010 should also receive 2 doses. Children who have received at least 2 doses of seasonal influenza vaccine, including at least one dose of either 1) seasonal influenza vaccine since July 1, 2010 or 2) monovalent 2009 H1N1 vaccine in 2009-2010 should receive 1 dose.
>
> Additional Language that Could Be Added
>
> For simplicity, this algorithm takes into consideration only doses of seasonal influenza vaccine received since July 2010. However, providers may consider on a case-by-case basis administering 1 dose rather than 2 to children who are known to have received either at least 2 doses of seasonal influenza vaccine previously, including at least 1 dose of seasonal influenza vaccine since July 1, 2010 or at least 2 doses of seasonal influenza vaccine previously plus monovalent 2009 H1N1 vaccine in 2009-2010.

The recommended intervals, dosage, and contraindications and precautions for TIV will remain unchanged.

Discussion Points

Dr. Duchin made an alternative suggestion for the proposed additional language that could be added to the TIV footnote, because "consider on a case-by-case basis" should not be included. If a child's history is known of receiving 1 or 2 doses, they should only receive 1 additional vaccine. Instead, he suggested phrasing the language, "If physicians can ascertain that a child

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

has either 1 or 2 doses, that child should receive 1 dose rather than 2." He also requested that "2 total doses" be changed to "a total of 2 doses" as Dr. Marcy suggested for the recommendation.

Dr. Santoli clarified that the VFC resolution is intended to reflect what ACIP agrees upon as a group. It was unclear whether they needed to return to that discussion, given that this was not intended to alter that in any way.

Dr. Baker replied that there should not be any discussion about the intent, which is that if a physician has the information, 1 dose rather than 2 can be given. She thought all of the members agreed with that.

Dr. Keitel requested that they vote on the intent of the resolution rather than the exact language.

Dr. Baker thought they should vote on the intent, and work on the language later.

It seemed to Dr. Schuchat that the VFC was indented to ensure 2 doses are VFC-eligible for children under 9 years of age rather than all of the details. She would be anxious about something that would be quite restrictive and could result in someone not receiving vaccine due to confusion on the part of the physician or parent.

Dr. Santoli indicated that ACIP has the option to state something different in the VFC resolution than is stated in the recommendation. There are a couple of examples, and it was up to the digression of the committee if there was a preference to be more general in the VFC resolution. Reviewing the information presented, she thought this would mean removal of the footnote as described. The LAIV portion would remain "2 years through 8 years."

Vote: VFC

Ms. Ehresmann made a motion to accept the VFC statement, with language to state that children through age 8 can receive up to 2 doses of influenza vaccine per season. Dr. Keitel 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:	Baker, Bennett, Bocchini, Coyne-Beasley, Duchin, Campos-Outcalt, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Hepatitis B Protection for Healthcare Personnel (HCP)

Introduction

Mark Sawyer, MD, Chairman
Hepatitis Vaccine Working Group

Dr. Sawyer thanked Dr. Baker for her leadership and acknowledged his colleagues who would be leaving ACIP after this meeting.

He reminded everyone that the term of reference the Hepatitis Vaccine Working Group was now addressing was to ensure hepatitis B protection for healthcare personnel (HCP), including trainees, who received hepatitis B (HepB) vaccination in the past without post-vaccination serologic testing, or who no longer have a record of post-vaccination serologic test result. The working group deliberated this topic with a 10-year time frame in mind, with the expectation that over that timeframe additional information would become available on the long-term duration of protection of HepB vaccine that will further information decisions on this topic.

Although currently, post-vaccination serologic testing with the measurement of antibody to hepatitis B surface antigen (anti-HBs) is recommended 1 to 2 months after HepB vaccination for HCP who are at high risk for exposure to blood and body fluids[1], an increasing proportion of HCP are entering training and the workforce having received HepB vaccine as an infant, young child, or adolescent who did not receive post-vaccination serologic testing[2] [[1]*MMWR* 2011; [2]*MMWR* 2005]. Therefore, there is a growing population of HCP for whom adequate vaccine response status is unknown.

The working group has spent the last several months reviewing several potential strategies to address this issue, which include the following:

Post-exposure evaluation
1. All sources (HBsAg-negative, positive, or unknown)
b. HBV-positive or unknown sources

Pre-exposure evaluation
2. Anti-HBs testing; HepB dose if necessary
3. HepB dose and anti-HBs testing

Hybrid evaluation
a. Pre-exposure HepB dose; post-exposure, all sources

Working group activities have included 10 working group teleconferences, ACIP presentations in February 2012, and a Healthcare Infection Control Practices Advisory Committee (HICPAC) presentation in June 2012. During the June 2012 ACIP meeting, presentations were delivered regarding model inputs for cost-effectiveness analyses, results of cost-effectiveness analyses, and recommendations under discussion. The working group has engaged in a number of spirited discussions, and there is not yet clear consensus among the members regarding which of these strategies would be the best.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Overview of Hepatitis B Protection

Sarah Schillie, MD, MPH, MBA
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

During this session, Dr. Schillie reported on the 2011 HepB immunization recommendations for HCP [*MMWR* 2011], assessment of serologic evidence of protection, the changing context of occupationally-acquired hepatitis B virus (HBV) infections among HCP, and then approaches discussed by the working group.

According to the 2011 recommendations for immunization of HCP, HCP are defined as "All paid and unpaid persons working in healthcare settings who have the potential for exposure to patients and/or to infectious materials . . ." The definition specifically states that students and trainees are considered HCP. A 3 or more dose HepB vaccine series is recommended for all unvaccinated HCP whose work- and training-related activities involve risk for blood and body fluid exposure. The vaccination series should be completed before trainees have contact with blood and body fluids. Post-vaccination serologic testing 1 to 2 months after the last HepB dose is recommended for all HCP at continuing high risk for blood and body fluid exposure. Post-vaccination serologic testing determines the need for revaccination and guides post-exposure prophylaxis. No HBV post-exposure prophylaxis is required for vaccine responders, or those with serologic evidence of protection, regardless of the hepatitis B surface antigen (HBsAg) status of the patient who was the source of the blood and body fluid exposure [*MMWR* 2011].

Serologic evidence of protection is assessed by antibody to hepatitis B surface antigen (anti-HBs) measured 1 to 2 months after a HepB vaccine series[1]. Anti-HBs ≥10 mIU/mL has been interpreted as serologic evidence of vaccine-induced protection[1]. Protection has been documented to exist for 22 years or more[2] among immunocompetent adults who are vaccine responders. Anti-HBs levels after the HepB vaccine series wane over time and can decrease to less than10 mIU/mL. However, even when anti-HBs decreases to less than 10 mIU/mL, breakthrough HBV infections are uncommon in immunocompetent vaccine responders[2] [[1]*MMWR* 2005; [2]Leuridan, CID 2011].

Because anti-HBs levels wane over time, levels less than 10 mIU/mL at a time distant from vaccine completion do not distinguish[1,2] among initial responders who account for approximately 93% of healthy vaccines, delayed responders who respond to revaccination and account for approximately 5% of vaccines, or non-responders who remain susceptible to infection after 6 doses of vaccine and account for approximately 2%[3] of vaccines or have chronic HBV infection [[1]*MMWR* 2005,[2]Averhoff; Am J Prev Med 1998].

In situations when anti-HBs decreases to less than 10 mIU/mL, a challenge dose of HepB vaccine can be used to induce an increase in antibody and, therefore, provide serologic evidence of protection. An increase of anti-HBs to greater than or equal to10 mIU/mL following a challenge dose of HepB vaccine indicates immune memory is intact, and is thought to correlate with protection. Dr. Schillie indicated that in the presentations during this session, the term "challenge dose" would be used to determine if immune memory is intact. Note that the purpose of challenge dose differs from the purpose of a booster dose. The purpose of a booster dose is to provide rapid protective immunity against breakthrough infection [Leuridan, CID 2011].

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The proportion of persons responding to a challenge dose is lower among persons vaccinated at less than 1 year of age versus those vaccinated at age 1 year or older. The proportion of responders also declines as the time since vaccination increases. The meaning of failure to respond to a challenge dose is not currently understood.

Because of the changing context for occupationally-acquired HBV, health care schools and institutions are seeking guidance regarding ensuring protection for HCP who received HepB vaccine series in the remote past without post-vaccination serologic testing. This includes HCP who were vaccinated as infants as part of universal infant vaccination, and adults who never had post-vaccination serologic testing performed or no longer have a record of post-vaccination serologic test result.

An increasing proportion of HCP entering training and the workforce have received a HepB vaccine series in the remote past as a result of the recommendation for routine infant HepB vaccination in 1991 and catch-up vaccination for children 0 through 18 years of age in 1995 and 1999. Vaccine coverage is approximately 90% for infants and adolescents[1,2]. Post-vaccination serologic testing is not recommended after routine infant or child HepB vaccination[3]. Approximately 95% of infants who receive post-vaccination testing as a part of a clinical trial have serologic evidence of protection after vaccination[4] [[1]National Immunization Survey, data provided by Rodewald L.; [2]*MMWR* 2011; [3]*MMWR* 2005; [4]Hadler, Curr Clin Top Infect Dis 1992].

Over time, more HCP will have been vaccinated at less than 1 year of age instead of at age 1 year or older. This is significant because years after vaccination, persons vaccinated at less than 1 year of age more often have anti-HBs less than 10 mIU/mL compared to persons vaccinated at age 1 year or older.

Projected HepB vaccination coverage of 3 or more doses by age at first dose and age group in the general US population for the years 2013, 2018, and 2023 roughly corresponds to the time horizon of approximately 10 years currently under discussion. Note that these figures are not specific to healthcare personnel. Persons aged 18 through 20 years in 2013 will have high vaccine coverage of approximately 90%. Approximately 80% of these persons, those aged 18 through 20 years in 2013, will have been vaccinated at less than 1 year of age. In 2013, coverage will likely be lower among the age groups of persons 21 and older, and most of those vaccinated will have been vaccinated at age 1 year or older. For 2018, vaccination coverage increases compared to 2013. In 2018 compared to 2013, an increasing proportion will have been vaccinated at age less than 1 year. The trend continues for 2023, although some persons who are unvaccinated in 2013 might be vaccinated by 2023. In conclusion, HepB vaccine coverage will likely increase and an increasing proportion of HCP will have been vaccinated in the remote past at less than 1 year of age [Lu, Vaccine 2011. National Health Immunization Survey 2009, National Immunization Survey-Teen 2010, National Immunization Survey 1994-2010, prepared by Reilly M].

Policy also has changed the context for occupationally-acquired hepatitis B infection. The Needlestick Safety and Prevention Act directed the Occupational Safety and Health Administration (OSHA) to revise the Occupational Exposure to Bloodborne Pathogens standard, and established in greater detail requirements that employers identify and use effective and safer medical devices. This became effective in 2001 [http://www.osha.gov/SLTC/bloodbornepathogens/standards.html].

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

With data from the Exposure Prevention Information Network (EPINet) from 1997 through 2009, the annual rate of percutaneous injuries (e.g., needlesticks, cuts, bites) decreased from 30 to 40 injuries per 100 occupied beds prior to the Needlestick Safety and Prevention Act to about 20 injuries per 100 occupied beds in 2009. Mucosal exposures (e.g., blood and body fluid contact with mucous membranes or non-intact skin) demonstrated a decline from about 10 exposures per 100 occupied beds in 1997 to approximately 7 exposures per 100 occupied beds in 2009 [http://www.healthsystem.virginia.edu/pub/epinet/rates.html].

In addition to policy changes, epidemiological changes might affect the risk for occupationally-acquired Hepatitis B. The number of reported acute hepatitis B cases has declined since 1990. In 2009, approximately 3400 acute hepatitis B surveillance cases were reported to CDC. After adjusting for asymptomatic cases and under-reporting, the estimated number of new cases was 38,000. Although rates are declining, cases of acute hepatitis B among HCP are still being reported to CDC [National Notifiable Diseases Surveillance System (NNDSS)]. Between 2005 through 2010, there were 203 cases of acute hepatitis B among HCP reported to CDC. Of these, 75 reported their degree of blood contact to be frequent, defined as several times weekly. These cases represented a subset of cases for which occupation was ascertained. Among the 203 cases, the median age was 41 years, 60% were female, and 28 of 168 (17%) reported an accidental stick or puncture with a needle or other object contaminated with blood in the 6 weeks to 6 months prior to their hepatitis B illness. The vaccination response history was sparse [NNDSS; Surveillance definition of HCP: persons employed in a medical, dental or other field involving contact with human blood].

In contrast to acute hepatitis B with a declining incidence, the prevalence of chronic hepatitis B has been stable. The number of chronic cases, as defined by the presence of both HBsAg and anti-HBc, has remained stable since 1976 affecting approximately 3 per 1000 persons [NHANES, 1976–2010]. Chronic cases serve as an important reservoir for transmission. An estimated 800,000 to 1.4 million[1] persons in the US have chronic hepatitis B, most of whom are asymptomatic. The prevalence likely varies by healthcare setting, with greater prevalence in dialysis facilities and settings with large foreign-born populations. Approximately 54,000 additional cases of chronic hepatitis B are imported yearly from immigration[2] [[1]*MMWR* 2008; [2]Mitchell, PLoS One 2011]. Therefore, the risk of Hepatitis B for HCP will continue.

Given the changing context for occupationally-acquired hepatitis B infection, the working group discussed the following 5 approaches for ensuring hepatitis B protection among HCP vaccinated in the past without post-vaccination serologic testing:

Post-exposure evaluation

1. All sources (HBsAg-negative, positive, or unknown)
b. HBsAg-positive or unknown sources

Pre-exposure evaluation

2. Anti-HBs testing; HepB dose if necessary
3. HepB dose and anti-HBs testing

a. Hybrid evaluation Pre-exposure HepB dose; post-exposure, all sources

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The post-exposure approaches are similar. No pre-exposure action is taken. In the event of an exposure, the HCP is tested for anti-HBs and source patient is tested for HBsAg simultaneously. Hepatitis B Immune Globulin (HBIG) is administered if indicated. Under Approach 1, all HCP with anti-HBs of less than 10 mIU/mL would receive 1 additional HepB vaccine dose regardless of the source patient's HBsAg status, followed by 2 additional HepB vaccine doses in a small percentage of HCP expected to lack a serologic response. Under Approach b, revaccination of HCP with anti-HBs less than 10 mIU/mL only occurs when the source patient has a positive or unknown HBsAg status. Therefore, under Approach 1, most HCP would be protected from future hepatitis B exposures. Under Approach b, many HCP will not be protected from future exposures.

With pre-exposure Approach 2, all HCP are tested at baseline for anti-HBs. Those with anti-HBs levels less than 10 mIU/mL will receive 1 HepB vaccine dose followed by post-vaccination serologic testing. The small proportion whose anti-HBs remain less than 10 mIU/mL would receive 2 more HepB vaccine doses followed by post-vaccination serologic testing. Under pre-exposure Approach 3, all HCP will receive 1 HepB vaccine dose at baseline followed by post-vaccine serologic testing. The small percentage of HCP with anti-HBs less than 10 mIU/mL will receive 2 more HepB vaccine doses followed by post-vaccination serologic testing. For both Approach 2 and 3, HepB post-exposure prophylaxis is necessary only for the small proportion of HCP who are non-responders after the second 3-dose series. In contrast to the post-exposure approaches, these pre-exposure approaches offer additional protection against unrecognized or unreported exposures. With the hybrid approach, all HCP would receive 1 HepB vaccine dose at baseline, but no post-vaccination serologic testing at that time. All HCP will require post-exposure evaluation similar to that which occurs with Approach 1.

In summary, healthcare schools and institutions are seeking guidance regarding ensuring protection for HCP who received HepB vaccine series in the past without post-vaccination testing. The risk for occupationally-acquired hepatitis B has decreased over time, yet still exists. The working group has identified two approaches, 1 post-exposure and 1 pre-exposure, for further discussion. The numbering is a carryover from working group discussions and does not reflect preference. Among the 5 approaches, the working group favored Approaches 1 and 2 for proposed recommendations.

Risk of Exposure and Antibody Levels Over Time

Meredith Reilly, MPH
Division of Viral Hepatitis
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Ms. Reilly reviewed results of the cost-effectiveness analysis model considerations and structure, focusing on the non-cost related model inputs including the following:

- Risk of blood and body fluid (BBF) exposure
- Likelihood of reporting BBF exposures
- Probability of hepatitis B surface antigen positive source patient
- Risk of hepatitis B virus transmission to exposed HCP
- Serologic evidence of protection after hepatitis B vaccine series
- Serologic evidence of protection after a challenge dose of hepatitis B vaccine

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Prior to determining the values for the model inputs, the working group discussed key model considerations and made a distinction between trainees and all other healthcare personnel. The provisional definition for trainees was, "persons entering school and/or obtaining new job skills that involve contact with patients or with blood or other body fluids (BBF) from patients in a healthcare, laboratory, or public-safety setting." This distinction was made because trainees have a high continuing risk for BBF exposure, and higher rates of BBF exposure than non-trainees [Provisional Work Group definition adapted from *MMWR*. Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Post-exposure Prophylaxis. June 29, 2001/50(RR11);1-67]. The working group also considered the impact of age at vaccination on long-term serologic evidence of protection, given that HCP vaccinated at age <1 year may experience earlier waning of anti-HBs levels compared to HCP vaccinated at age ≥1 year. An increasing number of trainees are being vaccinated at age <1 year.

Because of these key model considerations, separate analyses were performed for trainees and non-trainees. The primary analysis focused on trainee values, with the sensitivity analyses incorporating a range of input values for the trainee. A secondary analysis was performed to assess the cost-effectiveness of the options specific to non-trainees.

To estimate the risk of blood and body fluid exposure, the working group reviewed data summarizing the proportion of HCP who sustained ≥1 percutaneous injury (PI) or mucosal/non-intact skin exposure (ME) to blood, tissue, or other potentially infectious body fluid in the past 12 months. These data did not account for unrecognized exposures. PI injuries can be caused by a needlestick, cut, or bite. MEs occur when HCP come into contact with mucous membranes or non-intact skin (e.g., skin that is chapped, abraded, or with dermatitis). The literature review was limited to studies of occupational BBF exposures that occurred in 2002 or later, which followed implementation of the Needlestick Safety and Prevention Act. Data were extracted from 6 studies that used cross-sectional surveys to collect information on the annual proportion of non-trainee HCP who sustained BBF exposures during 2002 or later. Physicians were not included, but estimated rates among physicians suggest a similar or slightly higher risk compared to non-physician HCP. Considering the available data, the median proportion who sustained a percutaneous injury was 10% and ranged from 4% to 16%. The median proportion who sustained a mucosal exposure was 13% and ranged from 3% to 16%.

Because the data allowed for an estimate of the annual proportion of exposures sustained by non-trainees only, the working group wanted to find out whether there was a difference in the frequency of exposures between trainees and non-trainees, and if so, the magnitude of the difference . To answer this question, the working group identified additional studies that presented data on the rates of exposure that allowed for comparisons of risk between trainees and non-trainees. The 5 studies collected data from percutaneous injury and occupational health and safety surveillance systems, cross-sectional surveys, and emergency department billing codes. The risk ratios for BBF exposure for trainees versus non-trainees were derived from the 5 studies. The risk for trainees compared to non-trainees varied by occupation. The overall risk for BBF exposure was 1.75 times higher for trainees compared to non-trainees.

These recent data suggest that despite policy changes and engineering and work practice controls, HCP continue to experience BBF exposures. The non-trainee values of 10% and 13% were used as a baseline to estimate that 18% of trainees sustain percutaneous injuries each year, and 22% of trainees sustain mucosal exposures. The values for the sensitivity analyses for percutaneous injury were 6% to 27%, and for mucosal exposures were 5% to 29%.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Once the risk for BBF was estimated for HCP, the working group wanted to know to what extent HCP were reporting or not reporting these exposures, and whether reporting behavior was similar or different for trainees and non-trainees. The working group explored this question and defined the model input as "the proportion of blood and body fluid exposures reported to an occupational health clinic or emergency department in past 12 months." Again, the literature review was limited to studies on occupational exposures occurring in 2002 or later. Data were extracted from 7 studies that used cross-sectional surveys to evaluate the annual proportion of BBF exposures reported to occupational health during 2002 or later. Four studies examined non-trainees, and three studies examined trainees. Reporting of exposures was similar for trainees and non-trainees. Overall, the annual proportion of percutaneous injuries reported by both trainees and non-trainees was 54%. An estimated 17% of mucosal exposures were reported. The sensitivity analysis for percutaneous exposures ranged from 38% to 67%, and for mucosal exposures ranged from 7% to 44%.

Dr. Schillie previously described the steady state of chronic hepatitis B in the US, which directly affects the probability that upon sustaining a blood or body fluid exposure, the source patient is infected with the hepatitis B virus indicated by a positive HBsAg test. The third model input was defined as, "the proportion of source patients testing hepatitis B surface antigen (HBsAg) positive, a marker of chronic or acute infection. Of 7170 exposures across 3 US healthcare systems during 2000 through 2012 [[1]UNC Healthcare, UPMC Health System, Alaska Native Tribal Health Consortium (unpublished data)], approximately 0.9% of source patients tested HBsAg positive. BBF source patients were identified in an estimated 94% of occupational exposures. This value was used for both the trainee and non-trainee analyses. While approximately 0.9% of source patients are thought to be HBsAg positive, this is known to vary a great deal across populations. Other populations, such as hemodialysis patients, may pose a higher risk for HBsAg. The working group considered the wide variation of chronic hepatitis B prevalence across patient populations and chose a range of values for the sensitivity analysis, with 0.3% selected as the lower limit for the probability of a HBsAg positive source patient. A 10% probability of having a HBsAg positive source patient was considered the upper limit for the sensitivity analysis.

It is known that blood and body fluid exposures continue to occur and that the pool of chronic hepatitis B among the US population has remained relatively stable for some time. The next input explored the risk of hepatitis B virus (HBV) transmission to exposed HCP. In other words, what is the probability of serologic evidence of hepatitis B infection among susceptible HCP after sustaining a blood or body fluid exposure contaminated with HBV in the absence of post-exposure management? The risk of hepatitis B infection was calculated as a weighted sum, accounting for the hepatitis B e antigen (HBeAg)* status of a HBsAg positive source patient. An estimated 34.5%[1] of HBsAg-positive source patients are HBe antigen-positive, and the probability of infection from a percutaneous injury from a HBeAg-positive, HBsAg-positive source patient is approximately 50%[2]. Sustaining a percutaneous injury from the remaining two-thirds of the HBeAg-negative, HBsAg positive source patient population presents about a 30%[2] risk for infection [[1]Cruz 1987, Friedman 1998, Kohn 1996, Kumar 1987, McMahon 1993; [2]*MMWR* June 29, 2001/50 (RR11), assumes percutaneous injury; *Marker of high viral replication/highly infectious patient]. Putting this together, both trainees and non-trainees have an estimated 37% risk for HBV transmission from a percutaneous injury. The risk of HBV transmission from a mucosal exposure was estimated at about half the risk from a percutaneous injury at 19% for both trainees and non-trainees. The sensitivity analysis values for percutaneous injuries were 25% to 46%, and for mucosal exposures were 13% to 23%.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Recalling that Dr. Schillie indicated the challenges associated with assessing HepB vaccine-induced protection, especially when serologic testing for HBsAg is performed years following the primary series, Ms. Reilly described the findings related to serologic evidence of protection after a HepB vaccine series. Serologic evidence of protection after a HepB vaccine series was defined by the proportion of HCP with anti-HBs of greater than or equal to10 mIU/mL. Serologic data were reviewed for subjects vaccinated at varying times since vaccination, and were stratified by age at vaccination according to subjects vaccinated at age <1 year and subjects vaccinated at age ≥1 year. Data were extracted from a literature review of HepB vaccination studies conducted in the US from 1985 to the present. Available data were extrapolated to estimate seroprotection proportions at 18 to 25 years since vaccination, which are common ages of matriculation into nursing school or medical school for example.

The majority of current trainees are vaccinated at age >1 year. Over the next 10 years, the proportion of trainees vaccinated at age <1 year will increase substantially. To determine the proportion of subjects with serologic evidence of protection indicated by anti-HBs of greater than or equal to 10 mIU/mL, 5 US studies provided serologic data for subjects tested up to 17.5 years since vaccination [Dentinger 2005, Hammitt 2007, Middleman 2012, Petersen 2004, Samandari 2007]. These data were fit to a linear trend line to estimate the proportion of persons with serologic evidence of protection at 18 and 25 years since vaccination. It was estimated that 16% of persons vaccinated at age <1 year would have serologic evidence of protection at 18 years since vaccination, and that approximately 9% of persons would have evidence of protection at 25 years.

For serologic evidence of protection by years since vaccination at age ≥1 year, a similar trend line was fit to available data, suggesting that about 74% of persons vaccinated at age 1 year or older will have serologic evidence of protection at 18 years since vaccination [Funderburke 2000, McMahon 2005, McMahon 2009, McMahon 2011, Stevens 1992, Tohme 2011, Watson 2001, Williams 2001, Williams 2011]. An estimated 67% of persons will have evidence of protection at 25 years.

Compared to persons vaccinated at age <1 year, persons vaccinated at age ≥1 year maintain higher proportions of serologic evidence of protection over time when measured at the same time intervals since vaccination. An estimated 20% of trainees will have serologic evidence of protection after a hepatitis B vaccine series. This estimate was weighted toward the proportion of HCP vaccinated at age <1 year with serologic evidence of protection. Figures used for the sensitivity analysis reflect the range of values for trainees from 10% to 50%. The working group decided on 80% for the non-trainee analysis as a result of reviewing the seroprotection data for HCP vaccinated at age ≥1 year.

Now there is a sense of what proportion of HCP will have evidence of protection at a certain follow-up period. Recalling that some of the approaches under consideration for a recommendation include anti-HBs testing followed by an additional dose or an additional dose followed by testing, Ms. Reilly presented data for serologic evidence of protection after an additional dose, or a challenge dose, of HepB vaccine. The working group wanted to know the proportion of HCP who had anti-HBs of less than10 mIU/mL at follow-up after receiving a complete series of HepB vaccine and what proportion responded with anti-HBs greater than or equal to 10 mIU/mL after a challenge dose of HepB vaccine. The working group reviewed data to answer this question according to time since vaccination and age of vaccination. Data were extracted from the same literature review of HepB vaccination studies conducted in the US previously described. Following the same methods for estimating proportions of serologic evidence of protection after a HepB vaccine series, available data were extrapolated to estimate

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

the proportion of subjects with evidence of protection after a challenge dose at 18 and 25 years since vaccination.

Regarding the proportion of subjects who had anti-HBs of less than 10 mIU/mL before a challenge dose and had serologic evidence of protection after a challenge dose among subjects vaccinated at age <1 year, four US studies provided serologic data for subjects who received a challenge dose up to 17.5 years since vaccination [Hammitt 2007, Middleman 2012, Petersen 2004, Samandari 2007]. A linear trend line was added as a guide to help forecast expected proportions of anti-HBs after a challenge dose up to 25 years since vaccination. The available data allowed the working group to estimate that if the response rates follow a linear trend, 64% of persons vaccinated at <1 year will respond to a challenge dose at 18 years since vaccination, and 50% will respond at 25 years since vaccination. For subjects vaccinated at age ≥1 year, the available data from 3 US studies allowed the working group to estimate that if the response rates follow a linear trend, 75% of persons vaccinated at age ≥1 year will respond to a challenge dose at 25 years since vaccination [McMahon 2009, Tohme 2011, Williams 2001]. An estimated 60% of trainees will respond to a challenge dose according to the proportion of HCP vaccinated at age <1 year with serologic evidence of protection. Sensitivity analyses reflect the possible range of values for trainees of 35% to 70%. The non-trainee value of 75% was derived from an estimation of proportions of HCP vaccinated at age ≥1 year who responded to a challenge dose.

To summarize, the risk of blood and body fluid exposure is approximately 1.75 times higher for trainees versus non-trainees, and 17% to 54% of trainees and non-trainees report exposures. Approximately 0.9% of source patients are HBsAg-positive according to recent estimates, though prevalence varies by patient population. Additionally, the proportion of HCP with serologic evidence of protection at time distant from vaccination is less among HCP vaccinated at age <1 year compared to those vaccinated at age ≥1 year. An additional challenge dose of HepB vaccine induces memory response in 60% to 75% of vaccinees regardless of age at vaccination.

Discussion Points

Dr. Schuchat requested clarification regarding the evidence base for correlation between response to a challenge dose when remotely vaccinated and risk of disease.

Dr. Schillie replied that response to a challenge dose means that immune memory is intact, and that corresponds to protection against disease. The meaning of failure to respond to a challenge dose, however, is unknown. She confirmed for Dr. Schuchat that the immunology of infant vaccination and the failure to respond is unknown.

Dr. Bennett noted that they were shown surveillance data in the two presentations that differed with respect to how much was percutaneous and how much was mucosal. She was curious as to whether those were just one series of studies and the other surveillance data. She also requested that someone speculate on why there is such a huge difference with respect to the maintenance of immunity over time based on whether children were immunized before age 1 or after.

Ms. Reilly responded that the data she presented were proportions or frequencies, and numbers of exposures that occurred in a year out of a number of HCP; whereas, Dr. Schillie's presentation showed rates per hospital beds, so the denominator was different. That may be the reason for the differences. Ms. Reilly's studies regarding risk of exposure were from cross-

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

sectional surveys during the past year, so they were not active surveillance. One study she showed comparing trainees to non-trainees was an active data source. In terms of the reasons for the difference in the waning of antibody between those vaccinated at age <1 year versus those age ≥1 and older, she thought they could speculate that one reason might be the immature immune system in those age <1 year compared to those age ≥1 year and older.

Dr. Bennett wondered whether this meant that ACIP should reconsider its recommendation for hepatitis B vaccine in children.

Dr. Keitel thought the geometric mean titers (GMTs) must be known in infants after they receive the 3-dose series versus an adult or older child, so she would speculate that the GMTs are probably higher in older age groups than infants. She inquired as to whether the risk for acquisition of infection after a mucosal exposure was known.

Ms. Reilly replied that the risk of hepatitis B virus transmission to a HCP exposed to an infected source patient was 19%, which is about half of the percutaneous exposure estimate.

Dr. Marcy asked whether, in the review of the literature, any cases were found of chronic hepatitis B or hepatocellular carcinoma (HCC) associated with hepatitis B in a fully immunized person.

Ms. Reilly responded that the studies reviewed in the literature excluded any subjects who may have had an indication of chronic hepatitis B at baseline. There were a few breakthrough infections.

Dr. Marcy's impression was that it is very rare and that cell mediated immunity is a large part of the immunity to this condition, in addition to antibody. Someone may seroconvert, but may not be very sick and will not get chronic hepatitis B.

Ms. Reilly replied that of the studies reviewed, there were no symptomatic infections.

Referring to Dr. Schillie's slide 18 that defined the current extent of the problem (e.g., acute hepatitis B cases that occurred among HCP), Dr. Schaffner (NFID) wondered how much investigation went into these cases in terms of whether these were individuals who had been vaccinated, partially vaccinated, or were eligible for vaccination but had not been vaccinated; and whether it was confirmed that these infections were acquired occupationally as opposed to recreationally.

Dr. Schillie replied that the vaccination history on these cases is sparse. In some instances, the working group questions the accuracy of the history because sometimes the date a case patient gave for their vaccination was before hepatitis B vaccine was licensed. CDC is in the process of going back to the cases to obtain more detailed information about their vaccination history and their vaccine response history. More likely than not, not all of these cases acquired their hepatitis B virus infection from an occupational exposure. In fact, about 17% reported an accidental stick or puncture with a needle in the 6 weeks to 6 months prior to the development of symptoms. Therefore, all of these cases are not thought to be the result of an occupational exposure.

Dr. Foster (APhA) noted that they have always been taught that immunologic memory protects from hepatitis B, so they are still dealing with titers instead of actual cases. He requested an explanation regarding the numbering used for the proposed recommendations.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Schillie responded that the working group began with the numbers 1, 2, and 3. After the working group discussed those three approaches, two additional approaches were identified and were called Variant b, which is very similar to Approach 1, and Variant a. They are 5 unique options. The numbering system is completely arbitrary and does not reflect a preference.

Dr. Elward (HICPAC) indicated that this was presented to HICPAC the previous week, and that she wanted to follow up on the comments made by Drs. Schuchat and Marcy regarding the question of the lack of serologic response or detection of antibody years after vaccination and whether that correlates with true risk of disease transmission in the setting of an exposure. One of the suggestions from HICPAC was to do a sensitivity analysis and cost-effectiveness model, thinking about if 98% of people respond to a primary series initially, then there may be a very low percentage of people who are truly susceptible and have not responded.

Dr. Schillie responded that Dr. Hoerger would present data during the next presentation to address that.

Dr. Brady (AAP) inquired as to whether there was any difference in those who received human vaccine compared to the yeast derived vaccine in potential responses.

Ms. Reilly responded that based on the data shown, subjects received about a 50/50 ratio of plasma to recombinant in their primary series. When the serologic evidence of protection was assessed at the time distance from primary vaccination, a difference was not observed. The one difference noticed was that the response to the challenge dose might be slightly lower for those who received a plasma vaccine, but that is a speculation and further studies would be needed to make a conclusion about that.

Dr. Sawyer reminded everyone that as they thought about this issue, there were two populations: 1) the people with waning immunity and the question of whether their cell-mediated immunity will protect them; and 2) the group who never responded in the first place, which is the group that cannot easily be identified. The ACIP working group estimated them to be 5% of fully HepB immunized persons, and HICPAC suggested going down to 2%.

Dr. Keitel noted that the response to the challenge dose was only 60% to 75%, which is relatively low if assuming 95% plus for initial responders. She wondered whether any potential risk factors were analyzed for non-response amongst those who were given a booster dose, such as the development of a chronic illness, advancing age, and other factors associated with poor responses.

Ms. Reilly indicated that they do not have this information.

Dr. Keyserling (SHEA) noted that the response to the booster dose was only for the first dose. By the time the first-dose non-responders received the second and third doses, in most series, they were up to the 95% level. Although it is unknown whether not responding correlates with susceptibility, it is still a very small population who will need to receive HBIG after an exposure.

Based on the data, it appeared to Dr. Gorman (NIH) that the actual risk of hepatitis B virus transmission could be calculated for a single random needlestick, and he requested that number.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Reilly replied that this was 37% for percutaneous exposure and 19% for mucosal exposure.

Dr. Gorman (NIH) clarified that those were the transmission rates, and he was asking whether a random needlestick in a random facility would be 37% times 0.9%. He calculated that assuming everything else was equal, if there were 1000 needlesticks, there would be 3 cases of Hepatitis B in an average population.

Ms. Reilly confirmed that this would be correct.

Dr. Loehr (AAFP) asked whether anyone had followed those who converted to determine what happened to them (e.g., they become asymptomatic, they become chronic carriers, et cetera).

Dr. Schillie replied that as far as the CDC surveillance data, they have not been followed up in terms of whether they developed chronic infection. However, CDC hopes to elicit information about this in the near future.

Hepatitis B Protection among HCP: Cost-Effectiveness Considerations

Thomas J. Hoerger, PhD
Public Health Economics Program
RTI International

Dr. Hoerger presented the cost-effectiveness considerations for hepatitis B protection among HCP. With regard to the methods, the study question is, “How do we manage health care personnel (HCP) who are known to have received a full series of HepB vaccination previously, but whose current seroprotection status is unknown?” It is unknown whether HCP have a current anti-HBs level greater than or equal to 10 mIU/mL or ever had an anti-HBs greater than or equal to 10 mIU/mL after vaccination (anti-HBs = antibody to hepatitis B surface antigen [HBsAg]). It is known that HCP are at risk for exposure to hepatitis B virus infected blood and body fluids through percutaneous injury and mucosal exposure, and that appropriate management strategies may reduce the probability of transmitting hepatitis B virus from infected patients to HCP. However, it is also known that management strategies have costs. The question RTI International addressed in its analysis was, “Does the cost of management provide good value?”

They began by assessing the three primary management strategies laid out by Dr. Schillie:

1) Post-exposure: If an HCP is exposed and the exposure is reported, anti-HBs testing would be conducted. If anti-HBs is less than 10 mIU/mL, the HCP receives either HepB vaccine or HepB vaccine plus HBIG, depending upon whether the source patient is negative or positive for HBsAg.

2) Pre-exposure: All HCP initially receive an anti-HBs test. If anti-HBs is less than 10 mIU/mL, the HCP receives 1 dose of hepatitis B vaccine and later receives another anti-HBs test. If anti-HBs remains less than10 mIU/mL, the HCP receives 2 additional doses of vaccine.

3) Pre-exposure: All HCP initially receive 1 dose of hepatitis B vaccine and a subsequent anti-HBs test. If anti-HBs is less than 10 mIU/mL, the HCP receives 2 additional doses of vaccine.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The strategies were compared to each other and to a "do nothing" strategy where no management is provided. While this is not advocated as an actual strategy, it provides a useful benchmark to measure the probability of infection and associated cost of infections if no management occurs. The reason that is a good benchmark is that the "best" that any possible strategy could do would be to completely eliminate the probability of infection and, therefore, the associated cost.

Following RTI International's initial analysis, consideration was given to whether anything could potentially reduce the costs of some of these strategies. This is where the alternative strategies arose. Variant (a) as suggested by a member of the working group, which is why it received the term (a) and Variant (b) was suggested by Dr. Hoerger, which is why it received the term (b):

- Variant (b) is a post-exposure variant to Strategy 1. It does not include HCP vaccination if the source patient is HBV negative. It produces the same protection as Strategy 1 in first year, but results in lower costs.
- Variant (a) is a hybrid pre-exposure hepatitis B vaccine dose, which will protect most people. This is a variant to Strategy 3, but does not have anti-HBs testing prior to exposure. Follow-up is done for those who are exposed. This variant results in slightly more infections than Strategy 3, but costs less.

Separate analyses were done for trainees and non-trainees. Trainees are more likely to have been vaccinated at age < 1 year. That means they are less likely to have current anti-HBs greater than or equal to 10 mIU/mL and lower response rates to additional doses of hepatitis B vaccine, and are more likely to have BBF exposure. A small difference is that this study assumed the trainees to be 10 years younger than non-trainees, which means that the medical costs and QALY loss associated with an infection are slightly higher for trainees than non-trainees, but that is a relatively small difference in this analysis.

For the general model framework, two intervention timeframe were used, including a 1-year analysis for the intervention and a multi-year analysis covering up to 10 years of exposure. In terms of the analytic horizon for hepatitis B infections, consideration was given to hepatitis-related costs and QALY losses for HCP's remaining lifetime. Discounting was done at a 3% annual rate, the societal perspective was taken, and costs were in 2010 dollars. The model framework consisted of two parts. The first component was a decision tree analysis for each management strategy to determine the intervention cost and the probability of infection arising from each strategy. The CDC Hepatitis B Cost-Effectiveness Model (Zhou et al., *Pediatrics*, 2003) was then used to estimate the hepatitis-related costs and QALY loss associated with an acute hepatitis B infection in an adult HCP. This analysis accounts for asymptomatic infections and a 6% probability of chronic infection. The chronic infection included the possibility of cirrhosis, decompensated cirrhosis, hepatitis related carcinoma, and all of the consequences. Taking into account asymptomatic infections and the probability of chronic infection, the result was an estimated hepatitis-related cost of $7176 per infection and an estimated QALY loss of 0.7794. A cost-effectiveness analysis was done for which the summary measure was the incremental cost-effectiveness ratios (ICERs), which represents the change in net costs divided by change in quality-adjusted life-years (QALYs):

$$\frac{\text{(intervention cost) – (hepatitis-related costs averted)}}{\text{change in QALYs from averting infections}}$$

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Most of the exposure variables were similar for trainees and non-trainees, with the major difference being in the probability of exposure. For the seroprotection variables, there were differences. The difference for the evidence of seroprotection prior to any intervention for the trainee was 0.2 and for the non-trainee was 0.8. This is the primary reason there are different results for trainees and non-trainees. The cost inputs included administrative costs for vaccine ($14.42), blood drawing cost for anti-HBs test ($3.00), cost of anti-HBs test ($15.12), cost of discovering exposure source's status via HBsAg test ($14.53), cost of hepatitis B core antibody ($16.96), cost per vaccine dose ($52.50), occupational health costs associated with an injury ($85.30), cost of HBIG ($745.42), and outpatient visit cost ($61.31). For the most part, these costs came from either Medicare fee schedules or from the cost per vaccine dose from the CDC price list for vaccines for private patients. Of the costs, probably the most important are the administrative costs for a vaccine, the cost of the anti-HBs test, the cost per vaccine dose, and the cost for HBIG.

Sensitivity analyses included a one-way sensitivity analysis and a probabilistic sensitivity analysis. For the probabilistic sensitivity analysis, input values were drawn from distributions simultaneously and 10,000 draws were run. The cost-effectiveness ratios and a 95% credible interval were calculated. In terms of the probability of hepatitis B infection over one year, infections were relatively rare in the primary analysis. For trainees, the "do nothing" probability of infection was 0.00076. If there were 100,000 trainees, this would mean 76 infections. That number, depending upon the outlook, is either pretty small or not so small. Going through the different strategies, the probability of infection was reduced. Strategies 1 and Variant (b) resulted in a fairly sizable reduction for trainees of 0.00047. Variant (a) has a still lower probability of 0.00019. Strategies 2 and 3 have the lowest probability of infection at 0.00004. The reason that Strategies 2 and 3 are so low is that protection is being provided against reported and non-reported infections. A similar pattern was shown for non-trainees, but perhaps most evident is that the probability of infections for non-trainees is substantially lower than for trainees.

As noted, infections were relatively rare in the primary analysis. The probability of infection was calculated as follows: the probability of BBF exposure x the probability source patient is HBsAg+ x the probability that the HCP is not seroprotected x the probability of infection given source patient is HBsAg+ and HCP is not seroprotected = 0.398 x 0.009 x (1 – 0.2) x 0.267. The 0.009 probability that the source patient is HBsAg+ is pretty low to begin with, and drove much of the results for the probability of infection. As mentioned, Strategies 2 and 3 and Variant (a) provide protection against unrecognized and unreported exposures. The probability of infection is lower for non-trainees than for trainees, the biggest reason being that the probability of prior seroprotection is higher for non-trainees than for trainees (0.8 vs. 0.2).

In terms of the cost-effectiveness for trainees in the 1-year analysis for the "do nothing" strategy per trainee, the cost related to the infection was $5.49, with a relatively low QALY loss of −0.0006, given the low probability of infection. All of the other strategies cost more, with the cheapest strategy being Variant B at about $26.44 per trainee and an ICER of about $91,000 per QALY saved. Next was Strategy 1 at about $128,000 per QALY saved relatively to "do nothing." Strategies 2 and 3 had nearly the same costs and, therefore, nearly the same cost-effectiveness ratio. The fact that Strategy 2 was slightly more expensive than Strategy 3 meant that just reviewing this analysis, Strategy 3 might be preferred over Strategy 2; however, there is little difference between the two at about $1.00 difference in the overall costs and both offer about the same amount of protection. Strategies 2 and 3 provided the most protection and had the highest costs. Their ICERs were similar and were well above $50,000 per QALY saved. Strategy 1 provided less protection, cost less, and had a lower ICER than Strategies 2 and 3,

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

but it was still above $50,000 per QALY. Variant (a) cost less than Strategies 2 and 3, yielded more infections, and had a somewhat lower ICER. Variant (b) cost less than Strategy 1, had the same number of infections, and had a lower ICER.

With regard to the cost-effectiveness results for non-trainees in the 1-year analysis, the probability of infection in the "do nothing" case offered a lower value of 0.00011. That led to much higher ICERs for all of the strategies, including some that were very much higher. In this case, Strategy 2 ($692,833) was much cheaper than Strategy 3 ($1,405,861). That was driven by the fact that in Strategy 3, everybody would be given the vaccine initially even though 80% would already have evidence of seroprotection. In this case, testing anti-HBs first would be cheaper. ICERs for all strategies were much higher for non-trainees than for trainees. The primary reason was due to the probability of prior seroprotection being higher for non-trainees (0.8 vs. 0.2), and due to fewer infections, even in the "do nothing" case. The ICERs for all of the strategies were higher at > $300,000 per QALY saved. Strategy 2 was less costly than Strategy 3, though both have the same probability of infection.

Looking at 10 years of exposure, the cost-effectiveness ratios were lower for all of the strategies. In the case of Strategies 2, 3, and (a), the cost-effectiveness ratios were below the $50,000 per QALY saved benchmark. Especially Strategies 2, 3, and (a) provided more protection to everyone at the outset, which would incur a fairly high initial cost. However, the benefits of protecting against exposures over those 10 years began accruing, which meant that the cost-effectiveness ratios would decrease. In summary, the ICERs fall because management today provides protection against exposure in subsequent years. Strategies 2 and 3 provide protection upfront to almost all trainees, so the costs in later years would be relatively small. ICERs fall more rapidly, and would eventually be lower than for Strategy 1.

With respect to the multi-year analysis for non-trainees, the cost-effectiveness ratios were lower over time. Again, Strategy 2 was better than Strategy 3 in terms of cost-effectiveness ratios. In this case, non-trainees had the lower probability of exposure and the greater evidence of prior seroprotection, resulting in no cost-effectiveness ratios below $150,000 per QALY. In summary, ICERs again fall as the duration of exposure increases. Strategy 2 was always much lower than Strategy 3, and lower than Strategy 1 after a couple of years. All of the ICERs remained above $150,000 per QALY.

In terms of the one-way sensitivity analyses for Strategy 1 for trainees in the one-year model, as mentioned, there is variation in the probability that the source patient is positive. A probability of 10% would result in a much lower cost-effectiveness ratio of about $20,000 per QALY. A lower probability that the source patient is positive would result in a much higher cost-effectiveness ratio. Recall that the initial value was 0.9%, so 10% was a pretty large change. Also considered in the sensitivity analyses were the lab test costs in terms of what a hospital might charge a first year medical student, which resulted in a very high cost-effectiveness ratio; whereas, potentially lower costs did not have very much effect on the cost-effectiveness ratio. If the probability of infection was increased, there was a reduction in the cost-effectiveness ratio and vice versa. The probabilistic sensitivity analyses assessed the cost per QALY in trainees in a 1-year analysis based on 10,000 simulations. The credible interval was relatively wide, but the only strategy that had a credible interval including $50,000 per QALY was Variant (b).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Like any analysis, the RTI International analysis has a number of limitations. The first limitation is that it was assumed that HCP with anti-HBs levels less than 10 mIU/mL are not seroprotected. In the analysis, achieving an anti-HBs level equal to or greater than 10 mIU/mL after additional vaccine dose moved the person from no seroprotection to seroprotection. An alternative is that some persons with measured anti-HBs levels less than 10 mIU/mL actually have immunity. Having immunity in the absence of the evidence of serologic protection would increase the ICERs for all strategies. A second limitation is that average values were used of BBF exposure and the probability that the source patient is HBsAg+. Some HCP probably face a higher probability of BBF exposure, which would result in decreased in ICERs. If a trainee or non-trainee served a higher share of HBsAg+ patients, ICERs decreased. That variable seemed to be very sensitive. Another limitation is that unrecognized exposures were not included in the model, given that there are really no data on the probability of unrecognized exposures. QALY losses and costs associated with a hepatitis B infection were based on a simulation model of lifetime outcomes for persons infected with hepatitis B virus, so a lot of assumptions were made necessarily, but the model is generally considered to be valid. Adverse events associated with vaccination were not included; however, the HepB vaccine is generally considered to be very safe.

The following tables summarize the results for trainees and non-trainees:

RTI International

Comparison of Options: Trainees

	Cost per QALY saved relative to "Do nothing even if exposed"			Protection for unrecognized/ unreported exposures	Incidence of HBV infection/10^5 1 Year
	1st Year ($)	10th Year ($)	Year when < $50,000		
Do nothing even if exposed					76
1. Post-exposure: All sources	$128,565	$57,756	> 10	No	47
b. Post-exposure: HBV positive or unknown sources	$91,087	$56,056	> 10	No	47
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$247,754	$42,275	~ 7th	Yes	4
3. Pre-exposure: HepB dose, anti-HBs testing	$245,807	$ 42,047	~ 7th	Yes	4
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$190,356	$46,298	~ 8th	Some	19

RTI International

Comparison of Options: Non-trainees

	Cost per QALY saved relative to "Do nothing even if exposed"			Protection for unrecognized/ unreported exposures	Incidence of HBV infection/10^5 1 Year
	1st Year ($)	10th Year ($)	Year when < $50,000		
Do nothing even if exposed					11
1. Post-exposure: All sources	$360,416	$252,970	> 10	No	7
b. Post-exposure: HBV positive or unknown sources	$326,967	$267,446	> 10	No	7
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$692,833	$169,334	> 10	Yes	0
3. Pre-exposure: HepB dose, anti-HBs testing	$1,405,861	$250,833	> 10	Yes	0
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$1,267,840	$260,627	> 10	Some	2

Discussion Points

Dr. Keitel requested that the numbers about the risks be put into context. For example, what is the risk in the general population for hepatitis B infection over a year and among diabetics under 65 years of age. She also wondered whether there would be a way to include an adjustment in the model for the known fact that most cases that are acquired are asymptomatic and resolve without chronic sequelae.

Dr. Hoerger replied that the CDC Cost-Effectiveness Model does account for the fact that most infections are asymptomatic. That is built into the estimates and is one of the reasons why the costs and the QALY losses associated with infection are perhaps lower than might be expected.

Dr. Schillie responded that according to the 2009 surveillance data, there were about 1.1 reported acute cases per 100,000 population. A factor of about 10 is taken into account for under-diagnosis and under-reporting. There would be about 10 cases per 100,000. For persons with diabetes, using a relative risk of 2, there would be about 20 cases per 100,000.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Pickering requested a reminder of the definition of a trainee, and whether there are differences in terms of the types of trainees. He also wondered what happened to the results when the assumption of a healthcare worker working 7 years was changed in duration.

Ms. Reilly responded that the working group's provisional definition was, "Persons entering school and/or obtaining new job skills that involve contact with patients or with blood or other body fluids (BBF) from patients in a healthcare, laboratory, or public-safety setting."

Dr. Hoerger responded that the number of years a healthcare worker works was taken into account in the 10-year analysis. Some HCP may work 5 years, while some may work 20 or 30. When moving from 1 year to 2 years, the number of infections prevented is reduced to half. That has a large effect on the cost-effectiveness ratio. When moving from 10 to 11 years, the number of infections prevented is reduced by a factor of one-tenth, so there is a relatively small effect on the cost-effectiveness ratio. In addition, the cost in QALYs associated with those preventive interventions will be discounted because they are so far in the future. Basically, this will flatten out after 10 years.

Dr. Keitel inquired as to whether "public safety" would include all EMTs, firemen, policemen, et cetera.

Dr. Schillie responded that the goal was to be consistent with past recommendations. Certainly, some of the past recommendations do include non-medical personnel such as public safety workers and laboratory workers in a non-medical setting in the definition of HCP. The working group had not fine-tuned the definition at this point, but anticipates addressing those other groups of persons.

Dr. Warshawsky (NACI) noted that the fact that someone has no titer does not necessarily mean that they are susceptible, and the model was based on that assumption. But 50% to 60% boost when challenged, which would imply that they are not susceptible. If that was included in the model and was a known, it seemed to her that cost-effectiveness would be substantially higher.

Dr. Hoerger responded that what the base assumption should be was the subject of a lot of debate when they were working on the model. One of the reasons they chose this reasoning was that it is unknown whether someone who has no evidence of seroprotection is a non-responder or if they really are protected but just do not have evidence. Someone who is exposed who does not have evidence of seroprotection is going to be treated as if they do not have seroprotection.

Regarding the modeling of the multi-year analysis, Dr. Gorman (NIH) noted that several graphs of the decay of seroprotection were shown. He wondered whether any of those particular slopes were used, or whether there was a fix value for seroprotection throughout the 10 years.

Dr. Hoerger responded that for that analysis, it was assumed that if after the first year, someone showed evidence of seroprotection, they would be seroprotected for the remainder of the 10-year period.

Dr. Gorman (NIH) thought evidence was offered in the first two presentations that that might not be an appropriate model because the slope decays for protection.

Dr. Hoerger replied that the same effective level was kept.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Orenstein (NVAC) said that clearly this was important because it had implications well beyond healthcare workers. He thought if they went this route, they were obligated to consider other people with high risk conditions. Much of this seemed to be based on infection prevention as opposed to disease, chronic infection, and prevention of complications. He wondered how sensitive the analysis would be if, in fact, the cost-effectiveness was assessed per chronic carrier prevented or acute illness as opposed to serologically susceptible. He thought everyone would agree that serological susceptibility was not a good correlate based on the long-term follow-up studies.

Dr. Hoerger replied that they tried to estimate the acute infections and the corresponding chronic infections related to that.

Dr. Orenstein (NVAC) clarified that he was talking about clinical acute infections as opposed to asymptomatic infections.

Dr. Hoerger responded that the model does give this breakdown behind the values for the costs and QALYs, but those are not actually calculated and presented explicitly.

Dr. Orenstein (NVAC) thought the data available on long-term follow-up was that virtually all infections that have occurred have been asymptomatic transient infections. He wondered whether that was correct or if there were data showing long-term follow-up on vaccines associated with chronic infections, complications, and acute disease.

Dr. Schillie replied that among vaccine responders, chronic infections are very rare.

Dr. Sawyer clarified that the model is anticipating that some people were not responders, and those are the ones who then had chronic infection, and that is all built into the model.

Dr. Middleman (SAHM) agreed that it is an issue that it cannot be assumed that because titers are below 10 that there is no seroprotection. In her study in Houston, of the 319 adolescents who were immunized in the first year of life and had pre-test dose levels below 10, 90% of them ended up with seroprotection if measured with a titer greater than or equal to 10 mIU/mL. So she thought that not having a level above 10 means one is not protected is an incorrect assumption.

Dr. Baker clarified those were 16 to 19 year old healthy adolescents.

Dr. Keitel wondered what the results would be if the model asked what they really are interested in, which is, “How much is it going to cost to prevent a case of symptomatic or chronic hepatitis?” Rather than looking at all cases of hepatitis acquired by previously vaccinated HCP whose levels have decreased below 10, there is ample evidence to show that there is a high level of long-term protection despite loss of antibody.

Dr. Moore (AIM) requested clarity regarding whether the 6% probability of chronic infection was of all who were infected. The 6% is the population level of those who are infected who were not vaccinated before, and the 6% would apply to the 2% to 5% who never responded to vaccine in the first place. But 6% chronic infection would not apply to those who had ever responded to vaccine before. That may address the issue of where the chronic cases are coming from and how many there really are.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

It sounded to Dr. Schuchat as though the working group had a 10-year timeframe, and much of the discussion pertained to things that could be tried in the model. But she thought there was a lot of discomfort with assumptions about assumptions. She wondered whether the working group and committee members may want to think about what actual study questions could be addressed, whether they are measurable, whether some of the long-term follow-up from the recombinant vaccine are going to bear fruit, etcetera in terms of the hard numbers that could help clarify whether this cohort that was vaccinated as infants is going to have lifetime protection regardless of whether they enter high risk professions. Some studies or better follow-up of the surveillance could help to understood whether they are on the verge of a lot of breakthrough disease.

Future Considerations

Sarah Schillie, MD, MPH, MBA
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Schillie summarized that post-vaccination serologic testing is recommended 1 to 2 months after the HepB vaccination series for HCP with continuing risk for blood and body fluid exposure [*MMWR* 2005]. However, an increasing proportion of HCP entering training and the workforce have received the hepatitis B vaccination in the remote past without post-vaccination serologic testing. Antibody to hepatitis B surface antigen wanes over time and may no longer meet the level defining seroprotection of greater than or equal to 10 mIU/mL. Post-vaccination serologic testing for evidence of protection might not distinguish vaccine responders from delayed responders from non-responders. The implication of failure to respond to a challenge dose is currently unknown. Occupational risks to HCP continue. For example, HCP continue to sustain blood and body fluid exposures and some source patients are HBsAg positive. Healthcare schools and institutions are seeking guidance regarding ensuring protection for HCP who received hepatitis B vaccine in the remote past without post-vaccination serologic testing.

The working group's proposed recommendations apply to HCP who have documentation of a 3 or more dose HepB vaccine series, and who have no post-vaccination serologic testing record and have a reasonably anticipated risk for blood and body fluid exposure. Note that all HCP trainees are assumed to have a reasonably anticipated risk for blood and body fluid exposure; whereas, only some non-trainees have reasonably anticipated risks for blood and body fluid exposure. The working group prefers the same approach for trainees and non-trainees. An advantage to this approach includes increased compliance with recommendations associated with simplicity. A limitation is that the "best" approach may differ for trainees and non-trainees. The working group has narrowed the 5 approaches down to two recommendations for further discussions. The two approaches include a post-exposure approach and a pre-exposure approach. The post-exposure approach involves evaluation for all HCP regardless of the source patient's hepatitis B surface antigen status. The pre-exposure approach involves testing HCP for anti-HBs and vaccinating those with anti-HBs less than10 mIU/mL. The following table summarizes characteristics of the post- and pre-exposure approaches, including the incremental cost-effectiveness ratios, number of infections, protection for unrecognized and unreported exposures, and burden on occupational health staff:

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Characteristics of Post- and Pre-Exposure Approaches

	(1.) Post-exposure		(2.) Pre-exposure	
ICER	1st year	10th year	1st year	10th year
Trainees	$128,565	$57,756	$247,754	$42,275
Non-trainees	$360,416	$252,970	$692,833	$169,334
HBV infections (per 100,000)				
Trainees	47	--	4	--
Non-trainees	7	--	0	--
Additional protection against unrecognized/ unreported exposures	No		Yes	
Burden on occupational health staff	"Less work now, more work later"		"More work now, less work later"	

ICER=incremental cost-effectiveness ratio

8

The post-exposure approach generally has lower ICERs, but more infections. It does not provide additional protection against unrecognized and unreported exposures. It involves less work now and more work later. The pre-exposure approach generally has higher ICERs but fewer infections. It provides additional protection against unrecognized and unreported exposures. It involves more work now and less work later.

Future considerations include ascertaining vaccination and vaccine response history from HCP surveillance cases, identifying implementation issues, determining the working group's preference, and clarifying whether the current HCP recommendations should be updated or replaced.

Discussion Points

Dr. Loehr (AAFP) wondered whether anyone knew approximately how many HCP there are in the US who would fall into this category.

Dr. Schillie replied that about 10% of the adult population or the work force are HCP. Depending upon the numbers used, that translates to about 13 million people.

Dr. Turner (ACHA) indicated that he is on the working group and noted that there had been some pretty robust debates about pre-exposure versus post-exposure. Being at a student health center at a major university, he deals with all of the incoming nursing and medical students. What concerned him about considering pre-exposure, as had arisen a number of times, the risk of infection is not yet known in someone who was vaccinated as an infant. Those data are missing and an educated guess is being taken about where to go with this. Implementation for him represents an enormous issue and an enormous cost, which he did not think could be reflected in the data presented. He shared a back-of-the-envelope calculation to show how this would impact him in the fall at the University of Virginia. The university has 237 new nursing and medical students in total. With the pre-exposure recommendation, all 237 would need to have their titers tested because virtually all of these students were vaccinated as infants. Of those 237 students, 80% would be seronegative. Of those, 80% will be vaccinated, 64% of them will respond, and the remainder will have to have the rest of the 3-vaccine series and post-titer vaccination. So those 237 students will have to have 821 visits for venipuncture testing or vaccination. He has a hard time keeping track of PPDs and influenza vaccines. When he presented these data to their nurses, they could not believe it, all without really knowing what the risk of acquiring hepatitis B is among these people.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In the cost-effectiveness analysis, Dr. Loehr (AAFP) inquired as to which study the 6% assumption of probability for chronic infection came from.

Dr. Schillie responded that she thought it was from the CDC model.

Dr. Keitel thought it probably was based on healthy adults who acquire acute hepatitis B, and their risk for developing chronic hepatitis. It is usually quoted at around 5% plus. This is a different case scenario in which these people have been vaccinated previously.

To offer a different perspective from Dr. Turner, Dr. Beigi (ACOG) indicated that one of the other jobs he does in his hospitals is to run the credentials committee. It is worth knowing that at least all of the physicians are already tested when they come in for various things, including hepatitis B. He presumed that this would not necessarily be a new cost at many institutions across the country, given that it is already going on. While he could speak for the physicians, he could not speak for the nurses, but presumed that they have similar requirements.

Dr. Baker indicated that this is a requirement by her facility's credentials committee as well; however, it does not result in anything.

Dr. Brewer (ANA) added that most nursing schools do have entry requirements that include vaccination history or serologic proof of immunity. She emphasized that consideration must also be given to all of the non-professional healthcare providers who make up the majority of the 13 million and how it affects their training programs and their entry.

Pertussis Vaccines

Update: Pertussis Vaccines Working Group

Mark Sawyer, MD
Chair, ACIP Pertussis Vaccine Working Group

Dr. Sawyer reminded everyone that the terms of reference under which the Pertussis Vaccine Working Group was formed several years ago are as follows, the majority of which have been completed:

1. Review the existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate these recommendations into a single statement. The goal is to have a draft of this statement prepared by the end of 2012.

2. Review new data on tetanus and reduced diphtheria toxoids (Tdap) including:
   - Effectiveness of previous ACIP recommendations
   - Interval between previous tetanus-diphtheria (Td) booster and subsequently Tdap (eliminated the interval)
   - Use of Tdap in adults ages 65 years and older (recommended, with the policy statement to be published 6-29-12 in *MMWR*)

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- Pregnant and breastfeeding women (expanded use to try to decrease the burden of disease in young infancy)
  - Use of Tdap
  - Cocooning strategies
- Vaccinated healthcare personnel and need for post-exposure prophylaxis (PEP)
- Tdap revaccination (currently addressing)

3. Review updated epidemiology of tetanus and diphtheria

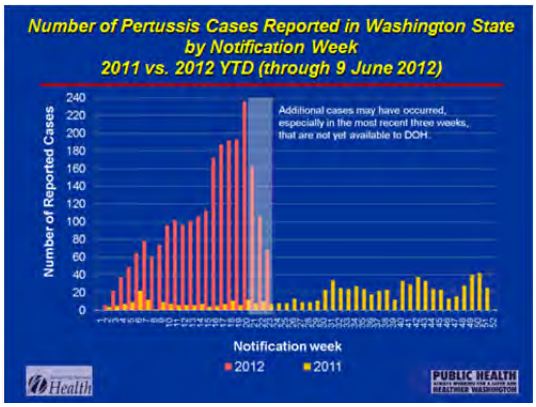
The working group understands that Tdap revaccination is a question on everyone's mind. Dr. Sawyer reported that when Dr. Marcy recently gave a CME presentation in New York, of the 40 questions he received on vaccines, 22 pertained to when a Tdap revaccination recommendation is needed. Dr. Sawyer assured everyone that the working group is working on this and will present a detailed discussion on this topic to the October 2012 ACIP meeting that will address safety, immunogenicity, vaccine effectiveness, duration of protection, timing of revaccination, special populations (e.g., pregnant women, healthcare personnel), and cost-effectiveness.

Update: Washington State Pertussis Outbreak

Jeff Duchin, MD
Public Health: Seattle & King County
University of Washington, Seattle

Dr. Duchin presented data regarding the Washington State pertussis outbreak that were contributed by the Washington State Department of Health (WA DOH), Public Health: Seattle & King County, and Children's Hospital of Seattle.

Based on data from Washington State of reported cases of pertussis between 1985 through June 2012, looking at when polymerase chain reaction (PCR) diagnosis first became available in 1998 to the present, it was clear to see that the number of cases spiked by 2500 according to the most recent outbreak report. In terms of the cases by notification week, the following illustration shows a comparison between 2011 and 2012:



The last three weeks represent time when cases are still being ascertained, so they are expected to continue to rise.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In terms of the age distribution for pertussis cases in 2011 compared to 2012, in both years there was a large proportion of cases among those under one year of age. The second highest peak was in 10 to 13 year olds, which was significantly higher in 2012 than in 2011. Regarding the median age of reported pertussis cases in Washington from 1989 through 2011 and 2012 year-to-date, the median age had jumped significantly ($p < 0.001$) from an average of 2 years to about 10 years from 1995-2005. The median age has now returned to about where it was in 1995 at approximately 8 years old.

About 70% of cases in King County less than 18 years of age have been immunized. The incidence rate in children under 1 year of age is about 106 per 100,000 and in children 10 to 13 years of age is about 135 per 100,000 [Preliminary data from King County (population 2 million, 30% of the state) reported from January 1, 2012 through June 9, 2012]. Compared to 2005, which had the highest reported pertussis activity in King County in the past decade at just under 15 cases by week 23, there has been a significant increase in 2012 to a little over 40 cases by the same week. This represents cases that are not fully ascertained.

Data from Seattle Children's Hospital virology laboratory from January 1, 2012 through June 10, 2012 show that pertussis is the second most commonly recovered pathogen among children presenting to Seattle Children's Hospital with respiratory pathogens and respiratory symptoms. The first most common pathogen is rhinovirus. There have been virtually no cases of *Bordetella parapertussis* or *Bbordetella holmesii.* Seattle Children's Hospital uses PRC-specific primers to diagnose those species [Courtesy of Xuan Qin, Jenny Strapp, Seattle Children's Hospital].

Response activities related to the Washington State pertussis outbreak have included the following:

- Public messaging (e.g., TV, radio, print media, web-based, social media, YouTube)
- Governor Gregoire, Senator Cantwell, Washington Secretary of Health have been speaking publically about pertussis
- Health care provider education
- Local health jurisdiction communications from WA DOH
- Resources for schools, camps, child care, and businesses
- Revision of surveillance, reporting, and investigation guidelines to harmonize and streamline them, because the volume of cases made it impossible to conduct the type of case investigation possible with sporadic cases being reported
- Increase in vaccine access for un- and under-insured
    - GIFT (AmeriCares/Sanofi Pasteur) program: Over 19,000 doses distributed statewide through May 1, 2012
    - Federally funded Tdap for un- and under-insured adults: 27,400 doses distributed to local public health and tribes
    - Community vaccination clinics

Some of the challenges included the following:

- Major resurgence of disease in a largely immunized population
- Non-optimal clinical case definition for case management
- PCR is expensive
- No point-of-care rapid diagnostic test

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- Diminishing local public health resources compromises outbreak response
  - The increased FTEs devoted to the pertussis response was over 10-fold at Public Health Seattle-King County
- Adolescent and adult immunization coverage
  - Access to vaccine for un- and under-insured adults

Dr. Duchin has received many questions about why there has been a resurgence of disease in a largely immunized population, and whether it is because the vaccine does not work. He has used the analogy that while about 90% of children of kindergarten age are current on pertussis vaccine, just like seatbelts that are used by most people, people wearing seatbelts in accidents do get injured. Just because people who are injured in car accidents are wearing seatbelts, this does not mean that seatbelts do not prevent injury. The challenge in communicating is to let people know that in a highly immunized population, a lot of people who get disease will be immunized.

Discussion Points

Dr. Baker noted that like the California outbreak, Washington State's highest rates of hospitalization were in children less than 1 year of age and elders. While it was great that they had not yet had any infant deaths, she wondered how they were addressing the very young. For example, the pregnancy recommendation might impact the first few months of life.

Dr. Duchin replied that there were 2 infant deaths due to pertussis in 2011 and none so far in 2012. There has been much activity, with most of the communications messages focusing on protecting infants (e.g., vaccinating pregnant women, keeping people with symptoms of pertussis away from pregnant women and infants). Free vaccines were offered to anyone who cares for pregnant women or infants. The primary communications messages have been focused on the theme of pregnant women, infants, and anyone who is in contact with them needing to be vaccinated. Specific materials have been produce for ObGyns about pertussis and pregnancy. Flyers and fact sheets were produced that were distributed through communication channels to healthcare providers and others who work with pregnant women.

Dr. Baker indicated that she had dinner a couple of weeks earlier with an ObGyn who is very pro-vaccine who said that the problem is that a visit lasts 5 minutes. That means ObGyns must understand pertussis, recommend pertussis immunization, and have vaccine in their offices. While the medical contact is good, infrastructure continues to be a great challenge.

Dr. Duchin noted that the uptake has been high, and that the materials are freely available on the Public Health: Seattle & King County website.

Ms. Rosenbaum wondered whether, given the poverty level of children and young families at this point, the state Medicaid agencies or other payers take any additional steps in terms of managed care plans in a situation such as this. She underscored that as important as the Affordable Care Act (ACA) was for previously uninsured poor adults, they will be covered in 2014, assuming the expansions go forward, for everything, including preventive immunizations. Ironically, for the poorest adults, the ones who are currently eligible for Medicaid, preventive services are an option. A lot of states do not cover preventive benefits for adults (e.g., screening, immunizations). Recalling the morning's discussion about the relationship between immunization and conditions of participation for dialysis centers, Ms. Rosenbaum would like for ACIP to take some step toward a working group on preventive benefits and financing. ACIP is the advisory committee on immunization practice, and she does not consider it to be just the

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

practice of the clinician being advised on clinical protocols. It is practice from a systemic practice point of view. It would be a real contribution for ACIP to make a statement about recommended steps pertaining to Medicare and Medicaid coverage of immunizations. Under ACA, states will receive a small financial incentive for expanding preventive benefits, but they do not have to.

Dr. Duchin replied that in general, there has been little activity on the part of payers. Seattle & King County Health Department received numerous complaints initially that they could not immunize adult family members or adults in general who were not covered by Medicare. It is preventive rather than post-exposure prophylaxis, so there was a large problem in terms of coverage for adults. Free vaccine was offered, but there are other barriers associated with the use of those.

Being next door, Dr. Hahn (CSTE) indicated that Idaho is watching the Washington situation very carefully. She inquired as to whether Washington had made any changes with regard to its post-exposure prophylaxis recommendations. Prior to this outbreak, she thought that Washington and Oregon were cutting back on public health's role in post-exposure prophylaxis.

Dr. Duchin replied that due to the progressive deterioration of infrastructure over the past 10 years, the ability to do anything clinically, especially in the community, has been decreasing. Prior to the outbreak, his healthcare extension focused on prevention of pertussis among the highest risk persons. Even prior to this time, they would only provide or facilitate post-exposure for pregnant women, infants, healthcare workers, and contacts of those people; whereas, previously household members of cases, classmates in schools, and those in workplaces also received vaccine through the health department. The health department advises healthcare providers to treat those people, but no longer actively facilitate this any longer through the public health department.

Dr. Marcy thought that the organisms seemed to be under pressure from the vaccine to be evolving genes that are now coding for non-vaccine antigens, and he did not believe this was receiving the attention it deserved. He asked whether anyone knew how much of a problem this was.

Dr. Clark (SME) replied that the currently circulating strains in the US are mismatched against the specific alleles used in the vaccine strains, but there still are vaccine antigens and there is some known cross-protection. The occurrence of those changes over time appears to be more like drift in the US than vaccine pressure. The specific occurrence of changes does not correlate with the dramatic changes observed in the epidemiology. This differs from country to country, but does not seem to be vaccine pressure in the US.

Dr. Kimberlin (AAP) noted that one of the graphs Dr. Duchin presented showed 394 cases, yet he said that as of the previous day there were approximately 2500 cases. Dr. Kimberlin requested further clarification about this.

Dr. Duchin indicated that that was for Seattle-King County, which represents about 30% of the population of the state, and the time of the presentation had over 400 cases. The state has about 2500 cases.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Janna Bardi (Washington State Department of Health) said she very much appreciated Ms. Rosenbaum's comments, because the discussions about coverage for Medicaid and Medicare have taken a considerable amount of time and have not resulted in any really good answers for people who are covered by those health plans. The Washington State Medicaid office has worked very hard to try to help people with billing, make sure that Tdap is available, and work through all of those efforts. However, the majority of Medicaid coverage is through managed care. With capitated systems, there is another level of work that has to occur. In many areas of the state, Washington has depended upon the provider community to pressure the hospital community to try to make sure they are provided the vaccine within the capitation. The problem with Medicare is that the vaccine is a Part D covered benefit rather than a Part B covered benefit, which makes it difficult for people with Medicare coverage to access that vaccination.

Dr. Whitley-Williams (NMA) inquired as to what the percent of exemptions is in Washington, and what percent of 10 to 13 year old patients were un- or under-immunized (meaning they did not receive their Tdap booster).

Dr. Duchin responded that in King County, 69% of the 10 to 13 year olds were current on vaccinations. Exemption is difficult to pinpoint, but King County is at about 90% at kindergarten entry for pertussis-containing vaccine. Multiple cohorts have been building up over the years of children who have not received the vaccine, so consideration must be given to what role they may play in facilitating an outbreak. Clearly, 70% of the children are immunized. But one problem may be children who were never immunized.

Dr. Orenstein (NVAC) commented that the pertussis situation was presented to the National Vaccine Advisory Committee. NVAC is particularly concerned with protection of young infants, and has formed a working group assessing pertussis as well as other vaccines recommended for pregnant women for protection of themselves and indirect protection of their offspring. The working group will take into account barriers and trying to overcome them. Interesting to him about the Washington outbreak was that the highest attack rate was in 10 to 13 year olds, 70% of whom were up-to-date on their vaccines. The definition of "up-to-date" for 11 years old and older was a Tdap, which is implies that a lot of these cases were potentially within a year or two of Tdap. With regard to Tdap, he wondered whether there was any evidence of changes in immunity. Clearly there are differences in pertussis vaccine. He wondered whether there were any data on vaccine failures for the various vaccines, and whether there were any plans to conduct any vaccine effectiveness studies.

Dr. Duchin responded that a CDC team is working with the state on statewide data to try to determine as much information as possible about those types of issues; however, there were no data analyzed on those points at this time. With time, more detailed data are expected with regard to the 10- to 13-year old "up-to-date" issue.

Dr. Clark (SME) added that a case-control study is planned in Washington, and another study is planned to address Tdap duration, brand, and other questions.

Dr. Beigi (ACOG) noted that one of the most effective outcomes of the last pandemic was the increase in vaccination rates in pregnant women from less than 15% to approximately 50%, so he thought many people at ACOG, including himself, would be interested in working with Dr. Duchin to use this as an opportunity to push that vaccine message.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Stinchfield (NAPNAP) reported that the Children's Hospital and Clinics of Minnesota where she works has had an admission per month for the first half of the year, though typically they will have 6 to 7 per year. They have all been children who are too young to be fully immunized. A pair of twins who survived the neonatal intensive care unit (NICU) went home for two weeks, were taken to a large family gathering, and ended up back pediatric intensive care unit (PICU) with pertussis. A pediatrician mom and emergency department dad became sick following exposure to their daughter's sports team, and they brought it to work. The stories emphasize that a multi-pronged approach is necessary, with a focus on pregnant women, cocooning, adolescents, and grandparents.

Dr. Baker reported that Texas Children's Hospital's pertussis admissions through May 2012 were triple what they were for the three previous years. She requested that Dr. Clark comment on whether it was anticipated that this would be a major pertussis year not only in Washington, but also in other locations.

Dr. Clark (SME) responded that over 13,000 cases had been reported thus far in 2012, which was ahead of any of the previous 5 years.

Dr. Baker inquired as to whether any of the representatives from the manufacturers could comment on single component pertussis vaccine in Europe. One of the observations people are making is that while there is now a safer vaccine, it seems to be of shorter durability based on the epidemiology.

Dr. Leonard Friedland (GSK) replied that GSK has a single acellular pertussis vaccine that was studied in the US by Dr. Joel Ward in a group of studies referred to as APERT, which were published in the *New England Journal of Medicine* (*NEJM*) a few years ago. This study showed a high degree vaccine efficacy with an acellular pertussis only vaccine. That vaccine is not currently under further investigation in the US [Joel I. Ward, M.D., James D. Cherry, M.D., Swei-Ju Chang, M.S., Susan Partridge, R.N., M.B.A., Hang Lee, Ph.D., John Treanor, M.D., David P. Greenberg, M.D., Wendy Keitel, M.D., Stephen Barenkamp, M.D., David I. Bernstein, M.D., Robert Edelman, M.D., and Kathryn Edwards, M.D. for the APERT Study Group; N Engl J Med 2005; 353:1555-1563; October 13, 2005].

Dr. Pickering wondered whether there were any lessons learned thus far from the Washington outbreak that differed from the California outbreak, and whether some of the questions raised during this session were being addressed for the California outbreak, particularly in terms of differences in vaccines in relation to disease.

Dr. Sawyer responded that the approach in California was similar to that in Washington, with the emphasis on surrounding babies with immunized people as much as possible, including pregnant women. One of the outcomes was the vaccine effectiveness study for DTaP. He hoped that out of the collective experience, there would be good vaccine effectiveness for Tdap, which would then inform the revaccination decision. He personally had not heard any detailed information regarding vaccine type that came out of the California experience.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Meningococcal Vaccines

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

Dr. Meissner reminded everyone that for Meningococcal Working Group members Chris Ehresmann, Michael Marcy, Carol Baker, and himself this would be the last meeting as ACIP members. He took a moment to acknowledge the incredible commitment of all of the working group members, many of whom have participated in this working group for well over 5 years, and who have continued to impress him with their thoughtful approach to complex questions. He also thanked Amanda Cohn for her tireless efforts in helping to keep the working group on track and moving forward. He also thanked Nancy Messonnier who, despite her many responsibilities, has often provided the working group with thoughtful counsel.

Four meningococcal vaccines have been the primary focus of the working group discussions:

- Quadrivalent polysaccharide vaccine
  - MPSV4 (Menomune, sanofi pasteur)

- Conjugate vaccines
  - MenACWY-D (Menactra®, sanofi pasteur)
    - Approved for 9 months through 55 years
  - MenACWY-CRM (Menveo®, Novartis)
    - Approved for 2 through 55 years
  - HibMenCY-TT (MENHIBRIX ®, GlaxoSmithKline)
    - Approved for infants at 2,4,6 and 12 months

- Investigational vaccine for infant use
  - MenACWY-CRM

The quadrivalent polysaccharide vaccine consists of capsular polysaccharide from four serogroups (A, C, Y, and W-135). It was licensed in 1981 for persons 2 years of age and older. Use of this vaccine is currently recommended for people over 55 years of age and for when MCV4 is not available. Meningococcal conjugate vaccines offer several advantages over the polysaccharide vaccine, including immunogenicity in children less than 24 months of age, lack of association with hyporesponsiveness with booster doses, and induction of herd immunity through reduction of nasal colonization. Three meningococcal conjugate vaccines are now licensed. Two consist of capsular polysaccharide from four serogroups (A, C, Y, and W-135) conjugated to carrier protein. In the case of Menactra®, the carrier protein is a chemically altered diphtheria toxin. The carrier protein for Menveo®, CRM_{197}, is a naturally occurring, non-toxic form of diphtheria toxin. The week prior to this ACIP meeting, a third conjugate vaccine was licensed by the FDA for use in infants as a 4-dose series. HibMenCY-TT, or MENHIBRIX®, consists of a polyribosephosphate from a capsule of *Haemophilus influenzae* type b conjugated to tetanus toxoid, plus meningococcal polysaccharide from serogroups C and Y conjugated to tetanus toxoid. Use of MenACWY-CRM, or Menveo®, as a 4-dose infant series is under review by the FDA. On June 14, 2012, the FDA approved the licensure of MENHIBRIX® manufactured by GlaxoSmithKline for active immunization for the prevention of N. meningitis C and Y and *Haemophilus influenzae* type b. The indicated age range for use of

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

this vaccine is 6 weeks through 18 months of age, making this the first meningococcal vaccine approved for use in infants. MENHIBRIX® is administered as a 4-dose series at 2, 4, 6, and 12 through 15 months of age.

Controlled trials of HibMenCY have demonstrated that the antibody response to Haemophilus influenza type b in HibMenCY is non-inferior to the Hib responses when compared to Hib-TT. HibMenCY is immunogenic against serogroups C and Y, in some infants as early as the second dose. The antibody persistence data after the 4th dose will be presented during the October 2012 ACIP meeting. The safety profile of HibMenCY appears to be comparable to monovalent Haemophilus influenza type b tetanus toxoid vaccine.

For several years, the working group has discussed whether infants should be vaccinated routinely against meningococcal disease. During these discussions, it has frequently been noted that although the incidence of meningococcal disease is low, the morbidity and mortality rates can be high. The prospect that some preventable cases of meningococcal disease might not be prevented is a troublesome concept. However, discussion has also focused on a number of additional factors, including the low burden of meningococcal disease and the relatively small amount of vaccine-preventable disease in this age group; the limited public health impact of routine immunization in this age group; the programmatic difficulties associated with an infant or toddler vaccine schedule; the immunogenicity data; the duration of protection and the possible need for a booster dose before the 11- or 12-year meningococcal vaccination in order to prevent a gap in protection; the high uptake of adolescent meningococcal vaccination and the possible impact of the adolescent vaccine program on reducing meningococcal transmission to infants; and the cost-effectiveness of infant or toddler vaccination. Guidance regarding use of HibMenCY is under consideration, and guidance regarding future infant vaccines would be deferred until they are licensed.

Data from Dr. Ortega-Sanchez's cost-effectiveness model, presented during the October 2011 ACIP meeting, incorporate the current epidemiology and the understanding of waning immunity. During the period from 1997 through 1999, infant vaccination would have prevented about 300 cases and 20 to 30 deaths. In contrast, during the years 2007 through 2009, infant vaccine would prevent only about 44 cases and 2 to 4 deaths. This means the number needed to vaccinate (NNV) to prevent one case is over 75,000 and the number needed to vaccinate to prevent 1 death is over 600,000. While understanding that meningococcal disease is dynamic and rates may increase in the future, the ACIP working group believes decisions about vaccination need to be made based on current disease burden.

Because HibMenCY was licensed by the FDA only one week before this ACIP meeting, several critical issues have not been resolved and will be considered by the working group before guidance can be issued. These issues include dosing intervals, minimum and maximum age, interchangeability with other vaccines, incomplete series, use of bivalent versus quadrivalent vaccines in special / high-risk populations (e.g., children at increased risk of meningococcal infection), and the GRADE evaluation of the immunogenicity and safety data. Language will be developed that will not include a routine recommendation, but will clarify when the vaccines may be used.

During the October 2012 ACIP meeting, presentations will include considerations regarding HibMenCY use related to safety, immunogenicity, and antibody persistence; the epidemiology and estimated impact of HibMenCY on meningococcal disease; programmatic considerations regarding use of other immunizations in the childhood schedule; and a cost-effectiveness analysis. A GRADE evaluation of HibMenCY will be presented. Language options regarding no

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

routine recommendation will be presented for an ACIP vote, as well as considerations related to inclusion the vaccine in the VFC program.

The next recommendation and report on the prevention and control of meningococcal disease is presently in CDC clearance. This will replace the 2005 supplement and will include ACIP meningococcal vaccine recommendations from 2005 through February 2012. Publication of this supplement is anticipated before the end of 2012. A GRADE evaluation for MenACWY-CRM (Menveo®) for infants is underway. Because of the unique epidemiology and the preponderance of serogroup A disease in the meningitis belt of Africa, a low-cost monovalent A vaccine has been introduced in a mass-vaccination campaign in sub-Saharan Africa as has been discussed in previous ACIP meetings. The impact of this vaccine on the burden of meningococcal disease is being closely monitored, as is the possibility of serogroup replacement. In many countries, the incidence of serogroup B disease is greater than the incidence in the US. In some European countries, the incidence of serogroup b disease is 10 times higher than in the US. The availability of non-capsular serogroup B, which is safe, immunogenic, and protects against the high proportion of serogroup B strains in infants would be a useful addition to the conjugated polysaccharide vaccines in many countries. Although far from licensure in the US, such a vaccine may be licensed in Europe in the near future. A 4-component protein vaccine for serogroup B has been submitted for licensure in Europe. A pentavalent A, B, C, W, Y vaccine is currently in clinical trials. The experience with these vaccines in other countries will be useful in helping to consider strategies for use of serogroup B vaccines in the US.

Discussion Points

Dr. Baker commented that although several members of the ACIP Meningococcal Working Group were rotating off of the ACIP, this did not mean that they could not continue to participate in working groups.

Given the dramatic fall of invasive disease in the US, Dr. Pickering inquired whether using the 2011 data to conduct the cost effectiveness analysis if there would be further decrease.

Dr. Meissner replied that he thought rates have continued to fall. The current rate is about 0.2 per 100,000, which is lower than the rates used in the cost-effectiveness analysis presented.

Vaccine Supply

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

During this session, Dr. Santoli presented a vaccine supply update for adult hepatitis A vaccine; varicella vaccine; Measles, Mumps, Rubella plus Varicella (MMR-V) vaccine, Pentacel® and Diphtheria, Tetanus, and Pertussis (DTaP).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Merck anticipates availability of its adult hepatitis A vaccine in the second half of 2012, with pre-filled syringe availability anticipated in August 2012 and vials anticipated to be available in the fourth quarter of 2012. Production and supply of GlaxoSmithKline's (GSK) adult hepatitis A vaccine and hepatitis A/hepatitis B combination vaccine currently are sufficient to meet demand for routine adult use of adult Hepatitis A vaccine.

Regarding varicella vaccine, there is a temporary backorder for the single-dose package only resulting from a one-time packaging scheduling issue that is not related to VZV bulk issues. This is expected to be short-term through mid to late July. Merck is continuing to take orders for this product during this time. The 10-dose package product, which represents about 99% of all varicella doses that are distributed, is not impacted. The overall supply of VARIVAX® is not impacted.

With respect to MMR-V, Merck projects that they will return ProQuad® to the market in full supply ready to meet full market demand on October 1, 2012.

Availability of Sanofi Pasteur's Pentacel® and DAPTACEL® vaccines is currently reduced, and this is anticipated to last throughout summer 2012. Sanofi Pasteur's single antigen inactivated polio and Hib vaccines are in sufficient supply to address historic use of Pentacel® as well as the single antigen vaccines. Regarding DTaP, production and supply of GSK's single antigen and combination vaccines is currently sufficient to address anticipated supply gaps for DTaP-containing products.

Given the current supply information, no changes are recommended in any of these vaccines for children.

CDC's Vaccine Supply / Shortage Webpage is available at the following:

http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Discussion Points

Dr. Keitel requested clarification about the single antigen DTaP.

Dr. Santoli replied that even though DTaP is a combination vaccine, it has been a combination vaccine for so long that it is sometimes referred to as a single antigen, meaning it is not Pediarix®, Pentacel®, or Kinrix®. However, referring to it as single antigen is not technically correct.

Dr. Baker indicated that she could certainly not have done her job the last three years without Dr. Larry Pickering, and that it was a particular pleasure to serve under the leadership of Dr. Anne Schuchat whom she first met as an Epidemic Intelligence Service (EIS) officer interested in Group B streptococcal disease in the US. She thanked them both for their support over the past three years.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

GRADE

Development of ACIP/CDC Vaccine Recommendations Using GRADE

Jon Temte, MD, PhD
Advisory Committee on Immunization Practices

Dr. Temte reminded everyone that the term of reference for the Evidence-Based Recommendations Working Group (EBRWG) was to develop a uniform approach to making explicit the evidence base for ACIP recommendations. He emphasized the importance of the aspect of transparency such that people know exactly what went into the development of a recommendation. The EBRWG's activities culminated on October 28, 2010 when ACIP unanimously voted to adopt a methodology to assist in the development of clear and uniform evidence assessment and reporting for future ACIP recommendations based on a modification of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) methodology pertaining to the labeling of evidence and recommendation categories, not the underlying methodology. The EBRWG has now officially disbanded following completion of the specified terms of reference set forth by ACIP.

Activity has been on-going. For example, in September 2011, a paper titled "Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC)" was published in *Vaccine* to discuss the methodology [Vaccine 29 (2011) 9171-9176]. Also since that time, Dr. Ahmed has written a guidance document for implementation of GRADE, which is available on the ACIP website, and a policy paper was published in the *MMWR*.

Everyone strives to make the right and good recommendations using the best of existing knowledge and experience. Unfortunately, oftentimes the evidence is not perfect and the tools used to develop that evidence are sometimes fairly blunt. A worthwhile paper to review is one that was published in the *Journal of the American Medical Association* (*JAMA*) in 2005 that reviewed all original clinical research in three major general clinical journal or high-impact specialty journals from 1990 through 2003 that were cited more than 1000 times each. Of the 49 highly cited studies, 45 claimed that the intervention was effective, 7 (16%) were contradicted by subsequent studies, 7 (16%) found effects stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged [Ioannidis JPA. JAMA 2005;294:218-228]. This has been a problem for a long time. Over 200 years ago, in Faust - Part One in 1806 Johann Wolfgang von Goethe stated. "Poor fool with all this sweated lore, I stand no wiser than I was before." Dr. Temte quipped that while Faust was willing to sell his soul for absolute knowledge, this was not one of the considerations within the EBRWG.

Thus far, implementation of GRADE has been used by ACIP's Meningococcal, Human Papillomavirus (HPV), Hepatitis B, Pneumococcal, and Influenza Working Groups. Dr. Temte said he had the pleasure of borrowing some information from Drs. Pickering and Smith who conducted a Strengths, Weaknesses/Limitations, Opportunities, Threats (SWOT) Analysis with the CDC lead staff on ACIP working groups. The formal review is on-going and should be available at a future date. Based on an informal review of the issues that have arisen among the working groups, there are perceived structural deficits in the GRADE system. For example, the grading of evidence may not address key factors such as burden of disease and indirect

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

benefit. While these do not fit easily into the GRADE methodology, they are very important in terms of immunization issues. There are limitations with safety assessments, given that post-licensure safety assessments are almost always observational in nature and the events are rare. There are also limitations in the categories of recommendations either in the type or alignment of a recommendation with the strength of evidence. In terms of procedural deficits, there is a feeling that there can be some arbitrariness, especially in terms of incorporating values, the thresholds used for upgrading and downgrading studies, and expert guidance. There is an over-reliance on randomized controlled trials (RCTs) and concern with the inherent lower quality that is placed on observational studies, especially in the field of public health. The reliance on external methodology experts from outside of CDC is also perceived as a procedural deficit.

Areas for clarification include ranking the importance of outcomes, determining what values and preferences should be considered, assessing the assignment of a recommendation category, drafting language, and how to go about upgrading / downgrading evidence. Consideration must be given to bias in industry-sponsored studies, blinding, statistical approaches, and levels of limitation (serious versus minor versus no). Other areas for clarification include whether additional categories are needed such as "no recommendation for or against due to insufficient evidence," whether certain recommendations should be time-limited, and whether the Evidence Tables need to be adjusted to be more useful for some vaccine issues. Clarification is also needed with regard to issues with the use of Safety Evidence, especially in the post-licensure period.

One of the working group leads submitted the following quote taken directly from the GRADE Guidelines, which is applicable to vaccination recommendations in general, "Recommendations that may be helpful but do not need grading are typically those in which it is sufficiently obvious that desirable effects outweigh undesirable effects, and that no direct evidence is available because no one would be foolish enough to conduct a study addressing the implicit clinical question." [GRADE guidelines 1 http://www.ceb-institute.org/fileadmin/upload/refman/j_clin_epidemiol_2011_64_383_guyatt.pdf].

In conclusion, Dr. Temte indicated that when he is teaching fellows, residence, and medical students, in terms of recommendations he started including a slide with a quote from band Coldplay ["The Scientist" A Rush of Blood to the Head, 2002] that brings out some of the essence of the GRADE methodology:

"I was just guessing
at numbers and figures
pulling the puzzles apart

Questions of science
science and progress
do not speak as loud as my heart"

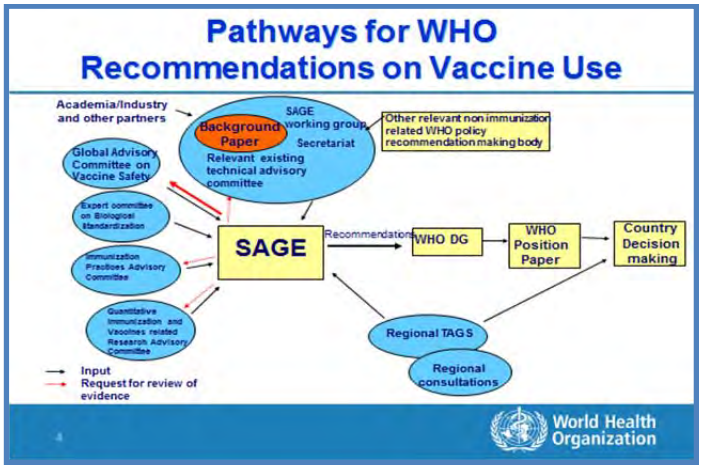
This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Updating World Health Organisation Vaccine Position Papers

Professor David Durrheim
University of Newcastle, Australia
Strategic Advisory Group of Experts (SAGE) on Immunisation Member

Professor Durrheim expressed gratitude to Dr. Baker for the opportunity to attend the meeting, commenting that it had been a very rich day and that he had enjoyed the agenda and the robust debate. During this session, he reported on how WHO approaches its vaccine position papers, SAGE and global policy making, the process of updating vaccine position papers, and SAGE's concerns about GRADE limitations and how they have worked with the GRADE Working Group to address these. SAGE is the principal advisory group to WHO for vaccines and immunization, which has direct access to WHO's Director-General Dr. Margaret Chan, and provides direct advice that has large-scale impacts on vaccine programs globally. SAGE is comprised of 15 members who are selected through an open and transparent external review process on the basis of their discipline, expertise, and geographic location. There are two meetings each year convened in April and November, and all meetings are comprised of open plenary sessions. Much like ACIP, there are working groups beavering away all of the time in the background with many wonderful skilled scientist volunteers.

The following diagram illustrates how SAGE relates to some of the other advisory groups within WHO and the pathway of WHO recommendations on vaccine use:



There is a very strong Secretariat that contributes enormously to the preparation of background papers. SAGE makes strong evidence-based recommendations to the Director General drawing on the expertise within the Global Advisory Committee on Vaccine Safety, The Expert Committee on Biological Standardization, the Immunization Practices Committee, and the Qualitative Immunization and Vaccines Related Research Advisory Committee. Following recommendations to the Director-General of the WHO, a position paper is produced for implementation at the country level. It is very important to realize that the Regional Technical Advisory Groups (TAGS) contribute to SAGE's agenda, raising policy-relevant issues from the field.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The position papers are the key product of SAGE with a focus on the global population. SAGE takes a pragmatic view, which acknowledges groups like ACIP and countries that are well-equipped to make their own decisions and review their own data. SAGE has a particular focus on middle- and low-income countries. All vaccine position papers are published in the 6 official languages in the *Weekly Epidemiological Record (WER)*, and have a specific format, which includes an introduction, background (e.g., disease epidemiology, the pathogen, disease), information on vaccines (e.g., composition, safety, immune response, efficacy and effectiveness, cost-effectiveness, and any other relevant issue), and the WHO position on vaccine use. In addition to the position papers, there is supplementary information, which includes the GRADE tables, references, and summaries (e.g., one-pager and PowerPoint presentation) available on the web.

Given the considerable investment in preparing vaccine position papers it was heartening to see the results of a rapid survey of National Immunization Technical Advisory Groups (NITAGs) in middle- and low-income countries conducted in 2009, with 99 responses. WHO vaccine position papers were clearly the most important contributor to decision-making that occurs at national level. While countries rely on other resources as well (e.g., intercountry meeting reports, published studies, government reports, national committee statements, country level ICC, national institutions, unpublished research, other countries' decisions), position papers were the key source for informing decision making.

Producing and updating position papers is the work of the SAGE working groups. Each working group: is time-limited, has clear terms of reference that are determined by SAGE, includes at least 2 SAGE members and a group of experts selected particular to the subject topic, conducts an in-depth review of the evidence and related issues in preparation for SAGE discussion / decision, and is not permitted to make decisions or speak on behalf of SAGE. The SAGE working groups present a robust evidence-based set of recommendations to SAGE for decision-making. Declarations of interest are paramount and are published on the web.

A number of issues are taken into consideration by SAGE in developing recommendations, include the following:

- Epidemiologic features of the disease
- Clinical characteristics
- Vaccine and immunization characteristics
- Economic considerations
- Health system opportunities and existence of, and interaction with, other existing intervention and control strategies
- Social impacts
- Legal considerations
- Ethical considerations

WHO was one of the early adopters of GRADE. Since 2008, GRADE tables have been produced in support of key recommendations in WHO vaccine position papers. However SAGE members had residual concerns about GRADE's appropriateness for some immunization program evidence. Although SAGE members recognized that the GRADE system provided a marvelous tool for transparency, they were really concerned that some of the benefits vaccines can provide are less well dealt with by the GRADE system (e.g., herd immunity, post-marketing safety surveillance data, natural boosting, passive immunity). Helen Rees, current chair of GRADE, formed a discussion group. The key focus of this discussion group was how they

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

could constructively ensure that GRADE could more appropriately deal with immunization considerations rather than revolting against the approach.

Concerns had also been expressed about GRADE's application to public health programs by other public health professionals. During the Evidence 2011 BMJ conference held in London and attended largely by people working in public health, participants were asked to rate GRADE in terms of its applicability to rating the quality of evidence for public health interventions. About 300 people participated in this session and about 25% thought that GRADE was quite well-suited or ideally suited for ranking evidence for public health programs. The rest remained doubtful. SAGE decided to go the route of active engagement, and found the GRADE Working Group wonderfully accepting that they did not have the perfect solution and that they were keen to collaborate on any adaptations that would ensure that GRADE was more useful for public health programs, particularly vaccination.

The SAGE discussion group engaged in extensive and productive interactions with members of ACIP, European Centre for Disease Prevention and Control (ECDC), German Standing Vaccination Committee Ständige Impfkommission (STIKO), and WHO's Global Advisory Committee on Vaccine Safety (GACVS), and the GRADE Working group. GRADE was adjusted to accommodate vaccine-relevant evidence, particularly vaccine population effects and the inclusion of surveillance data. The following table reflects some of these changes:

Quality of evidence	Quality starting factor is first assigned base on Study Design	Quality score is lowered[1] if	Quality score is raised[1] if
We are very confident that the true effect lies close to that of the estimate of effect on health outcome (4)	Randomised trials	1)Limitation of design:[2] -1 Serious -2 Very serious 2)Inconsistency: -1 Serious -2 Very serious 3)Indirectness:[2] -1 Serious -2 Very serious 4)Imprecision: -1 Serious -2 Very serious 5)Publication Bias: -1 Likely -2 Very likely	1) Strength of association: +1 RR or OR>2 (or <0.5) in 2+ studies +2 RR or OR >5 (or <0.2) in 2+ studies 2)Dose response (population based): +1 Evidence of decreased risk with increased vaccine coverage including evidence of reversal at population level (disease returns when vaccine coverage is decreased) population based dose response +2 Very strong evidence of decreased risk with increased coverage 3)Antagonistic bias and confounding: +1 All major confounders would have reduced the effect or +1 Ability of design to control for confounding and avoid biases +2 If in addition to design, consistency across different settings, different investigators, and possibly different designs
We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (3)			
Our confidence in the estimate of the effect on the health outcome is limited. The true effect may be substantially different from the estimate of the effect (2)	Observational studies, disease surveillance and post marketing safety surveillance data		
We have very little confidence in the estimate of the effect on the health outcome. The true effect is likely to be substantially different from the estimate of effect (1)			

[1] 1= move up or down one grade (for example from high to intermediate), 2= move up or down two grades (for example from low to high)

[2] Should be commensurate with study design

Key changes included incorporating disease surveillance and post-marketing safety surveillance data, potentially increasing the score for stronger study designs including self-controlled case series and incorporating population dose-response effects. The changes shown in the table were recommended by the discussion group, and were adopted by GRADE. Clearly the GRADE process is not yet perfect but there is scope for further improvement over time.

In conclusion, Professor Durrheim shared the following quote from Austin Bradford Hill from 1965:

> "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8:30 next day."

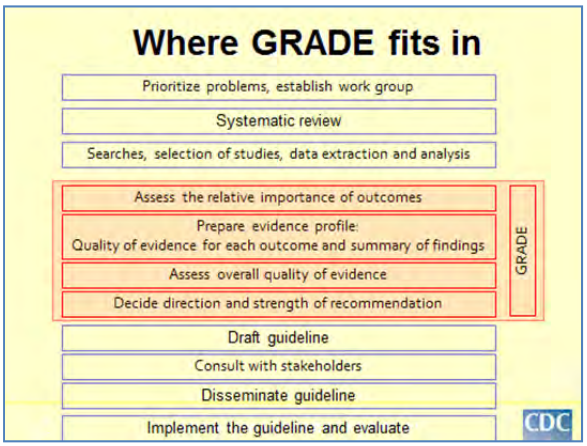
This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Update on GRADE

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

During this session, Dr. Ahmed presented information about the first international workshop on development of evidence-based vaccination recommendations, proposed additional GRADE criteria for upgrading observational studies, and resources for learning more about GRADE. He showed a screenshot of the GRADE Working Group's website, noting that the site had 51,000 unique visitors in 2011 from 165 countries. About 20% of the visitors were from the US. The GRADE Working Group membership consists of 308 members covering 32 countries, including: Australia, Austria, Bahrain, Brazil, Canada, China, Costa Rica, Denmark, Egypt, Finland, France, Germany, Hungary, India, Italy, Japan, Mexico, New Zealand, Norway, Poland, Portugal, Saudi Arabia, South Africa, Spain, Sweden, Switzerland, The Netherlands, The Philippines, Turkey, UK, Uganda, and the USA.

There are many steps involved in developing guidelines and recommendations, as shown in the following graphic, with the steps where GRADE fits in shown in red:



In the GRADE approach, there is a clear separation of the quality of evidence (High, Moderate, Low, Very Low) and the recommendation categories (Strong or Weak / Conditional). ACIP uses the labels Category A or Category B instead of Strong or Weak. Quality of evidence is only one factor that determines a recommendation category. Other key factors are the balance of benefits and harms, values and preferences, and cost-effectiveness.

GRADE is much more than a rating system. It is an approach to framing questions, choosing outcomes of interest, rating the importance of the outcomes, evaluating the evidence, incorporating evidence with considerations of values and preferences to arrive at recommendations, and is a guide to using those recommendations. GRADE is not "the final truth," without subjective judgments, a mechanistic solution to assess confidence in the evidence or the recommendations, limited to assessing quality of scientific evidence only, or a guide to the whole process of conducting systematic reviews or developing guideline recommendations. Grading evidence involves judgments that are inherent to any evidence evaluation system. One strength of the GRADE approach is that it requires explicit judgment that is made transparent to users so that disagreements can be resolved.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The 1st International Workshop on Development of Evidence-based Vaccination Recommendations was convened in Berlin in November 2012. Experts from Europe, Canada, and the US, including Dr. Temte and himself, participated in this workshop. Participants concluded that GRADE or a modification of this methodology is suitable for the grading of quality of evidence related to vaccine effectiveness and safety. International cooperation would be beneficial in order to avoid duplication of efforts, to build on existing strengths, and to support National Immunization Technical Advisory Groups worldwide [Vaccine;30:2399-2404, 2012].

Dr. Randy Elder, from CDC's Community Guide Branch proposed two additional GRADE criteria for upgrading observational studies during the GRADE Working Group meeting in January 2012:

1) Weight of evidence, which can be described as having a large number of studies in a body of evidence that provide consistent results that diminish otherwise plausible threats to validity

2) Baseline information on outcomes

With regard to how availability of baseline information can lead to upgrading, notable failures of observational studies (e.g., hormone replacement therapy) have two common characteristics: 1) selection bias, and 2) lack of directly relevant data on outcomes at baseline. Valid data on outcomes at baseline can greatly reduce the harms of selection bias. There are far fewer plausible threats to validity for estimates of change in an outcome than for differences in outcomes. Many of the remaining threats would be expected to be randomly, not systematically distributed.

There are certain characteristics that may lead to upgrading studies incorporating baseline information for a controlled before-and-after design or an interrupted time series design. Characteristics for the controlled before-and-after design include: intervention and comparison groups have comparable rates at baseline; the comparison group does not exhibit dramatic change in rates from pre- to post-intervention; there is minimal instrumentation threat to validity; and there is no evidence of cherry-picking comparison groups. Characteristics for an interrupted time series design are: stable trend at baseline; and observed change in the outcome is a step function rather than a change in slope. The GRADE Working Group would like to see more examples of studies that have this information in order to make their decision as to whether to accept this proposal.

Addition resources for learning more about GRADE included the following:

- ❑ GRADE Online Learning Module
  McMaster University
  http://cebgrade.mcmaster.ca/

- ❑ Teach Evidence Assimilation for Collaborative Healthcare
  Level #2: Policies and Recommendations for EBC
  Section on Evidence Based Healthcare, New York Academy of Medicine
  http://www.ebmny.org

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- "US Advisory Committee on Immunization Practices (ACIP): Handbook for Developing Evidence-Based Recommendations" http://www.cdc.gov/vaccines/recs/acip/grade/about.htm#resources

Discussion Points

Dr. Pickering inquired as to whether SAGE plays any role in implementation of the uptake of the vaccine recommendations it makes, and if he could be specific in terms of any flaws SAGE found in the GRADE process for which changes have been or will be made.

Dr. Durrheim responded that SAGE's role is really not in implementation. Implementation is supported through regional offices of WHO and occurs at the country level; however, feedback is welcomed by SAGE in terms of the ease of implementing recommendations in the field, and monitoring the epidemiological impact.

Post-marketing surveillance was a critical source of data that was not incorporated adequately in the traditional GRADE approach. The impact measured during surveillance and historical observational studies ethically precluded the conduct of additional RCTs. A poorly conducted RCT may be less valuable than a well-conducted observational study.

Dr. Temte added that there was a great example earlier in the day from Dr. Moore showing the trends in pneumococcal disease in adults after introduction of PCV13. That is what Dr. Ahmed was talking about in terms of the stair-step effect. This was negative with introduction, and then suddenly in 2012, a marvelous reduction occurred in the non-target group (e.g., people over the age of 64). That is the type of thing that everyone would like to feel comfortable about incorporating into decision-making, without feeling bad that it is not an RCT.

Dr. Durrheim indicated the potential for a population dose-response effect to confirm vaccine programme impact. Increasing the number of doses could result in improved protection, and a reversal effect with decreased coverage also provided useful evidence. For example, in the UK, when vaccine rates decreased there were profound outbreaks of measles and rubella. This is now welcomed as legitimate evidence.

Dr. Bennett expressed her gratitude for this presentation, given that it addressed a lot of the concerns that she has had with the GRADE process. She was happy to see the discussion of upgrading non-RCT evidence to be useful in deliberations. She requested comments on the opposite, which is downgrading RCT data. Frequently in vaccine trials, a very select population is used. Then the results are applied to much broader populations. It is obvious when it is an immunocompromised population or HIV population, but much less obvious are things like showing socioeconomic (SES) disparity. Frankly, most vaccine trials do not address diverse populations.

Dr. Durrheim replied that this is where SAGE carefully applies consideration of indirectness in its broader sense.

Dr. Ahmed made the very important point that the right questions must be asked. Some questions are very difficult to GRADE, and there is still subjectivity in the weighing of evidence. In terms of downgrading RCTs that do not actually focus on a comparable population, there is an opportunity to downgrade by 1 or 2 scoring points. SAGE has certainly done this when appropriate.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Baker expressed her gratitude to Dr. Durrheim for making GRADE more clear, and said she was glad that ACIP had not gotten to the point of revolution against GRADE. One of the early concerns about GRADE A and B evidence is that the US is a nation that learns that in school that an A is the best and no one wants a B. From a public and communication layman's perception, she wondered whether GRADE had caused any trouble like that.

Dr. Durrheim responded that SAGE tries to avoid B evidence. SAGE is expected to provide definitive evidence. That is the expectation from countries, so SAGE seeks to provide strong recommendations on the basis of evidence available or indicates that the evidence does not provide an adequate basis for a recommendation.

Dr. Baker requested that Dr. Durrheim translate that into what SAGE's grading would be if the vaccine was a parachute.

Dr. Durrheim replied that the grading would show that, on the basis of overwhelming observational data, SAGE would strongly support the recommendation of using a parachute.

Dr. Duchin requested Dr. Durrheim's thoughts on unpublished studies and obtaining data from entities that have data they may not wish to publish or have not yet published. Everyone obsesses over biases, but it seems that publication bias is not being addressed. For all of its faults, the recent review of antiviral treatment for influenza highlighted the fact that there are a lot of data that do not get published. Perhaps consideration should be given to these data as recommendations for immunizations are being made.

Dr. Durrheim indicated that SAGE was recently debating the population effect of a single dose versus two doses of HepA vaccine. At the population level it is very interesting. SAGE discovered that there were data available that manufacturers had chosen not to release. The key is, and where the GRADE process is wonderful, making available all data considered by SAGE to everyone for scrutiny.

Dr. Campos-Outcalt recalled that when GRADE was first presented to ACIP, the parachute example was used. It supports the GRADE system because it is a cohort study, and the magnitude of effect between a group that jumps out of an airplane without a parachute versus with is quite large. That study can actually be upgraded two points to make it Level 1 evidence. While this example is used a lot to make fun of evidence-based medicine, it works quite well in the GRADE system.

Dr. Tan (AMA) indicated that the Influenza Working Group is working through its recommendations using the GRADE process, and SAGE recently revised its own influenza recommendations. He thought it would be beneficial for Dr. Durrheim to present more about SAGE's deliberations to the ACIP Influenza Working Group. SAGE elevated pregnant women as a priority group and removed the direct contacts recommendation. He was curious about how the GRADE process influenced those changes in the recommendations.

Dr. Durrheim replied that in the past, the SAGE recommendations for influenza vaccines were largely developed-world focused as this was where the literature originated. This resulted on a focus on the elderly. The evidence coming out of the pandemic showed that pregnant women and the very young were also at risk of severe disease. Epidemiological and economic studies considering the burden of disease supported a shift in the focus not only for developing countries, but also for developed countries, away from the traditional target groups. SAGE was only prepared to rank pregnant women as the number one group for attention on the basis of

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

evidence review, and all of the other risk groups could be considered depending on the burden of disease in specific countries.

Dr. Marcy asked Dr. Durrheim's thoughts on the rigor with which the Cochrane Collaboration makes recommendations compared to GRADE. Many people view the Cochrane Collaboration as the gold standard for making a clinical decision.

Dr. Durrheim responded that the Cochrane Collaboration's philosophy is outstanding, pulling together the best quality of evidence to develop a rational, evidence-based scientific judgment. However when inclusion criteria are highly selective much available evidence is excluded. A key challenge is defining the specific questions and thus the appropriate studies to be included / excluded.

With regard to the evidence and foreign policy, Dr. Sun (FDA) seconded some of the points that were made about RCTs, especially with regard to concerns about publication bias. Oftentimes, trials may be published that are positive studies, yet when the FDA reviews the data, they may find issues and problems that do not appear in the publication. For example, some trials are published that the FDA cannot use as a basis for regulatory decisions for those reasons. One has to be very careful in looking at published RCTs. Many clinical trials are now on the registries. Perhaps now some of the trials that have not been published that have been registered can be reviewed in order to assess a whole body of data.

Dr. Duchin found it to be problematic that one branch of the government has access to data in one form, it gets mutated into another form, it is published, and then ACIP has access to only a limited dataset with which they have to make policy. He thought some work needed to be done to ensure that ACIP is making policy about using a product based on access to the same data that is reviewed by another branch of the government to license the product.

Dr. Temte pointed out that making it even more complicated is that occasionally, there are situations in which researchers are willing to share pre-publication data. However, ACIP is an open meeting. If researchers present data to ACIP, they go on the web and are open access. This can place a researcher's publication at risk, which is important for their promotion and tenure. The MMRV Safety Working Group had a wonderful experience with two pre-publication studies that were shared very openly with the working group that were instrumental in making policy. However, they have to figure out ways to utilize such data without jeopardizing publications.

Day 1: Public Comment

Frankie Milley
Founder and National Director
Meningitis Angels

Thank you. My name is Frankie Milley. I'm the mother of an only child who died from meningococcal disease. I am the Founder and National Director of Meningitis Angels. I personally have no conflicts. Meningitis Angels does accept unrestricted grants from some industry. First of all, I want to say thank you very, very much to this sitting ACIP committee, and especially you Dr. Baker. You have led an awesome committee over the last few years, and you guys have done some amazing things to save lives for children. I personally thank you, and

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

I thank you on behalf of all of the hundreds of Angels across this country who have either suffered from meningococcal disease or have had children debilitated. Words are not even enough to tell you what you have done. I'm very excited about the approval of MENHIBRIX®, and look forward to even more vaccines being out there to protect infants. I look forward and offer support to the new ACIP committee members who will be coming on with the tough decisions that you'll have to make over the next year regarding this issue. So again, I just want to say thank you very, very much.

Dr. Baker: Thank you, and you are certainly welcome from me personally.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat noted that the last time ACIP recommendations were published on Hib was in 1991. The content is being updated and revised by the Division of Bacterial Diseases (DBD) at CDC, with Dr. Elizabeth Briere leading the activity and will present to the ACIP in February 2013. This is a low-maintenance way to update a statement rather than through a full work group. Regarding the state and large city health department grant program, an FOA has been issued for a new cooperative agreement that will begin in January 2013. This is a streamlined cooperative agreement emphasizing priority activities, including many of the efforts that have been supported previously through the Prevention in Public Health Fund (PPHF) special funding opportunities. Among the issues that are being promoted for core work are the Immunization Information System (ISS) interoperability with electronic medical records; the ordering system for grantees, Vaccine Tracking System (VTrckS), and its interoperability with the states' registry programs if they prefer that option; and an emphasis on assisting states to develop the ability to bill insurance for people who present to health departments who are fully insured for vaccination services. There is currently a major push to make sure that all insured people have a network provider that can give them vaccines and be reimbursed. Health departments throughout the country have not necessarily taken the steps to be able to bill. CDC has a partnership with America's Health Insurance Plans (AHIP) that is trying to support local and state health departments with getting that capacity. AHIP is running a series of webinars over the summer for third-party reimbursement for vaccines targeting public health departments. This is going to be a key step in transitioning state and local health departments toward sustainability in this era of diminished resources, and hopefully in an era of better insurance for everyone.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance reported that in May 2012, CMS published a Proposed Rule for the Primary Care Rate Increase Revision in the ACA, which also included the long-awaited update to the VFC administrative fee schedule. Approximately 150 comments were received on the Proposed Rule, many of which related to immunization. CMS is working hard on the Final Rule. CMS is in the process of updating the Immunization Guide and anticipates releasing it in August 2012.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Discussion Points

Ms. Rosenbaum inquired as to whether it was known yet if immunization practices is a condition of participation for dialysis centers, and requested that she take a couple of minutes to describe the VFC changes in the Proposed Rule for which comments were made.

Dr. Hence replied that she received an email on that in the last few minutes. After having an opportunity to review it, she will get an answer to ACIP. The Proposed Rule included two components that addressed immunization. The VFC component simply updated the fee schedule. The fee schedule has not been updated since it was originally published in 1994. CMS has been working diligently to make an update, but has struggled to get it through. This simply updates the maximum amount that states can reimburse providers for the administration fee under VFC. It does not change the states' flexibility. States still have the option to decide what amount they want to pay. The second component is in Section 1202 of ACA, which is the primary care increase. This also identifies the vaccine administration codes. This is not specific to VFC. It is for all of Medicaid, but those codes are addressed. Immunization is included in what would be increased in the Medicare range under that provision.

Department of Defense (DoD)

Dr. Geibe provided an update on adenovirus vaccine, indicating that adenovirus vaccine was used approximately 12 years ago. It was noted that adenovirus was responsible for about 60% of febrile respiratory disease among the DoD recruits. Unfortunately, in 1996, the manufacturer of the vaccine ceased production and the last doses were administered in 1999. A gradual increase was observed in outbreaks of adenovirus and febrile respiratory illness. In March 2011, the FDA approved adenovirus vaccine against Types 4 and 7, which is an oral vaccine. Administration of the doses began in October 2011. Since that time, a sustained downward trend has been observed in febrile respiratory illness rates. Overall, there has been about a 75% decrease in adenovirus cases in the recruit setting. This highlights the success of the vaccine in this recruit setting. Thus far, DoD has administered over 100,000 doses of this vaccine since October 2011. At this point, the vaccine is licensed only for use by the Military.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that DVA's work on the development of a shared immunization medical record with the DoD is continuing as part of an overall integrated electronic record. The immunization work was one of the first sections of that joint record, and good progress is being made on this effort. The DVA agrees with Ms. Ehresmann's comments that having electronic records is highly important. Dr. Kinsinger's office continues to work on adding new and updating previous recommendations about immunizations. They put the ACIP recommendation that works within the DVA's system, and they are posted on an internal VA website for all VA staff to access. She thanked CDC staff who have been very responsive to DVA's questions to specific issues on which they have needed assistance. The follow-up on Dr. Duchin's presentation on pertussis in Washington State, the VA surveillance systems have also observed a slight uptick in the number of pertussis cases. There have been no inpatient admissions that she is aware of, but a few more cases have been reported among Veterans in the Washington area.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Food and Drug Administration (FDA)

Dr. Sun reported that since the last ACIP meeting in February 2012, the FDA approved MENHIBRIX®, the conjugated pneumococcal HibMenCY-TT. Also approved was for FluMist®, the live-attenuated influenza vaccine that is a quadrivalent formulation. Another noteworthy approval was a change in the dosing regimen of the anthrax vaccine on May 17, 2012 based on a study conducted by CDC. Currently the regimen is 0, 1, and 6 months as a primary series, with a booster at 12- and 18-months given intramuscularly. The FDA anticipates that there will be other quadrivalent TIV influenza applications submitted.

Health Resources and Services Administration (HRSA)

Dr. Evans reported that since ACIP last met, the Advisory Commission on Childhood Vaccines (ACCV) has approved a set of proposed additions to the Vaccines Injury Table. In August 2011, the IOM issued a report. This was a HRSA / CDC National Vaccine Program Office-sponsored contract that covered 12 vaccine combinations under the program. Five of the vaccines, such as varicella, had never been reviewed by the IOM. For the conclusions that were published, HRSA and the Immunization Safety Office (ISO) at CDC formed a working group called the HRSA-CDC Task Force to develop these proposed changes. Eleven injuries are being proposed for addition to the Vaccine Injury Table, 10 of which were in the IOM's strongest causation category, convincingly supports 4 for varicella vaccines, 1 for MMR, anaphylaxis is going to be added under 6 vaccines already listed on the table, and deltoid bursitis and syncope will be listed for all injection vaccines that are listed in the table. There are also clarifications and new definitions for the Qualifications and Aids to Interpretation, which defines conditions on the table. The ACCV unanimously approved all of the proposed changes, which is unprecedented. This is now under review by the department, Rule Making and public comment will follow, and a Final Rule with the changes will be effective 30 days after publication. He predicted that this would be out within a year or two. Further information may be obtained at the following: www.hrsa.gov/vaccinecompensation. Under the ACCV are all of the proposals, and a breakdown of changes.

Discussion Points

Dr. Baker announced that the 2012 Red Book site has the website and all of the changes posted.

Dr. Pickering inquired as to whether any Category 1 IOM recommendations that were not accepted.

Dr. Evans replied that if an injury was already listed, it would stay there. Of what he listed, 10 of the 11 were for changes where action would be indicated because they were not there. In contrast to previous efforts, there were no proposals to remove anything from the table.

Indian Health Services (IHS)

Ms. Groom reported that a 75% influenza vaccine coverage rate was achieved among IHS healthcare personnel. The rate has not change very much over the 4 years that this has been tracked. They are not particularly happy about this, and will continue to determine how that coverage rate can be increased among providers. Coverage among patients remains pretty stable this year compared to last year at about 33% of the population, so consideration is being given to what can be done to increase coverage. One of the strategies under consideration for

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

all adult vaccines is using IHS pharmacists more. Most IHS facilities have pharmacists, and they can provide vaccines. Some sites are doing this down to 13 years of age, depending upon what state laws allowed. IHS is working to get all of its pharmacists trained for all adult vaccine, which is believed to be critical to increase access to adult vaccines any many of its facilities. Pertussis has been observed in some native populations. The Portland IHS Area created a very nice video PSA with a multi-generational American Indian family. The 65-year old grandmother contracted pertussis and gave it to her 6-month old granddaughter for whom she was the primary caregiver. There was a happy ending thankfully, but this is a very compelling story that will be posted on the IHS website and will be made available to IHS's partners in the Washington and Oregon areas, the Immunization Action Coalition (IAC), and the California Immunization Coalition (CIC).

Discussion Points

Dr. Campos-Outcalt inquired as to why, when IHS facilities are federal, they are bound by state laws with regard to pharmacists administering vaccines

Dr. Groom replied that while they are not bound by state laws, they try not to be antagonistic.

National Vaccine Program Office (NVPO)

Dr. Gellin reported that in the past he had mentioned that following the pandemic, Dr. Koh, United States Assistant Secretary for Health (ASH), chaired a task force across the department to assess seasonal influenza as an opportunity to learn how to advance future pandemic preparedness. That has now evolved to an adult immunization task force that now has a structure that will align with the summit. Two companion documents have been posted that address what has been learned and what actions are being taken to address the lessons learned: "An HHS Retrospective on the 2009 H1N1 Influenza Pandemic to Advance All Hazards Preparedness" and "2009 H1N1 Influenza Improvement Plan." These can be found at: http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Pages/default.aspx

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that as mentioned the previous day, there was substantial discussion of immunization and pregnancy with regard to pertussis and influenza vaccines. NVAC is in the process of forming a working group to assess how to overcome impediments to implementing vaccination in pregnant women, as well as impediments to developing vaccines intended for pregnant women. NVAC also had reports from two on-going working groups. The Global Immunization Working Group is trying to make the case of the importance of sustaining US investments in global immunization for humanitarian reasons and for our own domestic health security. Some time was spent reviewing the recommendations, trying to explain the importance of the non-vaccine components of a vaccination program, such as administration, that are needed to achieve optimal prevention of vaccine-preventable diseases.

National Institutes of Health (NIH)

Dr. Gorman reported that one of Dr. Collins' signature projects has been funded, the National Center for Advancing Translational Sciences (NCATS). NCATS "strives to develop innovations to reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline in an effort to speed the delivery of new drugs, diagnostics and medical devices to patients." Dr. Guttmacher has been the director of the Eunice Kennedy Shriver

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

National Institute of Child Health and Human Development (NICHD) for about a year and a half. He instituted a visioning exercise, which is now complete. He has announced a proposed reorganization of NICHD, which will include the dissolution of three of the four NICHD centers and a renaming or rebranding of almost every branch. In terms of the National Institute of Allergy and Infectious Diseases (NIAID), there is a series of Division of AIDS (DAIDS) RFAs for the HIV Leadership Networks with various stages of release. Of some interest to ACIP, there will be a slight shift in focus of the leadership groups from AIDS to AIDS and associated infections. The HIV Leadership Networks will go from a permissive stance on studies in AIDS-associated infections to a stance that is mildly encouraging about assessing these infections. The major focus of this shift appears to be tuberculosis. DAIDS is looking forward to completing the process and making the awards. The RFA for the Antibacterial Resistance Leadership Group from DMID closed in June. The Division of Microbiology and Infectious Diseases (DMID) is looking forward to completing the process and making these awards. The RFP for the Vaccine and Treatment Evaluation Units (VTEUs) has been announced, and the full RFP is available on the NIH website. In 2002, DMID started a program to develop an animal model for the testing of antibiotics for pneumonic plague. This testing would go forward using the Animal Rule. The Animal Rule concerns the approval of new drugs or biological products when human studies are neither ethical nor feasible. Testing under the Animal Rule is a surrogate for human efficacy studies, but the safety of the product has to be demonstrated in a human model. To meet the requirements of the Animal Rule, animal studies have to be adequate and well-controlled. DMID presented studies of the use of ciprofloxacin for pneumonic plague in African green monkeys. DMID contended that the natural history of pneumonic plague was well-characterized as a result of these studies, and was comparable to human pneumonic plague. Ciprofloxacin treatment after documented infection with pneumonic plague was protective. This information was presented and review in a public meeting of the Anti-Infective Drugs Advisory Committee of the FDA. The committee voted 10 to 0 to allow labeling of ciprofloxacin for pneumonic plague based on the DMID data. This was the first antibiotic approved label using the Animal Rule.

IOM Vaccine Committee Report

Dr. Tracy Lieu
Dr. Guruprasad Madhavan
IOM Committee on Identifying and Prioritizing New Vaccines for Development

Dr. Lieu explained that “SMART Vaccines: A Prioritization Framework” was the result of a study that was conducted by the Institute of Medicine with the sponsorship of HHS and the National Vaccine Program Office, and is a unique work within the National Academies. IOM committees usually review literature and produce a report. This committee actually did something special in that it produced a model that will help people think about how to prioritize candidates for new preventive vaccines. This work is different from past IOM reports on ranking vaccine priorities. The committee did not develop a final list of which vaccine candidates should be prioritized, but instead produced a decision support tool that should help people of various perspectives (e.g., public health, industry, non-governmental organizations) think about how one should value different attributes of vaccines that one could prioritize. In addition, the work that was begun in the past year will also be enhanced in a follow-up project that is just getting underway. This has been a unique opportunity to look at the big picture and to think about what is valued when thinking about the development of new vaccines.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Madhavan reinforced that this work is not intended to produce a list of vaccine priorities. The goal is to produce a tool that will make users think about how to prioritize new vaccines. This work builds directly from the National Vaccine Plan (NVP) that was released in 2010. In fact, the launching point of the NVP's priorities for implementation was the first one, which is to "Develop a catalog of priority vaccine targets of domestic and global health importance." That is where the IOM project is situated in terms of the context. NVPO is envisioning to achieve the first priority through a three-step process. The first step focused on creating, validating, and enhancing the model—in essence, demonstrating a proof-of-concept. This was conducted by the IOM committee. The second step will be focused more toward building a data architecture to feed the model. The third step will be to test the model against actual vaccine candidates to produce perhaps a "library of vaccines" that could ultimately be prioritized by various stakeholders.

The charge to the committee was to:

1) Review domestic and global research and development prioritization activities relevant to identifying new preventive vaccine targets.

2) Develop an analytical framework and model for prioritizing vaccines of domestic and global importance. Engage stakeholders to inform the process of the model development and implementation.

3) Test and validate the model using two to three predetermined vaccines, including at least one vaccine candidate of domestic importance and one of global importance.

4) Prepare a report containing the analytical framework and model for evaluating and prioritizing vaccine targets along with recommendations as to how to use the model for reviewing the catalog of preventive vaccines every two to three years.

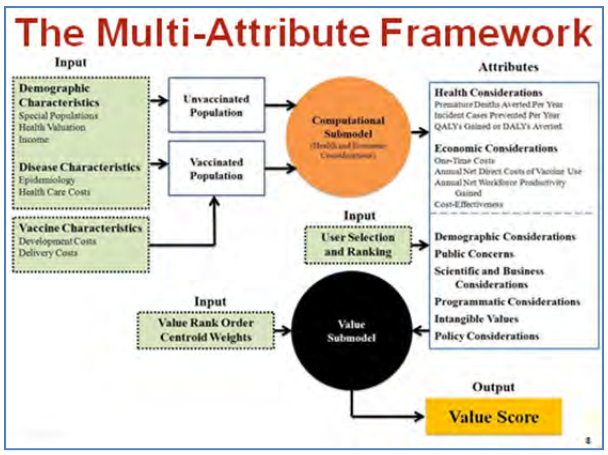
The unique product of this committee is software that is under development called Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines). The work also hinges on two previous IOM reports. The first was *New Vaccine Development: Establishing Priorities*, with Volume I released in 1985 and Volume II in 1986. This publication focused on establishing priorities based on the sole criteria of infant mortality. A list of vaccine targets for prioritization was developed. *Vaccines for the 21st Century: A Tool for Decisionmaking* was published in 2000, which used cost-effectiveness as a metric to help prioritize vaccines. There was an efficiency measure and cost-effectiveness was calculated as QALYs. That was the ranking criteria.

In terms of the approach, the committee was comprised of 16 interdisciplinary experts who had five meetings, the first two of which were devoted to identifying key attributes based on stakeholder feedback and committee discussions. Two public meetings resulted in feedback from various stakeholders that was extraordinarily helpful, and helped the committee think about significantly advancing the modeling aspect of the product that is under development. Two modeling consultants and two software designers helped the committee with software development. A unique aspect of this work was to engage 11 concept evaluators (e.g., Beta Testers) who were potential users of this program. They provided initial feedback even before the model went to the National Academy of Sciences' report review committee. Eighteen expert reviewers provided comments on this report during the review process.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The committee had six major considerations that it undertook in the modeling task. The first and foremost was that this has to be a broadly applicable toolkit that could consider a variety of perspectives. The previous two reports ranked vaccine priories based on a single attribute, respectively. The second consideration was to stand on a strong axiomatic foundation. The mathematical base needs to be strong but flexible, and could be easily adapted by multiple stakeholders. The third consideration regarded how to go about providing a priority score. The committee thought about it and looked at an ordinal methodology for ranking, so it is easy for the user to understand and provides the transparency of what the assumptions were. The fourth consideration was that the product also needs to feature options for conducting sensitivity analyses given its importance, and how inputs affect the final outputs. The fifth and sixth considerations included transparency and a user-friendly software base for a range of different users.

The following graphic depicts the schematic of the framework:



This is a generalized utility function framework that considers multiple perspectives. The overall model has two submodels that drive the framework: Computational Submodel and Value Submodel. The task was to focus on prioritizing new vaccines that do not yet exist, elaborations or modifications to existing vaccines, or vaccines that could be designed to tackle diseases that are emerging or reemerging. The computational submodel is the mathematically machinery that takes in data entered by the users such as demographic characteristics (special populations, health values, income), disease characteristics (epidemiology, healthcare costs), and vaccine characteristics (e.g., development costs, delivery costs). These are compared by the mathematical equations looking at the benefit and efficacy of the vaccines, so the efficacy of the vaccine is compared in a vaccinated and unvaccinated population. That computation results in health and economic attributes. There are 29 total attributes, which were developed from stakeholder feedback, and are shown in the following table:

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Health Considerations	• Premature Deaths Averted Per Year • Incident Cases Prevented Per Year • QALYs Gained or DALYs Averted
Economic Considerations	• One-Time Costs • Annual Net Direct Costs (Savings) of Vaccine Use • Annual Net Workforce Productivity Gained • Cost-Effectiveness
Demographic Considerations	• Benefits Infants and Children • Benefits Women • Benefits Socioeconomically Disadvantaged • Benefits Military Personnel • Benefits Other Priority Population
Public Concerns	• Availability of Alternative Public Health Measures • Potential Complications Due to Vaccines • Disease Raises Fear and Stigma in the Public • Serious Pandemic Potential
Scientific and Business Considerations	• Likelihood of Financial Profitability for the Manufacturer • Likelihood of Successful Licensure in 10 Years • Demonstrates New Production Platforms • Existing or Adaptable Manufacturing Techniques • Potential Litigation Barriers Beyond Usual • Interests from NGOs and Philanthropic Organizations
Programmatic Considerations	• Potential to Improve Delivery Methods • Fits into Existing Immunization Schedules • Reduces Challenges Relating to Cold-Chain Requirements
Intangible Values	• Eradication or Elimination of the Disease • Vaccine Raises Public Health Awareness
Policy Considerations	• Special Interest for National Security, Preparedness, and Response • Advances Nation's Foreign Policy Goals

There are 8 broad domains in terms of the attributes themselves, and collectively there are 29 of them. Seven attributes in the domains of health and economic considerations are quantitatively computed by the computational submodel. Qualitative entries from the users are unique to this work because only two things are expected from the user, one to provide the data and two to rank what is important for the user. There are 22 qualitative entries for which the user selects drags and drops and places a rank order on them, which is computed into weights by an algorithm and ultimately provides a value score.

According to its charge, the committee was to assess two to three vaccine candidates with a domestic component and a global component. For this round of proof-of-concept, the committee used the US and South Africa. For the US, three vaccine candidates were assessed (influenza, tuberculosis, and group B strep). For South Africa, tuberculosis was the candidate.

In terms of how the user ranks are converted into weights, the scores are between 0 and 1. If only 1 attribute is selected, that would receive a full 100% as the only weight. If 2 attributes are selected, one would receive a 75% weight and the other would receive 25%. After 7 or 8 attributes, the weights precipitously drop and do not matter too much. One can include 29 attributes or 89 attributes. It does not matter, but the mathematical construct suggests that after 7 or 8, all of the attributes included do not carry that much weight.

Dr. Madhavan then went through the screenshots of the software that is under development, and invited comments on them. The legal disclaimer states that this is supposed to serve as a decision support tool and not a decision-maker itself. One of the applications that the committee imagines is that this could be used as a conversation facilitator or discussion enhancement device. It is a formalized way of bringing people from different domains onto one page so that they can engage in discussion. This is a 7-step process, the first of which is the user selecting and ranking the values that are important to them. The way the program has been developed is that it is modular and stackable, so new entries are easy to add to the existing schematic. For example, if the user wants to focus only on health and economic considerations, they may just click premature deaths averted per year and drag it into the box. The second step is the population profile. The data for this can easily be imported from standard tables. One of the possible applications of this software is that a number of countries

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

can be clustered to create a super nation to assess how vaccines may work in that setting. Step 3 is the disease profile, which includes two types of entries, the health profile and the economic profile. The herd immunity threshold in this model is assumed to be 100% for simplicity, but more dynamic herd immunity thresholds need to be programmed in future versions of the software. Step 4 is the vaccine profile, which includes the population, product profile, and complications. These are all guesses because these vaccines do not yet exist. Step 5 is the qualitative attributes, which begins the value submodel of the framework with the 8 attribute categories. This includes accordion style menus, and this is where the user selects the level of the values. Step 6 is the computed use. The dashboard shows all of the data that have been entered. At this stage, sophisticated users could download the data and do a manual sensitivity analysis, but the committee is considering a more dynamic sensitivity analysis on this screen. What-if scenarios would then be possible here. Step 7 is where the final priority score comes about. This is a soft score and does not have an inherent meaning in itself. Because of the mixed metrics, each of the data entered has different levels and units. This is just a number to provide the user a form of thinking. At this stage, the user can change the original rank that they said in the first step.

Regarding the potential applications, the committee assessed potential scenarios. For example, users may enter the same attributes but different values. For example, A Health Minister of a country may prioritize very differently from a Program Manager at PAHO or NIH may place its priorities on research potential as compared to a vaccine manufacturer, which may be interested in the economic aspects. Similarly, the program can also be used to assess cases with the same values but different attributes, such as 1-dose versus 3-dose vaccines or risk of development versus cold-chain requirements. The current model structure places considerable demand on the user in terms of data entry. That is an area that requires community-level help.

The committee is looking for data philanthropists or data donors to come up with the framework that could feed into this software. Some data (e.g., cost, efficacy) are pure guesses by the user. The current model has only limited sensitivity analysis capabilities. The current model allows subjective weights on attributes to be chosen by the user. The weights in the model are computed using the Rank Order Centroid (ROC) method. This is a simple mathematical method that is used to give organization to this. The program does this. The user just has to enter the data and provide what is in their mind in terms of the rank. Most of the data shown were all point estimates. Many of them were guesses and do not have distributions or confidence intervals around them. Even the final priority score is a point estimate with no distributions. To consider risk elements or uncertain elements, it would be helpful to have distributions. Right now, the model is structured as a single cohort population that terminates when they die or reach the age of 100. More instantaneous changes are needed, especially in terms of understanding the epidemiologic spread of the diseases or the impact of vaccines and how the efficacy of a vaccine spreads in a particular population. That requires dynamic tools and is something that the committee is considering for the next round. Disease interactions (e.g., HIV+TB) are crucial, but are not currently in the model.

In the next phase of the study, version 1.0 of the software, the committee plans to convene a public workshop in the fall to solicit feedback from potential users and evaluators in order to refine the model and enhance the software. Based on the charge, 3 more vaccine candidates will be added for a total of 6 candidates. More work will be done on the sensitivity analysis and uncertainty as well. During the next phase, there will be usability evaluators who will “test-drive” the software to determine how much time it takes and so forth. Recommendations will be offered at the strategic level with regard to what it would take to further develop the software and how to maintain continuation of this.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The report is available at:
www.nap.edu

Feedback can be provided at:
SMARTVaccines@nas.edu

Discussion Points

Dr. Baker requested a definition of "Rank Order Centroid method."

Dr. Madhavan replied that from a statistical standpoint, this is the mean of a uniform probability distribution in an n-dimension cube.

Dr. Lieu added that when the user chooses a set of characteristics or attributes, these are given some weighting and are ranked. If 5 is chosen and the characteristics are ranked 1 through 5, someone has to decide how 1 is weighted relative to 5. It turns out that if each individual is permitted to do this, it becomes a very difficult task for them in terms of assigning a percentage to a 1 through a 5. In her view, the ROC method is a consensus of how attributes should be assigned weights. It really just simplifies the task for the user and creates a more standard and uniform approach mathematically. It has been pretty well-tested in the management sciences.

It seemed to Dr. Baker that the choice of the user could be subjective and biased, so she wondered how that would not occur in the choices made before it is place in the cube.

Dr. Lieu responded that she actually thinks the choices the end user makes are meant to be subjective, because the model is really just a decision support tool and everyone brings their own biases to these kinds of decisions. In a sense, it is trying to help people clarify what their values are.

Dr. Madhavan added that this is a simplistic mechanism to come up with a mathematical construct. If a user wants a tied weight, that is not possible. It forces the user to rank in a particular order so that that gets converted into the final priority score. At this stage, ties are not allowed and are not possible with the ROC method. Dr. Duchin expressed concern about all of the unknowns and assumptions about the efficacy and other attributes of a vaccine that is not even manufactured yet and how it would behave in populations and individuals. It is difficult enough to understand vaccines that are currently in use in terms of how well they are working, their durations of immunity, their adverse effects, and so on. He wondered whether this tool had been used to evaluate existing vaccines to assess what they were predicted to do and what they are actually doing. For instance, ACIP recently had several examples of vaccines that have been surprising in the way they have behaved in relation to the way they were predicted to behave.

Dr. Madhavan responded that the data burden is incredible on the user, with quite a bit of estimation and conjectural work going on. It forces the user to think about it, especially when a lot of finances or impacts are involved. The committee discusses this in detail in the report. Several people have suggested this application of this tool to recreate history. The committee is thinking about doing this in the next round.

Dr. Duchin noted that there is also the issue of assessing vaccines that have been newly developed and licensed in terms of how they are anticipated to behave, the predictions that would have been made based on those anticipations, and how they actually worked in reality.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Madhavan responded that a 6-month evaluation can be done as well to determine what was originally planned for and what actually occurred. That possibility exists.

Dr. Bennett wondered whether this tool could also be used to define essentially required attributes. For example, a potential vaccine would be ranked for its importance, but only if it achieved certain outcomes. She also wondered whether the committee had discussed how these tools can be used to establish national priorities, the extent to which stakeholder buy-in had been expressed, and how it might be expected to impact policy.

Dr. Madhavan responded that this is precisely how the committee envisions the use of this tool. It has 29 attributes, but is not limited to that. More attributes can be added. It is a customized tool, and is in no way an objective product. It is heavily subjective and user-reliant. When applied in a multi-stakeholder consortia or coalition, it offers a formalized way of making the assumptions transparent. While national priorities, buy-in, and policy impact are clearly the direction of the technology, he did not believe the committee would be making any recommendations during the next round because it is not in their charge.

Dr. Gorman (NIH) asked whether it bothered Dr. Madhavan, or drove the model in any way, that the values created are not independent variables.

Dr. Madhavan responded that the committee is acutely aware of potential double counting. For example, a user may enter a health variable and may also include another one that is related to it. At this stage, the committee forces the user to select just one QALY for example. There are interdependencies in this model, which is going to complicate this from the user standpoint in terms of the measurement.

Dr. Gorman (NIH) emphasized that it must be understood that the user only gets 7 real choices and after that they are not real, but will not affect the model. If one of the values is chosen that basically says “good for women,” that’s obviously also going to be good for children and infants and is probably going to be good for minorities and military. It struck him that those are all interdependent or coupled.

Dr. Madhavan indicated that it requires some form of data selection from the user. For example, in the Disease Profile, they could select HIV and then they would see Female, Male, and Special. It requires some quality assurance on the user’s side.

Dr. Gorman (NIH) inquired as to how much the vaccine module drives the eventual number. Every variable of the vaccine will be guessed because this is a candidate vaccine.

Dr. Lieu responded that some educated guesses can be taken. In general, in a traditional analysis, vaccine efficacy and disease efficacy tend to drive a lot of the prioritization. No one has ever tried to put so many variables into a model for a tradition analysis or cost-effectiveness analysis model. These usually just include health outcomes such as life years saved, disease state, and cost. With this new type of model with a lot more attributes, it will be interesting to explore which are the dominant drivers. This is really not known yet.

Dr. Gorman (NIH) asked whether the committee had considered this model to be a wonderful tool for reverse engineering in the sense that if the ideal vaccine is compared to how far a candidate vaccine falls off from the ideal vaccine, it could actually drive down selection.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Madhavan replied that they plan to put this in open source communities, so it will be available and could be engineered in any form or fashion as users wish. Those possibilities exist for sophisticated users.

Dr. Sun (FDA) understood that going beyond 7 attributes resulting in diminishing returns was based on some sort of algorithm. But in terms of prioritizing vaccines, subjectivity and certain predominant attributes are desired. He wondered why they were leaving it to the software to even this out.

Dr. Madhavan replied that there is potential to change the weighting schematic. At this stage, as part of the proof-of-concept, they wanted to use something automated to make it easier to think about in a philosophical way. The mathematics is very primitive, but could be more sophisticated going forward.

Dr. Baker thought that ACIP would be interested in hearing more about this project as it moves forward.

Dr. Gellin (NVPO) emphasized that this is an unusual undertaking for IOM; that is, to put out something that looks like a finished product but is really the beginning of a longer path. The reason to bring it to ACIP at this point was for everyone to see it early on and to encourage them to take a look at and to continue to raise questions, bring it out to their communities, and acquire as much input as possible about the model from the philosophy to the math. He expressed gratitude to ACIP for putting this on the agenda.

Adult Immunization

Introduction

Ms. Kristen Ehresmann, ACIP
Chair, Adult Immunization Schedule Working Group

Ms. Ehresmann reminded everyone that that the Adult Immunization Schedule Working Group focusing on updating the schedule, but has talked about the importance of drawing attention to the value of adult immunizations and how to make the adult immunization program stronger and more visible. Part of the goal of these presentations is to that, and to draw attention to that program in the hope that someday the adult program will be at least half as strong as the current pediatric program.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Non-Influenza Vaccination Rates Among US Adults

Walter W. Williams, MD, MPH
Medical Epidemiologist
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Williams reported on non-influenza vaccination coverage among US adults from the National Health Interview Survey (NHIS), and the steps being taken to expand vaccination coverage tracking. The NHIS is an annual in-home survey of the non-institutionalized US adult population. It asks questions on vaccinations of a randomly selected adult in the household, and provides national coverage estimates. The vaccination questions include questions on influenza, pneumococcal pneumonia, HepB, HPV, zoster, Td/Tdap, and HepA vaccines . Compared with 2009 NHIS estimates, there were modest increases only for Tdap vaccination (8.2%) of persons 19 through 64 years of age (a 1.6% increase), herpes zoster vaccination (14.4%) in those 60 years of age or older (a 4.4% increase), and HPV vaccination ≥ 1 dose (20.7%) in women 19 through 26 years of age (a 3.6% increase). Coverage for all other vaccines remained unchanged.

In terms of pneumococcal vaccination for high risk persons 19 through 64 years, overall coverage was 18.5%. Coverage among non-Hispanic whites was higher than that for Hispanics and non-Hispanic Asians. Overall coverage of pneumococcal vaccination for persons 65 years of age and older was 59.7%, and coverage for non-Hispanic whites was higher than that for non-Hispanic blacks and Hispanics. Overall coverage of tetanus vaccination during the past 10 years for persons 19 through 49 years of age was 64%, and coverage for non-Hispanic whites was higher than that for all other racial / ethnic groups. Overall coverage of tetanus vaccination during the past 10 years for persons 50 through 64 years of age was 63.4%, and coverage for non-Hispanic whites was higher than that for non-Hispanic blacks, Hispanics, and non-Hispanic Asians. Overall coverage of tetanus vaccination during the past 10 years for persons 65 years of age and older was 53.4%, and coverage for non-Hispanic whites was higher than that for non-Hispanic blacks, Hispanics, and non-Hispanic Asians. Overall coverage of tetanus vaccination including pertussis vaccine during the past 5 years for persons 19 through 64 years of age was 8.2%, and coverage for non-Hispanic whites was higher than that for non-Hispanic blacks and Hispanics. Coverage for persons living with an infant less than 1 year of age was 10.6%.

Hepatitis A vaccination coverage for persons 19 through 49 years of age who travel outside of the US was higher than that for persons who travel only within the US or to other countries with low Hepatitis A endemicity. Overall coverage for hepatitis A vaccination for those 19 through 49 years of age was 14.6%, and was 19.7% for those with chronic liver conditions. Overall coverage for hepatitis B vaccination in high-risk persons 19 through 49 years of age was 42%, and coverage was lowest among Hispanics compared to non-Hispanic whites. There were no other racial/ethnic differences. Overall coverage for herpes zoster vaccination for persons 60 years and older was 14.4%, and non-Hispanic whites had higher coverage than all other racial/ethnic groups. Coverage for HPV vaccination among females 19 through 26 years of age was 20.7%, which was a 3.6% statistical increase from 2009 estimates. Coverage for non-Hispanic whites was higher than that for Hispanics. There were no other racial/ethnic differences. Coverage for HPV vaccination among males 19 through 26 was 0.6%, and for males 19 through 21 years of age was 0.3%. The ACIP recommended vaccination of adult males 19 through 21 years in October 2011, and males 22 to 26 years of age may also be vaccinated. These estimates represent baseline coverage for those age groups. Overall

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

coverage for tetanus vaccination including pertussis vaccine for health care personnel over the past 5 years was 20.3%, and non-Hispanic white healthcare personnel had higher coverage than non-Hispanic black and Hispanic healthcare personnel. Overall coverage for hepatitis B vaccination among health care personnel was 63.2%, and there were no racial and ethnic differences.

In conclusion, overall coverage remains low at far below the Healthy People 2020 targets of 90% for 65+ years for pneumococcal vaccine, 60% for high risk 19-64 years for pneumococcal vaccine, 30% for 65+ years for zoster vaccine, and 90% for hepatitis B vaccine for healthcare personnel. There has been only limited improvement from 2009, with small increases only for Tdap in 19 to 64 year olds, zoster, and HPV vaccines. Racial and ethnic disparities remain, and much remains to be done to increase vaccine utilization among adults and to eliminate disparities.

Plans for Expanding Vaccine Coverage: Tracking US Adults Using BRFSS

Walter W. Williams, MD, MPH
Medical Epidemiologist
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Regarding plans for expanding vaccine coverage, Dr. Williams reported that starting in 2013, the 2012 Behavioral Risk Factor Surveillance System (BRFSS) “place of influenza vaccination” core question is to be rotated out of the core and replaced with a single Tdap question. In 2014, the current shingles optional module question is to rotate onto the 2014 core, replacing the Td/Tdap question. The “place of influenza vaccination” question is to rotate back onto the core in 2015. This rotating pattern is to continue on this three-year cycle with CDC supporting place of vaccination, Td/Tdap, and shingles optional modules in years when questions on these vaccines are not on the core. Rotating the Td/Tdap, shingles, and place of influenza vaccination questions will provide state-specific data on vaccination coverage for these vaccines filling important gaps in information on adult immunization and allow state comparisons to national estimates.

With regard to the rationale for rotating questions on the BRFSS core, interest is growing in states for data on vaccination coverage for Td/Tdap and shingles vaccines. The California pertussis outbreak enhanced interest in Tdap vaccination of adults, and knowledge of vaccination coverage for decision-making and program planning. Increasing the use nationally of shingles vaccine indicates a growing interest in protecting the target population. Due to cost constraints and competing priorities, many states are not able to use the optional modules for these vaccines. Rotating the questions provides a feasible, economical approach to obtain vaccination coverage data on a recurring basis to support state decision-making and program planning. Each state will be able to monitor its vaccination program’s level of success in the private and public sectors combined for Td/Tdap and shingles, the vaccines most recently recommended for routine use in certain adult populations. Rotating questions on the core as described will provide data that will be a major benefit to all states and will support the Healthy People 2020 adult preventive services composite measure that also includes influenza and pneumococcal vaccination.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Discussion Points

Dr. Keitel thought these figures were sobering and lamentable to say the least. She wondered whether there are questions on the survey about accessing healthcare and whether providers are recommending vaccination.

Dr. Williams replied that the NHIS includes a number of healthcare access variables, for example whether someone actually visits a physician during the year, insurance information, private versus public insurance, and questions regarding whether a doctor recommended a specific vaccine. It varies by antigen on the questionnaire. The report included in the ACIP members' background materials did not address those types analysis, but generally when information is reported on vaccination for specific vaccines, selected demographic variables, healthcare access variables, and other variables related to vaccination are addressed.

Dr. Vazquez inquired as to whether these questionnaires are conducted in Spanish, and whether there was any information regarding how many of the Hispanic persons interviewed are in the US legally.

Dr. Singleton (SME) responded that these are primarily in-person surveys that are conducted in multiple languages.

Dr. Williams added that there is a question regarding whether someone was born outside of the US, and whether they have been in the US 10 years or less or 10 years or more. Among those who are in the US for less than 10 years, the larger proportion is Hispanic and Asian, but their legal status is unknown.

Dr. Jenkins inquired as to whether the role of pharmacists in adult immunizations is captured in these surveys.

Dr. Williams replied that the "place of vaccination" question on the BRFSS captures place of influenza vaccination, but he was not aware of other surveys that have a place question for each of the adult antigens. The primary location where most people receive influenza and presumably other vaccinations is doctor offices. Pharmacies and other retail locations are playing an increasing role, but as of the last source of information, it was still less than 15% to 20% depending upon the age group and other variables.

Dr. Sawyer noted that ACIP has discussed many times the difficulty in obtaining documentation for adult vaccinations. In terms of this survey, he wondered what documentation was requested in these surveys, to what extent the survey participants have documentation, and whether anything was known about whether the participants are or know they are in an immunization information system.

Dr. Williams replied that the immunization reports in the NHIS are all self-reports that are not validated by record reviews. However, there are data from validation studies for influenza and pneumococcal vaccination showing that self-report is sensitive and specific.

Dr. Singleton (SME) added that an additional study is currently being analyzed to assess sensitivity and specificity for all of the vaccines Dr. Williams discussed, the results of which will be shared with ACIP in the future.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Rosenbaum expressed her gratitude for this session, because it drew the nexus between issues that have arisen for ACIP in the past and the question regarding whether vaccinations are getting to the people who need them. There certainly is an effort to bridge immunizations for adults and children, but these data are a sad testament to the fact that the US does not really have an adult immunization program. The amount of appropriated funding that would be available to support adult immunization efforts is simply so small at this point, it is not worth making a primary focus. Especially the zoster numbers suggest that there is something terrible wrong right now with the way Medicare immunization coverage is working. Zoster is the first foray into the split B/D problem, which merits follow-up discussions between ACIP and CMS. She thought they were also observing the problems that Dr. Schuchat referred to in terms of the trend for health departments to be out of network, and the absence of replacement programs for physicians administering adult immunizations that is comparable to the replacement program for pediatric replacement. That is absolutely crucial. It would be useful for ACIP, in discussions perhaps with NVAC, to use these data as a starting point for a study regarding care focused on why insurance advances cannot be translated into better numbers. There is a tremendous breakthrough under the ACA; however, Ms. Rosenbaum is not convinced that the adult vaccination numbers will increase under that either if active thinking is not done about how to make use of existing resources.

Regarding the zoster situation, Dr. Schuchat thought that Dr. Bridges' presentation would update ACIP on where the community is trying to go with Parts B and D. She reminded everyone that this vaccine was recommended for people 60 years of age and older. Most people 60 to 65 years of age are insured, and their insurance generally will fully cover zoster vaccine as opposed to Medicare Part D that does not fully cover the vaccine in terms of what the ACA does. Now that supply is good, there is an opportunity for all stakeholders to try to take advantage of a good vaccine for a very common bad disease in at least the population who was not previously accessing it because of supply.

Ms. Rosenbaum emphasized that there are many reasons, including simply the behavior of people about responding to new vaccines, that would contribute to the terrible numbers just shown. There are also very significant financial issues. The appropriated levels for 317 are alarming and are only growing more so. There is no capacity on the part of local, state, federal governments to fill in these kinds of gaps. ACIP is literally the only committee that is spending time thinking about whether any of what is being done is actually getting to the people who need it. To the extent that it is not and that financing and delivery play a role, ACIP has a role to play.

Ms. Ehresmann thanked Ms. Rosenbaum for her comments. Being at the state level, she recognized that having to implement policy decisions from the state down to the local level could be challenging. She thought these data highlight the problems with the adult program, or lack thereof. The intent of the working group was to draw attention to that, and to request assistance through funding and through the work of ACIP and all of its partners to help improve these levels. She thanked everyone for their attention to and interest in this, and expressed her hope that this would continue to be an important topic for discussion.

Dr. Fryhofer (ACP) agreed that zoster has been of concern. In her office, access to vaccine has been the primary issue. Now that she has access, it will be interesting to see what happens. However, that does not explain the other vaccines. While the information presented during this session was helpful and very sobering, it showed that the excitement shared among those in the room must go outside to physicians and other providers. The ACP is involved in some new initiatives. The Georgia Chapter has a new initiative titled, "Hit Me With Your Best Shots: Taking Actions to Improve Adult Immunizations." They are hoping to add a creative component,

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

perhaps a musical interlude, which is still in the planning process. This will be unveiled during the ACP Georgia Chapter meeting, and ACP is also going to the South Carolina Chapter. There is a quality improvement arm, so if it is successful, ACP may go on the road. In addition, the ACP now has its own ACP Adult Immunization app on iPad for which they are still trying to "get the bugs out," and are soliciting input about how to improve it.

Dr. Temte noted that when he sees children in his practice, it is largely focused on well care. When he sees a child for well care, vaccines are a major focus. When he sees a typical older adult for well care, he is juggling 6 to 8 co-morbid problems simultaneously. The EMR is more difficult, given that the amount of time he has to spend with documentation doubles the amount of patient care time required. Medical homes do a much better job with adult vaccines than other locations, but having reminder systems flawlessly built into EMRs is critically important. For example, there are approximately 7000 ICD-9 codes that can trigger pneumococcal. The rate of pneumococcal coverage for individuals with high risk conditions is 17%, which is atrocious. The fact that 15% of the time people with chronic hepatitis receive hepatitis A or B vaccine is atrocious. However, in the context of the incredibly busy, chaotic, uncontrollable days, most practitioners have learned how to ignore the warnings that pop up on their EMR screens. Well-done reminder systems are imperative.

Dr. Turner (ACHA) offered perhaps a more positive twist on the adult immunization issue. CDC has funded a network of colleges nationally (N=19) that upload de-identified electronic health records into a central database. ACHA assessed a subcategory of Freshman entering three major institutions that have pre-matriculation vaccine requirements. Major colleges are doing remarkably well with 86% uptake of hepatitis B, 43% uptake of HPV among women, 70% of uptake of Tdap, and 81% uptake of MCV. The point is that when policies and procedures are in place that can capture young adults as they are entering college for example, 60% of adults nationally pass through higher education at some point in their lives. Thus, that is an opportunity to capture perhaps two-thirds of the population. If policies and procedures are in place and are enforced, it is possible to boost vaccination rates.

Dr. Keitel said she was glad ACIP recommended HPV vaccines for boys, because clearly uptake is not doing well among girls. She inquired as to whether Dr. Temte's practice also had standing orders for administration of a vaccine that popped up on an EMR screen in terms of whether it would be given.

Dr. Temte replied that while they are working on this, the problem is with standing orders for vaccines that are indicated for high risk conditions. It is very easy to issue a standing order for pneumococcal for those over 65 years of age, but the nuance lies with the patient with non-alcoholic steatohepatitis (NASH). He could not identify a single medical system that would be willing to do that. If there was a system in which high risk categories could reliably be identified, they certainly could have standing orders. However, there must be a lot of upfront thought in terms of identification of those conditions, and getting people comfortable. That being said, it turns out that even in high risk hepatology clinics dealing specifically with people with hepatitis C receiving transplants are atrocious in terms of vaccine coverage. Pulmonary clinics are atrocious at covering pneumococcal disease. The philosophical twist between the care of children and the care of adults in this country is difficult to understand, and demonstrated by the data Dr. Williams presented. There is much to be done, it must be incremental, and more emphasis is certainly important.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Bennett indicated that Monroe County has the highest rates of pneumococcal immunization in the country for those over the age of 65 at over 80%. She found this discussion to be very painful, given that this is something they have been dealing with this for many years. The positive aspect is that it can be achieved. This requires very intensive effort and change in the healthcare system, in which Monroe County providers have engaged. However, without the public health infrastructure driving that change, it is not going to occur. The short answer is that it is important to address coverage issues, as well as the tremendous reduction of resources available to public health. This cannot be done without centralized local and state health department work, which is critical to this effort.

Dr. Baker said that she became a pediatrician because she was convinced that the best kind of adults are parents, and they typically make good choices for their children. Unfortunately, part of the problem is that adults do not do a very good job of taking care of themselves.

Report on First National Adult Immunization Summit

Carolyn B. Bridges, MD
Associate Director for Adult Immunizations
Immunization Services Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Bridges thanked Ms. Ehresmann for her leadership of the Adult Immunization Schedule Working Group, and said that she would miss her. She then delivered a brief report on the First National Adult Immunization Summit in Atlanta, Georgia May 15-17, 2012. This summit was patterned after the National Influenza Vaccine Summit and was co-sponsored by the AMA, NVPO, and CDC. The goals of the summit were to:

- Convene adult immunization stakeholder organizations to represent all facets of the adult immunization process, from manufacturers to vaccinators to advocacy groups, public health and policy;

- Facilitate identification of specific actions that can be taken by summit members that will lead to improvements in vaccine uptake, such as through reducing barriers for payment, increasing access to vaccines and vaccinators, and increasing awareness of adult immunization recommendations; and

- Develop and sustain working groups within the summit whose goals is implementation of specific actions identified.

Five working groups were developed prior to the summit, including the following: Patient Education, Provider Education, Access and Collaboration, Quality and Performance Measures, and Education and Promotion of Adult Immunization to Decision-Maker (there were no federal participants on this 5th working group). These working groups initially met pre-summit to identify key issues and potential solutions to serve as a starting point for discussions during the summit. During the summit, the working groups presented their summaries and solicited additional feedback, suggestions, and interest in working group participation. Following the summit, working groups will be reconvening and will revise their lists of priority action steps based on the feedback and suggestions received at the Summit. Working group participation will be revised based on interest in participation that was expressed by people who attended the summit. In

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

addition, key action items will be identified for the summit to work on over the next year, which will be reported back the summit next spring.

The summit was opened by Dr. Koh who is the Assistant Secretary for Health at DHHS. He provided an important message of support and commitment from DHHS, and discussed how the summit would be aligned with the newly initiated DHHS Interagency Task Force on Adult Immunization. The Task Force will include the first 4 of the 5 summit working groups, and the summit working groups will inform the HHS Task Force and vice versa. The summit was the first part of the work, but capitalizing on the energy and interest and future work of the working groups will be key to success. In addition, aligning the federal efforts with those of the summit will be key to support the summit's work and vice versa.

There were 288 attendees with 150 different organizations represented, including: Coalitions; local, state, and federal public health; provider organizations (e.g., physician, nursing, pharmacy, physician assistant, nurse mid-wives, community vaccinators); aging and other advocacy groups; vaccine manufacturers and distributors; insurance providers and billing organizations; academic and policy groups; and other federal partners (e.g., other DHHS agencies, DoD, VA). The opening session provided background for other discussions pertaining to current coverage, public health resources for adult immunization, NVAC Adult Immunization Recommendations, immunization provisions in the ACA, USPHS Task Force summary of what interventions work to raise vaccine coverage in adults, and subsequent sessions provided background for each working group and working group summaries. Each session was followed by opportunities for discussion, suggestions, and participation.

One of the goals was to actively solicit comments, suggestions, and involvement. As could be imagined, when 300 people are asked for comments, there are likely to be many pieces of feedback information. But there were some common themes that Dr. Bridges discussed during this session. The feedback generated 100 verbal comments, 67 feedback forms, and 102 "post-it" comments. In terms of communications, it was suggested that the culture needs to be changed in terms of increasing the awareness of and demand for adult immunization. There was a call for unifying the overall promotion / advertising strategy to help change the culture and behavior, as well as the need for development of the information required to meet the needs of specific groups. The value of immunizations for adults must be better conveyed, and there was a request for a central point needed for providers, patients, and others to find available materials regarding adult immunizations. There was also a call to increase engagement with employer and employee groups, including unions, and to promote adult immunizations within the context of other preventive services for adults. There must also be improved documentation and communication through IISs and EHRs. Other themes were to ensure that EHRs include prompts for immunizations and communicate with IISs, and to decrease policy and legal barriers for all vaccine providers, including pharmacists. It is also important to evaluate the means to increase education and incentives for providers through performance or quality measures; decrease the complexity of the ACIP Adult Vaccine Schedule such that when individual vaccine recommendations are made, consideration is given to where those vaccinations fit into the overall adult schedule; and engage and encourage adult immunization champions and leadership in key sectors, including among adult provider organizations and other key groups.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

A preliminary list of resources for provider and patient education was compiled by the Immunization Action Coalition (IAC), CDC, and patient and provider working groups. This is posted on the IAC website: www.immunize.org/adult-vaccination. This is a work-in-progress. If people find that their group's materials are not included and would like them included, they can contact Dr. Bridges or Dr. Wexler at IAC. Slides from 2012 Influenza Vaccine Summit and Adult Immunization Summits are available at: www.preventinfluenza.org.

Regarding follow-up steps over next several weeks, AMA, CDC, and NVPO are in the process of reviewing and organizing comments, and sharing those with the HHS Task Force and Summit. There are also plans to develop an initial list of key action items, review the working group composition and welcome new members to working groups, prepare a meeting summary for participants, and prepare proceedings for submission to a peer-reviewed journal. The summit working groups are to drive the action. Over the course of the next year, working groups will identify 2 to 3 actionable items to accomplish, based upon suggestions from the summit. They will also secure commitment from stakeholders to assume leadership roles for specific actions. All working groups will be supported and sustained. CDC/NVPO staff will keep the summit working groups informed of HHS Adult Immunization Task Force activities and vice versa.

Discussion Points

Ms. Rosenbaum noted that there is a lot on behavior. She wondered how much is known about what it takes financially, behavior-wise, et cetera to maintain a practice that achieves good uptake. Rather than thinking about it as individual behaviors of individuals, clinics, or doctors, she asked whether any thought had been given to assessing practices with very high performance to determine what they do in terms of organization, finances to maintain a practice with high results, et cetera. Perhaps if an administration focus was brought to this, something could be learned beyond the classis lessons of behavior.

Dr. Schaffner (NFID) found the creation of the Interagency Task Force on Adult Immunization to be very exciting and optimistic. He requested further information about the goals of that group and how it would function.

Dr. Gellin (NVPO) explained that this Task Force began by specifically assessing influenza, and then it was recognized that there are opportunities to consider adult immunization overall. This offers the opportunity to bring together the assets of HHS, and to dovetail in with the ACIP working groups to figure out where there are opportunities the federal government can leverage to advance this effort. It is still to be defined, but is trying to align with what the summit is doing.

Dr. Middleman (SAHM) noted that one of the most successful measures for adolescents and young children has been mandates or requirements for specific privileges. She inquired as to whether there was any discussion during the summit about changing the culture in terms of developing requirements for other privileges adults acquire such as a driver's license, or thinking in a more voluntary way, some incentives in terms of insurance premium decreases if someone is fully immunized. Adults do not go to the doctor quite like children do, so the initiative is probably not going to be as provider-driven as it is for pediatrics.

Dr. Coyne-Beasley requested that the summary from the summit and Dr. Bridge's slides showing the resources pages be made available to the ACIP members.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

It seemed to Dr. Duchin that a lot of what makes the childhood vaccination program successful might be rolled into a national adult immunization strategy. He wondered why there was no suggestion for a "vaccines for adults" program or something similar, because that seems to be the backbone of success in the childhood vaccination program. The approach to adult vaccines seems to be very piecemeal without a coordinated, unified national strategy that is analogous to the childhood vaccination program. He thought they should be advocating for a cohesive federally-driven adult vaccination program similar to the childhood program rather than all of the different agencies producing brochures, flyers, informational materials, and ad hoc solutions.

Dr. Baker pointed out that vaccine refusal among adults for themselves, as well as among parents who refuse to vaccinate their children, needs to be addressed as well.

Dr. Zahn (NACCHO) noted that 317 funding is so inconsistent and uncertain in terms of processing on an annual basis, developing a program from a public health standpoint is virtually impossible. Having a more consistent sense of funding, direction, and goals will make it infinitely easier on a public health local level to plan and advocate in the community.

Dr. Lewin (BIO) encouraged people to review the NVAC Adult Working Group report and recommendations, given that it covers many of the topics discussed during this session.

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Bocchini reported that the HPV Working Group took a hiatus following the October 2012 ACIP meeting. The working group's presentation during the October 2012 meeting included a series of recommendations to ACIP to modify the recommendation for the use of male HPV vaccine that led to approval of modification of the recommendations. Subsequent to that, there was a publication in the *MMWR* of those recommendations for use of quadrivalent HPV vaccine in males.

In terms of the evolution of HPV vaccine recommendations in the US, ACIP made the first recommendation for the quadrivalent vaccine in 2006 for routine use in females 11 or 12 years, and in females 13 through 26 years of age in those who were not previously vaccinated. The recommendations were changed in October 2009 with the licensure of the bivalent vaccine for routine use of the quadrivalent or bivalent vaccine in females 11 or 12 years, and in females 13 through 26 years of age in those who were not previously vaccinated. A permissive recommendation was also made at that time that the quadrivalent vaccine may be given to male 9 through 26 years of age for the reduction of incidence of genital warts. The most recent recommendation change was in October 2011 based on additional data regarding the reduction in incidence of anal intraepithelial neoplasia (AIN) in males and females as well as other data. The recommendation was for routine use of quadrivalent vaccine in males 11 or 12 years of age, and males 13 through 21 years of age for those not previously vaccinated. A permissive recommendation remained for males 22 through 26 years of age, and two special groups were recognized. Men who have sex with men (MSM) and immunocompromised males were recommended to receive vaccine routinely through 26 years of age.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

During this session, presentations were delivered on IIS sentinel site data with regard to uptake of HPV vaccine in the US, and an update on HPV vaccine.

ISS Sentinel Site Data: Update of HPV Vaccine in the US

Karen A. Cullen, PhD, MPH
Immunization Services Division
Centers for Disease Control and Prevention

During this session, Dr. Cullen reported on the current uptake of HPV vaccine in the US using data from the Immunization Information System (IIS) Sentinel Site project, including background of IIS and the IIS Sentinel Sites; methods and results of a study conducted to assess HPV vaccination coverage for males and females; the distribution of doses administered over the past few years; and age at first vaccination.

There are several sources of data that can be used to examine vaccination coverage in adolescents, two of which include the National Immunization Survey (NIS)-Teen and IIS. There are many other sources such as NHIS, BRFSS, claims data, and VSD. The official vaccination estimates come from the NIS-Teen. Since 2006, NIS-Teen has collected vaccination and sociodemographic information from parents or guardians regarding adolescents aged 13 through 17 years. Each year in August, estimates of vaccination coverage from the NIS-Teen are published in an *MMWR* article. The most recent NIS-Teen data is for 2010, which indicated that 48.7% of adolescent females had received at least one dose of HPV vaccine, and only 32% had completed the series.

IIS are another tool that can be used to examine adolescent vaccination coverage. Timely estimates from IIS allow for examination of HPV vaccination since the ACIP recommended it for routine use in males in October 2011. IIS are confidential, population-based computerized data systems based usually in state health departments that were designed primarily to consolidate vaccination records for all children within a geographic area from multiple vaccine providers. Among the capabilities of an IIS are the ability to generate vaccination coverage reports, patient reminders, or recalls for past due vaccinations; inform vaccine providers of upcoming patient vaccination needs; and communicate with electronic health record (EHR) systems. The primary sources of IIS data are downloads of birth certificate information, billing data, and clinical data from providers. Since most IISs are population-based, birth data for all newborns are imported into the IIS from Vital Records in that state or jurisdiction. Most clinical data are submitted via the internet. However, an increasing percentage of data are being reported to IIS via data exchange with clinical information systems, including EHRs. Few providers report to IIS using paper or fax. IIS can be found in nearly all states in the US, and a handful of major cities. Participation in an IIS is high, with more than 80% of children 4 months to less than 6 years of age and 61% of all adolescents participating in an IIS. Additionally, there are over 50,000 public and private provider sites in the country that participate in an IIS. On average, 6 weeks elapses from birth to the establishment of a child's demographic record in an IIS, and 71% of vaccination records are received by IIS within 30 days of vaccine administration.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In 2004, CDC established the IIS Sentinel Site project to conduct vaccination studies and data quality enhancements. In order to be a Sentinel Site, each site had to meet high data quality criteria, including having at least 85% of children and at least 85% of providers in their jurisdiction participating in the IIS, and at least 70% of vaccinations reported to the IIS within 30 days after administration. For the 2008-2012 project period, CDC funded 8 sites covering subsets of Arizona, Colorado, Oregon, and Wisconsin and all of Michigan, Minnesota, North Dakota, and New York City. These sites include 6.7 million children under 19 years of age. Their high data quality and timeliness provided CDC with a unique opportunity to examine vaccination coverage and uptake of new vaccines soon after ACIP's recommendation. The HPV data presented during this session is one such example.

In the fall, CDC developed a query for the Sentinel Sites to complete that would allow for the examination of HPV vaccination coverage and the distribution of doses administered for males and females from October 2009 until March 2012. CDC also sought to determine the age at first vaccination for males and females. Aggregate data were collected from each site. Birth cohorts were defined based on quarter to include all adolescents ages 11 through 12, 13 through 15, and 16 through 18 year olds. Age was determined as of the last day of the quarter, as was vaccination status, and included vaccinations given at any point up to the end of the quarter. Sites reported the number of vaccine recipients by quarter, age group, gender, and the number of doses of HPV vaccine received. This allowed CDC to calculate vaccination coverage using denominator data from the US Census. Doses administered were also reported for multiple time periods between October 2009 and March 2012 by age group and gender. The number of adolescents first vaccinated at each year of age were reported by age group and gender for selected quarters.

In terms of the percent of adolescent females who received at least one dose of HPV vaccine for 11 through 12 year olds, 13 through 15 year olds, and 16 through 18 year olds from the fourth quarter of 2009 until the first quarter of 2012, coverage at most increased only 10 percentage points for 16 through 18 year olds and at most only 4 percentage points for 13 through 15 year olds. Coverage for 11 through 12 year olds remains fairly steady. When the same data are examined for males, a steady increase is observed across all 3 age groups from the fourth quarter in 2009 until the first quarter in 2012. By the end of March 2012, 8.1% of males 11 through 12, 10.6% of males 13 through 15, and 8.8% of males 16 through 18 had received at least one dose of HPV vaccine.

With regard to the number of doses administered by week to 11 through 18 year olds, there were a number of important contextual events: The ACIP recommendation in October 2009, the publication of the subsequent *MMWR* in 2010, the October 2011 ACIP recommendation for routine use in males, and the subsequent *MMWR* in December 2011. In addition, Thanksgiving and back-to-school timeframes both led to decreases and increases, respectively, in the number of doses being reported by week. A similar pattern was observed for males for coverage, with the number of doses administered increasing steadily over time. For females, it appears as though the same cyclical pattern existed, with no increase in doses administered. This too backs up data observed on coverage for females. However, a change in the shape of the curve was seen following back-to-school, suggesting that more females were vaccinated later in the fall of 2011 than in the fall of 2010.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Also noteworthy is that even though the number of doses administered to males is increasing, it is still below that for females. However, this does vary by site. For New York City, the increase in the doses administered to males was more dramatic, and the number of doses administered to males actually exceeded that administered to females at the end of 2011. For the other 7 sites, the number of doses administered to males was still below that for females by the end of March 2012. In order to easily compare doses administered in time points in 2010 versus 2011, the total number of doses administered by calendar month was graphed for 2009 through 2012, which confirm that the patterns seen in 2010 were similar to those in 2011. Regarding the age at first vaccination for 13 through 15 year olds, among those 13 through 15 during the specified quarters, at the end of 2011, 74% of 13 through 15 year old females who had received at least one HPV dose had received that dose before their 13th birthday. A larger proportion of males were vaccinated prior to their 13th birthday than females in time periods shortly after their respective recommendations for routine use.

In summary, an increase in uptake was observed in males, which resulted in coverage for 1+ doses in 13 through 15 year old males to reach over 10%. On the other hand, no increase was seen in the number of doses administered to adolescent females and there was little change in coverage. For those adolescent females who were getting vaccinated, more were vaccinated at the recommended age in 2011 than in 2007. The 2011 NIS-Teen estimates will be available at the end of August 2012. While the results may not be generalizable to the entire US population, data from the IIS Sentinel Sites present a unique opportunity to examine HPV coverage and vaccine administration in a very timely manner. These population-based data allowed CDC to examine the provider-verified vaccination status for more than 2.9 million adolescents. Incomplete vaccination histories may be a result of non-participating providers and non-reporting by participating providers.

HPV Vaccine Update

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

Dr. Markowitz indicated that the purpose of this presentation was to give a brief update on a variety of different topics to ACIP, including HPV vaccine monitoring in the US, international vaccine introduction, vaccine schedules with less than 3 doses, and future ACIP HPV Vaccine Working Group plans.

Post-licensure vaccine monitoring in the US includes a variety of areas including coverage, safety, and impact on infection and disease. The last presentation provided some data on coverage and, as mentioned, the next data from NIS-Teen will be available in August 2012. There have been periodic updates to ACIP on HPV vaccine safety, most recently in October 2011. Dr. Markowitz briefly mentioned the most recent safety review at FDA, and then presented some data on impact monitoring.

In May 2012, there was an FDA Gardasil Pediatric Utilization and Safety review for the Pediatric Advisory Committee (PAC). This review was triggered by the 2009 and 2010 approvals for prevention of genital warts in males and AIN in males and females. The objective of the review was to provide a targeted safety review, focusing on the time frame following approval of Gardasil for the prevention of genital warts to one year following the approval for the prevention of AIN and anal cancer in males and females ending in December 2011 to determine if there

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

were any new safety concerns. While the review focused on data among individuals through age 16 years, the data reviewed included those from VAERS, VSD, and the manufacturer's post-marketing commitments.

Data from VAERS, VSD, and Merck's active surveillance program for females in a managed care organization were presented to ACIP October 2011. The VAERS data analysis found no new adverse events or clinical patterns. The VSD study found no statistically significant safety signals for any of the pre-specified events. Merck's active surveillance program for females in a managed care organization found no safety signals for pre-specified autoimmune diseases. Data from Merck's pregnancy registry, which was the 5th annual report, were also reviewed but have not yet been presented to ACIP. The conclusion was that the overall rate of congenital anomalies and miscarriages was within the estimated background rate. Review of congenital anomalies and deaths did not identify any unusual patterns. The conclusion of the review was that almost six years of post-marketing safety surveillance in females demonstrate the safety of Gardasil®. The uptake in males has been low, so there are less data in that group. Syncope still a common adverse event. On-going safety studies in males and females will provide additional data. The FDA recommended continued monitoring of safety, with attention to any unexpected differences between females and males.

As presented to ACIP in the past, the monitoring of impact of vaccine on HPV infection and associated disease in the US includes a variety of endpoints. The earliest impact will be observed on type-specific HPV prevalence and genital warts. The impact on cervical pre-cancers will be observed next. The impact on HPV-associated cancers might take decades to observe. Baseline data from several HPV associated endpoints have or are being summarized and published. This includes baseline data on HPV prevalence among females, data on cervical pre-cancer lesions, and data on cancers. Data on HPV-associated cancers using standardized criteria were summarized in a monograph in 2008, and were presented to ACIP at past meetings. An update was published recently in the *MMWR* in May 2012.

Dr. Markowitz then presented data from an analysis to evaluate one of the early HPV-associated endpoints, genital warts, using administrative claims data. This analysis used the MarketScan® commercial claims and encounters database 2003 through 2009. The purpose of this analysis was to estimate annual prevalence of anogenital wart diagnoses in a large group of privately insured US patients, and to identify changes in prevalence that might be attributable to HPV vaccination. This analysis included persons aged 10 through 39 years of age who were continuously enrolled within a given year, for an estimated 50.5 million person-years of data. Cases were defined using ICD-9 CM codes or medication codes combined with diagnosis or procedure specific codes. If the record had the ICD-9-CM diagnosis specific for condyloma acuminata, additional criteria such as a procedure codes were not required. Of the cases in the analysis, 88% had a specific code for condyloma acuminata.

In terms of the prevalence of anogenital warts by 5 year age group, from 2003 to 2009 among males, as noted, the prevalence of genital warts increased in most age groups during this time period. Regarding the prevalence by 5 year age group from 2003 through 2009 in females, the lowest prevalence was in the 10 through 14 year olds and the highest was in the 20 through 24 year olds. This is consistent with what other studies have shown for genital warts. Prevalence among females aged 15 through 19 years significantly declined from 2.9/1000 persons years in 2006 to 2.2 in 2009. In women aged 20 through 24, prevalence increased from 4.0 to 5.5 in 2007, and then remained level through 2009. Prevalence among females in older age groups increased during this time period, as was observed in most age groups for males. The increase in genital warts prevalence in the males and older females is unexplained, but other data

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

sources have also found increases over time. There are limitations to administrative claims data, including the fact that inference cannot be made to the general population, all are privately insured, and there are some limitations to using ICD-9 codes. Nevertheless, these data suggest early evidence of impact of vaccine in the age group in which an impact would first be expected. Impact monitoring data from other monitoring systems will be available to share with ACIP during the October 2012 meeting.

With regard to what is occurring internationally, in 2009 WHO recommended HPV vaccination inclusion in national immunization programs if cervical cancer and HPV-related disease is public health priority, introduction is programmatically feasible, sustainable funding can be secured, and cost-effectiveness has been considered. From 2009 through 2011, few middle- or low-income countries actually introduced HPV vaccine due to the cost of vaccine. During this time, private donations led to demonstration projects in a variety of countries. Many of these donations were through manufacturers, and there were national introductions through donation programs in 2 countries: Bhutan and Rwanda. Tiered pricing of vaccine, including through mechanisms like the PAHO Revolving Fund, allowed some middle income countries to introduce vaccine. In November 2011, the Global Alliance for Vaccines and Immunisation (GAVI) announced opening a funding window for introduction of HPV vaccine. GAVI-eligible countries can apply for national introduction based on demonstrated ability to reach the target age group, or for demonstration projects followed by national introduction in countries that do not have experience with HPV vaccine. Applications are expected in 2012, with introduction expected to occur in 2013.

There has been emerging interest in schedules with less than 3 doses for a variety of reasons. These schedules could facilitate implementation; may be more convenient for providers, parents, and vaccines; and would be cost-saving. Several jurisdictions have decided to use an extended 3-dose schedule or a 2-dose schedule. These include Quebec, British Columbia, Mexico, and Switzerland. In the extended 3-dose schedule, doses 1 and 2 are given in early adolescence 6 months are apart and dose 3 would be given 5 years later, so it is a 0-, 6-, and 60-month schedule. Quebec was the first jurisdiction to introduce this schedule. British Columbia changed from a 3-dose to an extended 3-dose schedule in 2010 after results from an immunogenicity study. Switzerland changed from a 3-dose to a 2-dose schedule for those under 15 years of age. A 3-dose schedule is recommended for those 15 years of age or older. This change occurred in early 2012.

Decisions to use this schedules have been based on a variety of different data. No data on efficacy with less than 3 doses have been published from the large manufacturer-sponsored pivotal efficacy studies. However, there are some data from other studies on immunogenicity and one on efficacy. For the bivalent vaccine, there are data from immunogenicity studies and from an efficacy study in Costa Rica. For the quadrivalent vaccine, there are data from an immunogenicity study and there will be data in the future from a trial in India of 2 versus 3 doses, which may provide some data in the future on efficacy against endpoints of cervical disease.

Data from the bivalent vaccine trial in Costa Rica were published in 2011. This trial was an RTC in which women were randomized to receive either bivalent vaccine or hepatitis A vaccine. This study was not designed to evaluate the number of doses, but among women enrolled in the trial, about 20% received less than 3 doses allowing an analysis of 1, 2 or 3 doses. The endpoint was incident infection that lasted for at least 10 months. As noted, there was high efficacy among women who received less than 3 doses. The similar incidence in the control arms

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

among women who received 1, 2, or 3 doses suggests equal exposure among women who received the different number of doses.

There are a several immunogenicity studies that have been or are being conducted. Although Dr. Markowitz did not review all of these during this session, she mentioned one study in Canada which was used to provide data for the change in schedule for British Columbia. This study compared a 2-dose schedule at 0 and 6 months among 9 through 13 year olds to standard 3-dose schedules in 9 through 13 and 16 through 26 year olds. The main analysis was comparing the two dose schedule at 9 through 13 years with 3 doses at 16 through 26 years, looking at GMTs at month 7. Month 36 data were presented last year. As noted, the GMT ratio is greater than 1 and non-inferiority criteria were met for all 4 types. In the comparison of the 2-dose schedule at 9 through 13 years with 3 doses at 9 through 13 years, the GMT ratio was less than one. There was non-inferiority at 7 month, but this was lost for HPV 18 by month 24 and HPV 6 by month 36. As mentioned, the main comparison for this study was 2 doses at 9 through 13 versus 16 through 26 years.

While some countries have adopted a 2-dose schedule or an extended 3-dose schedule, there are limited efficacy data available to date for schedules with less than 3 doses. Even if efficacy against early endpoints is demonstrated in further studies, outstanding important questions will remain, including: Will there be differences in duration of protection for 2 versus 3 doses? Will there be differences for special populations? Data from on-going trials, post-licensure effectiveness evaluations in the US and elsewhere, and monitoring data will provide more information on this topic.

The HPV Working Group is continuing to meet, although not as often as before, and will continue to review data on the US vaccination program, vaccine impact, effectiveness, safety and other studies from a variety of sources.

Discussion Points

Dr. Coyne-Beasley requested further insight regarding the extraordinarily high rates of vaccination among young males in New York City in terms of the successful strategies that were used.

Dr. Zucker (New York City Department of Health and Mental Hygiene) replied that the uptake in males actually occurred in males following the permissive recommendation. New York City Department of Health and Mental Hygiene promoted the permissive recommendation among all of its providers. One thing that may differ about New York City from other parts of the country is that about three quarters of children are eligible for publically funded vaccines. The percentage is somewhat less for adolescents. Because so many of New York City's children are eligible for VFC vaccine, some of the financial constraints other providers and locations may have were not quite as prominent for New York City. Because all of the recommendations were promoted, when the routine recommendation was made, there had been several communications with their providers. New York City's immunization information system was updated to include the male recommendation, so any provider who goes through New York City's web application for the registry will receive a reminder that any male between the ages of 11 and 18 is due for the HPV vaccine. There are also reminders for females, second dose, and the third dose. Providers are also informed that the vaccine can be given as early as 9 years of age. There are many other evidence-based features that the provider can access to pull out those data. For example, they can request a list of males who need to return for vaccination. The registry interoperates with

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

over 200 provider offices' EHRs. Some of those offices are bringing New York City's decision support right into their EHRs.

Dr. Meissner found the data that suggested early impact in genital warts to be very exciting. It suggests that the quadrivalent rather than the bivalent vaccine is being used. He requested further information about the relative use of those two vaccines.

Dr. Markowitz replied that while she could not give exact numbers, it is known that the vast majority of vaccine being used in the US is quadrivalent.

Dr. Turner (ACHA) added that looking at the ACHA's network of 19 schools, of about 12,400 doses administered, 98% to 99% were quadrivalent.

Dr. Schuchat commented that in general with vaccines for which there is more than one brand, typically the vaccine that is first to market starts to dominate.

Dr. Baker added that the quadrivalent was licensed first in 2006, so it had a big head start.

In terms of the rapid uptake in males, Dr. Gorman (NIH) reported that he heard a very definitive comment the previous day made by one practitioner, and he confirmed that with a group with which he was formerly associated, that the parents of young males seem to have less difficult imagining sexual activity of their boys than girls. Therefore, it is a much easier sell.

Dr. Baker found it fascinating that in terms of the age of onset of sexual debut, girls are about two years ahead of boys. Yet, this persistent myth continues.

Dr. Schuchat clarified that much of what has been observed is really exciting, the first year there were data on HPV coverage in girls, there was 25% uptake. There was a catch-up cohort with girls, but with boys the whole group is eligible. Whether it is New York City or the 8 sites, while they have not done a great job, there was a catch-up period and they are in stabilization mode. She thought in 2007 they had better data about the first use of HPV, which reached higher levels than the first year of meningococcal vaccines in the teenage group.

Regarding parents and linking sexual activity to this vaccine, Dr. Jenkins pointed out that many practitioners are still experiencing parents who refuse vaccine. She wondered whether the IIS system captures not only who received the vaccine, but also people who were offered and refused. That information could be beneficial in terms of the strategies to increase vaccination rates, and whether they should be aimed more toward providers in certain areas or toward further education to parents, and framing it as an anti-cancer vaccine as contrast to one that is linked to sexual activity.

Dr. Cullen responded that this information can be captured in the system, but it is not used very frequently by providers.

Dr. Markowitz added that those data are captured in NIS-Teen, so data regarding reasons for refusal can be presented to ACIP.

Dr. Middleman (SAHM) reported that Baylor has preliminary data that seem to indicate that providers significantly underestimate the importance that parents place on HPV vaccine. Providers assume that parents are much less willing to obtain the vaccine for their children than they are. She thinks providers are not as proactive with vaccine refusal regarding HPV as they

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

are with regard to other vaccines. It is important to educate providers that parents really do think this is an important vaccine. Parents really just want reassurance.

Dr. Baker inquired as to whether Baylor had assessed providers by gender. While most young pediatricians are female, she wondered whether there was a difference. Male pediatricians typically are fathers, and they are known to have somewhat different thinking perhaps than mothers about this issue.

Dr. Middleman (SAHM) responded that they have not yet assessed that data at the level of provider by gender.

Dr. Marcy said he had always been amazed that students cannot get into many colleges without protection against measles and pertussis, but they can get in without protection against cervical cancer. This does not make a lot of sense, and he thinks the universities and colleges ought to be more active in terms of ensuring that this vaccine is used at that level. He also had the feeling that if the issue were penile cancer, everyone would be immunized.

Dr. Vazguez reported that while Connecticut has had higher rates of HPV vaccination, they have a problem with completion of the immunization series. She requested further information about 2-dose series and 3-dose series completion.

Dr. Cullen replied that there are some data, but the percent of adolescent females is still less than 40%. For males, the highest is in the 13 through 15 year old age group at about 2.5%.

Dr. Bennett wondered whether there were data of coverage rates among young women; that is, those over the age of 18. There were major coverage barriers initially, and this is a very high risk group that was not being vaccinated.

Dr. Cullen replied that this project only collects data on those who are under the age of 19, so she did not have information on that. She thought data were presented in an earlier presentation.

Dr. Keitel confirmed that data were presented in an earlier presentation, and coverage for that age group is very low.

Dr. Turner (ACHA) reminded everyone that in the ACHA surveillance network, there is 46% uptake of 3 doses of HPV vaccine among females. That is substantially higher than the general population. Much of it has to do with the fact that the vaccine is being recommended, and women have access. The argument against requiring it is that HPV cannot be transmitted by sneezing or coughing in a classroom; whereas, measles can be. HPV clearly is an important reason that students see college health providers. It is the 8th or 9th most common reasons students present to a college health service. ACHA is working hard within the confines of the cost of the vaccine and state laws and mandates, and is doing pretty well. Regarding male uptake, in the ACHA network, 20% of the recipients of the vaccine are male. In fact, two-thirds of them are over the age of 21, even though the recommendation is only up to the age of 21. There has been no formalized work to market this vaccine to males over that age. There are advocacy groups and a lot of education among particular groups of men to promote the vaccine.

Dr. Marcy responded that while it may not be through sneezing and coughing, the University of Washington data indicate that HPV is rapidly acquired when one enters college.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Jenkins noted that at one point, ACIP was shown some data related to race/ethnicity and socioeconomic status differences. She inquired as to whether there was any sense about whether those gaps were widening or narrowing.

Dr. Cullen replied that they did not have data on race/ethnicity and SES.

Dr. Markowitz indicated that those data were from the NIS-Teen. The next survey results will be available in August 2012 and will be published in the *MMWR*. An update can be provided on this during the next ACIP meeting.

Reflecting on the discussion regarding modifications of GRADE the previous day, Dr. Temte inquired as to whether Dr. Markowitz would be willing to comment on the trends seen in Australia and possibly some dose effects and the relationship between higher coverage rates being observed.

Dr. Markowitz responded that she presented those data in October 2011. Australia has the first evidence of impact on genital warts. They have achieved very high coverage with 3 doses, and saw a very rapid decrease in new genital wart diagnoses in females. They also found some evidence of herd immunity, with a decrease in males as well. Those were the first data published on the impact of vaccination from a country-wide introduction.

Dr. Loehr (AAFP) seconded Dr. Marcy's idea. He did not know whether there was a national college health forum, but the fact that the meningitis vaccine has to be given or refused and signed off has made many more of his patients consider the meningitis vaccine that they might not have otherwise thought of. Even including HPV vaccine as a recommended vaccine might increase coverage.

Dr. Turner (ACHA) responded that there is a comprehensive list of recommended vaccines at ACHA.org. ACHA only provides clinical guidelines, and has no legislative capabilities. HPV vaccine has been recommended ever since it came out.

Dr. Baker added that Texas has a meningitis mandate that actually goes up to age 30 for all colleges systems. A former Presidential candidate for this year tried to mandate this, but HPV vaccine is different from meningococcal conjugate vaccines in more ways than one.

Ms. Rosenbaum thought it was worth reiterating that because of the new coverage for under 26 years of age and because all ACIP-recommended vaccines are covered without cost sharing, it might be worth developing a CDC/AHIP campaign to remind everybody that children are covered up to age 26 if they are ensured for everything, without singling out HPV.

Dr. Schuchat reported that in the surveys CDC has been conducting, cost is not on the list of barriers identified by parents. She thinks provider hesitancy is a big deal. Parents are raising this issue and practitioners are considering that they do not have time to get into this, and they are not following up with confident, strong recommendations. Certainly, reassuring folks that this is a strongly recommended, covered vaccines that insurers are supposed to be covering this with no co-pays and so forth would be beneficial.

Ms. Rosenbaum agreed that while physician behavior is a major issues, she is also sure that hearing the amount per dose is an issue for parents. A friend of hers was the person in Australia who negotiated the HPV vaccine entry on their schedule. The price Australians pay for the full series is quite sobering.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Considerations for AVA Post-Exposure Prioritization

Raymond A. Strikas, MD, MPH
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Strikas presented considerations for Anthrax Vaccine Adsorbed (AVA) post-exposure prioritization guidance. AVA prioritization has been recognized as a gap in multiple exercises for response to anthrax release. Following the March, 2011 Dark Zephyr exercise that simulated an anthrax release over a large metropolitan area of the US, the National Security Staff (NSS) tasked HHS, which then tasked CDC to develop a post-event AVA prioritization guidance. In terms of the timeline to developing considerations for AVA prioritization guidance, CDC formed a federal steering committee on August 24, 2011. Once the guidance document was developed with that committee, in December 2011 it was sent to 11 non-federal technical experts on anthrax and / or proposed activities for their review and comments. Their comments were addressed. In the winter and spring of 2012, briefings were delivered to senior federal agencies' leadership. CDC contracted with the Association of State and Territorial Health Officials (ASTHO) to conduct 20 focus groups in two US cities in April and May 2012 for input about the draft guidance. A stakeholder meeting is planned for August 2012 for final input on the draft guidance. The federal steering committee will meet on August 21, 2012 to finalize the guidance by moving it to departmental clearance.

The federal steering committee is comprised of the following agencies / representatives:

- The Centers for Disease Control and Prevention, DHHS
  - Nancy Messonnier
  - Raymond Strikas
  - Nicki Pesik
  - Tracee Treadwell
  - Zunera Mirza
- Food and Drug Administration, DHHS
  - Lewis Schrager
  - Cindy Kelley
- National Vaccine Program Office, DHHS
  - Bruce Gellin
- National Institutes of Health, NIAD, DHHS
  - Richard Gorman
- Office of the Assistant Secretary for Preparedness and Response (ASPR), DHHS
  - George Korch
  - Lisa Kaplowitz

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- Department of Defense
  - Patrick Garman
  - Scott Stanek

- Department of Homeland Security (DHS)
  - David Adams
  - Sally Phillips

- Environmental Protection Agency (EPA)
  - Cayce Parrish

- Department of Labor (DOL)
  - Jack Longmire

The committee has met in-person or via conference call four times (9.26.11, 11.9.11, 1.13.12, and 6.18.12), and has communicated additionally by email. As noted, the next meeting is August 21, 2012 to finalize the guidance by moving it to departmental clearance.

With regard to the document parameters, the document assumes there is a limited amount of anthrax vaccine available, and that all exposed persons will receive antibiotics for post-exposure prophylaxis. The timeframe based on the ACIP recommendations for post-exposure prophylaxis is that vaccination should begin no later than 7 to 10 days after the event. Vaccination for long-term exposure risks to anthrax aerosols (e.g., 6 months or longer) is not addressed. The document is directed toward federal, state, and local health and emergency management officials. The document does not consider prioritization for antibiotics; specific worker safety requirements (e.g., personal protective equipment [PPE]); policy decisions regarding pre-event AVA vaccination or vaccine reserve/held-back; or operational or implementation planning.

There are three principles for prioritization. The first and foremost is that the literature about risks associated with inhalation of anthrax caused by primary aerosol exposure compared to secondary aerosol exposure is large and varied. However, there was substantial, albeit not universal, agreement that inhalation of spores before they reach the ground, or primary exposure, poses a greater risk for inhalational anthrax than does activity generated from ground matter after the spores have hit the ground (e.g., secondary exposure). The risk decreases for inhalation anthrax the longer the spores stay on the ground, though risk of disease does continue for some time. The second principle is the entirety of the affected community must be considered. The third principle is responders' risk is based primarily on activities, not their job titles, and methods to limit exposure of responders exist in addition to antibiotics and vaccination. There is a separate document titled, "Proposed Guidance for Protecting Responders' Health During the First Week Following a Wide-Area Anthrax Attack" that is parallels the AVA prioritization guidance. The prioritization scheme for AVA post-exposure is based on risk of exposure to anthrax spores, and activities of persons involved in response to the anthrax release.

Regarding next steps, on August 20, 2012 the stakeholders will review the results of the focus groups, and will discuss the current draft guidance and offer recommendations for modifications and revisions. The federal steering committee will complete the guidance on August 21, 2012 for federal departmental approval.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

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

- ❑ Are the criteria for prioritization reasonable?
- ❑ Are additional criteria necessary?
- ❑ Do the prioritization tiers align appropriately with the criteria?

Discussion Points

Dr. Baker requested that AV check the microphones, given that there was considerable feedback coming from the podium.

Dr. Coyne-Beasley wondered whether any consideration had been given to people who are immunocompromised in terms of the criteria for prioritization.

Dr. Strikas responded that the federal steering committee, as well as the focus groups, discussed whether infants, the elderly, and others are at risk. The challenge with this is that there are precious few data about risk factors for severity of anthrax disease. They thought the simplest approach, given the data on risk of anthrax from primary and secondary aerosol, would be to say that anyone in a defined area should be treated. His sense was that one way to protect as many immunocomromised persons as possible was to define an affected area more broadly until more information is acquired about where an exposure may have occurred. Antibiotics should be given to everyone possible in that area.

Dr. Messonnier (SME) added that not only are there precious little data on risk factors for anthrax, but also there is precious little data on the immunogenicity of the vaccine in immunocompromised populations.

Ms. Ehresmann requested clarity about whether the guidance being directed toward federal, state, and local health and emergency management officials meant public health as opposed to just clinicians.

Dr. Strikas clarified that this guidance is focused toward people who would manage the response, because those are the people who will have to figure out how to direct vaccine. Vaccine prioritization is a narrow but important issue, and these managers will also handle all of the other issues involved in the response. This prioritization is part of managing the response, which would involve primarily public health responders. However, there has been discussion with other healthcare personnel about input for the guidance.

Dr. Campos-Outcalt requested a reminder about how many doses are given post-exposure, as well as the current policy in the military.

Dr. Strikas replied that post-exposure is given in 3 doses at 0, 2, and 4 weeks. Full protection is expected two weeks following the last dose, which is why the recommended antibiotic duration is 60 days. At the end of 60 days, if someone has received 3 doses in a timely manner, they should be protected via vaccine and antibiotic use can be discontinued. The current military policy is that all active duty personnel receive anthrax vaccine, with few exceptions.

Dr. Geibe (DoD) clarified that anthrax vaccine would be administered to personnel deploying to certain areas where anthrax is of concern, so not all active duty personnel receive anthrax vaccine.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Plotkin pointed out that they were dealing with a vaccine that was developed in the late 1950s. There basically has been no improvement since then. It is a vaccine that contains an antigen that essentially allows toxin to enter into the cell. It ignores the toxin itself, the capsule, spore antigens, and new adjuvants. His plea to NIH and ACIP was to stimulate industry to develop a better and more immunogenic vaccine that will give quicker protection.

Dr. Gorman (NIH) commented that NIH's present studies and any to be implemented within the next month could be found on www.clinicaltrials.gov. He emphasized that he could talk about them only after they became available for the general public.

Dr. Baker inquired as to whether the finalized guidance document would be posted on the *Federal Register* for public comment.

Dr. Strikas responded that at present, there are no plans to post the document on the *Federal Register*, given that wide input has already been sought.

Measles, Mumps, Rubella (MMR) Vaccine

Introduction

Jonathan Temte, MD, PhD,
University of Wisconsin
Chair, MMR ACIP Working Group

Dr. Temte said that it was with sadness that he went to the podium for the last time after being called by ACIP Chair, Dr. Baker. On behalf of the entire ACIP, he thanked her for her incredible services over these years.

He indicated that the Measles, Mumps, Rubella (MMR) Vaccine Working Group's terms of reference are to review available data and discuss potential changes to current recommendations dealing with these three viral infections. To achieve this, the working group's activities have been to review the epidemiology of measles, mumps, rubella, and congenital rubella syndrome (CRS); review the existing statements pertaining to MMR vaccine; review new data on MMR vaccine (e.g., safety and immunogenicity among persons with HIV; third dose for mumps outbreak control); and revise/update existing recommendations into a single comprehensive document.

The MMR Vaccine Working Group's activities to date have included discussing issues related to rubella vaccination policy; discussing revaccination of women of childbearing age who are rubella IgG negative; considering the exception for women of childbearing age born before 1957; reviewing changes to the MMR vaccine "evidence of immunity" requirements for health-care personnel; reviewing the vaccine safety of MMR-containing vaccines; and discussing recommendations for use of immune globulin for measles post-exposure prophylaxis (PEP).

The future activities of the MMR Vaccine Working Group are to draft and review an updated statement for prevention of measles, rubella, and mumps; and to entertain an ACIP vote on the updated statement and policy changes during the October 2012 meeting.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

This session included presentations on the following topics:

- ❑ Epidemiology of rubella and congenital rubella syndrome (CRS) in the United States
- ❑ Post-exposure prophylaxis for measles with immune globulin
- ❑ Review of policy considerations pertaining to prevention of measles, mumps, and rubella

Epidemiology of Rubella and Congenital Rubella Syndrome (CRS) In the United States

Huong McLean, PhD, MPH
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Prior to vaccine licensure, rubella incidence was highest among children ages 5 through 9 years and during the spring. Epidemics occurred every 6 to 9 years of varying intensity. The last major global rubella pandemic occurred from 1964 through 1965 [Witte JJ, et al. Am J Dis Child. Jul 1969;118(1):107-111]. During that pandemic, there were an estimated 12.5 million rubella cases and 20,000 CRS cases in the United States. In light of this devastating epidemic, there was an urgency to develop a rubella vaccine [National Communicable Disease Center. Rubella Surveillance Bethesda, MD: U.S. Department of Health, Education, and Welfare; 1969].

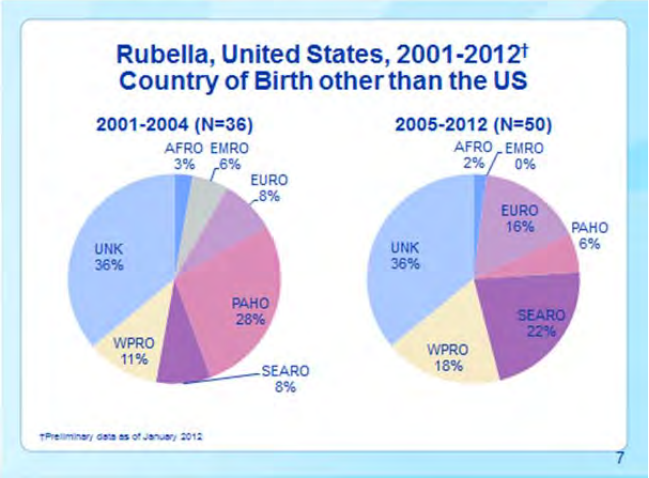
The rubella vaccine was licensed and recommended for use in 1969 in the US. Following vaccine licensure, the number of cases declined dramatically. However, incidence of both rubella and CRS increased in the late 1970s and early 1990s, primarily as a result of outbreaks in unvaccinated populations, particularly among older adolescents and young adults and in settings where unvaccinated populations congregated. By 2001 through 2004, reported rubella and CRS cases were at an all-time low, with an average of 14 rubella cases and 1 CRS case a year.

In 2004, rubella and CRS was documented and verified as eliminated in the US. Since 2004, annual reported rubella incidence remained below 1 per 10 million population and average annual reported CRS incidence is less than 1 case per 5 million births. In 2010, the Pan American Health Organization (PAHO) announced that the Region of the Americas had achieved the rubella and CRS elimination goals based on surveillance data. Although documentation of elimination is on-going, an expert panel unanimously agreed in December 2011 that rubella elimination has been maintained in the United States.

Dr. McLean then briefly reviewed the epidemiology since verification of rubella elimination. In terms of the characteristics of rubella and CRS cases in the US from 2001 through 2004 and 2005 through 2011, the period prior to verification of rubella elimination and after were very similar. There were very few cases, with median annual number of 9 cases, in 2005 through June 2012. Most of the cases have occurred among those 15 years of age and older, and about a third were born in the US. During 2005 through 2012, there have been 2 outbreaks, each involving 3 cases.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

The following two figures show the distribution of birth country for rubella case patients who were not born in the US. Notice that the proportion coming from the PAHO region has declined since 2004, which is likely due to the rubella elimination efforts in the region:



Since 2005, 6 cases of CRS have been reported, including 2 cases in 2012. Most of the mothers of these infants were foreign born and were unvaccinated or had unknown vaccination status. However, there was one infant, born in 2008, whose mother had documented receipt of 1 dose of MMR vaccine, did not travel outside the US during pregnancy, and had an unknown source of rubella infection. This is an unusual case, as reports of CRS in children of vaccinated mothers are extremely rare.

From the global perspective, the revised total estimates of infants with CRS born annually for all WHO member states declined from 120,000 in 1996 to approximately 112,000 in 2008. The impact of the rubella elimination activities is clearly seen in the Americas and European Region. However, there is still a significant burden of CRS, particularly in the African and Southeast Asian regions. As of 2010, 130 countries have rubella vaccine in their immunization program, or 41% of the birth cohort [Unpublished, Adams E, Vynnycky E].

In light of the global burden of CRS, in 2011, WHO recommended that all countries that are providing 2 doses of measles vaccine and have not introduced rubella vaccine, to consider including rubella-containing vaccine in their immunization program. In addition, in November 2011, Global Alliance for Vaccines and Immunisation (GAVI Alliance) opened a funding window for rubella-containing vaccine that will support countries to use the rubella vaccine, which will result in introduction of rubella containing vaccines in many more countries [Rubella vaccines: WHO position paper. Wkly Epidemiol Rec. 2011;86(29):301-16].

To summarize, elimination of endemic transmission of rubella was documented and verified in 2004. Maintenance of elimination from 2005 through 2011 was documented in December 2011. Globally, 2/3 of member countries have introduced rubella-containing vaccine. There is still a significant burden of CRS. WHO and GAVI Alliance financial support will likely result in introduction of rubella vaccines in more countries.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Discussion Points

Regarding the New Jersey CRS case, Dr. Baker inquired as to how the diagnosis was confirmed.

Dr. Greg Wallace (SME) replied that this was a complicated case. Although one of the initial infectious disease doctors had CRS in their differential, it was not tested for and did not come to the attention of public health until the child was 7 months old. There was positive serology and report of a PCR from a commercial laboratory, but CDC was unable to confirm this. Thus, the diagnosis was made based on clinical grounds and some supporting laboratory evidence. This was a very difficult case, and significant input was sought before classifying it as a CRS case. The child also had several other medical problems, which complicated the issue.

Dr. Kimberlin (AAP) reported that Alabama had the last case. Having never seen congenital rubella, he encouraged everyone to maintain vigilance. While it is still circulating, someone en route from Nigeria could bring it in at any time.

Dr. Baker emphasized that rubella should continue to be included in the differential diagnosis just as measles should be. Texas's last case of measles in 2011 was admitted as Kawasaki Disease (KD), with no attention to prevention of additional exposure until an old enough physician was able to make the diagnosis. While it is very important to keep these in the differential diagnoses, the second step should be to work diligently on diagnostic criteria.

Dr. Campos-Outcalt pointed out that this was a classic example of the lack of appreciation from the public and the professionals of the benefits of vaccines. At one point, congenital rubella syndrome was one of the leading causes of congenital deafness. This is no longer observed, and people just do not understand what life was like before vaccines.

Dr. Baker agreed that during the epidemic years, rubella was number one in terms of cause of deafness.

Post Exposure Prophylaxis for Measles with Immune Globulin

CAPT Mark Papania, MD, MPH
Measles, Mumps, Rubella, and Herpes Virus Laboratory Branch
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Papania reiterated that measles has not been endemic in the US for over a decade. What that means is that due to the US immunization program, the proportion of the population that is immune to measles is maintained at a level that is too high to support sustained measles transmission. However, this tremendous success has some epidemiologic and serologic implications for the use of passive measles antibody to protect the few remaining people who are susceptible and exposed to measles.

Human Immune Globulins (IG) are blood products used to provide passive antibodies for the short-term prevention of some infectious diseases, including measles. Immunoglobulin products are prepared from plasma pools derived from thousands of donors. By far the most common use of these products is for pre-exposure prophylaxis against measles and other diseases provided to tens of thousands of patients with immunodeficiency via frequent

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

administration of immune globulin given intravenously (IGIV) or subcutaneously (IGSC) in anticipation of a possible exposure. Post-exposure prophylaxis (PEP) with immune globulin given intramuscularly (IGIM) is recommended by ACIP for persons exposed to measles or at high risk of exposure for whom vaccine is either contraindicated or was not given within 3 days of exposure.

There are a number of specific issues for consideration. Multiple IG products are licensed in the US (e.g., IGIM, IGIV and IGSC). The role of each in post-exposure measles prevention needs to be defined. One of the effects of the long-term successful elimination of endemic measles from the US is that measles antibody concentrations have decreased in immune globulin (IG) donor populations. Basically, the antibody concentrations are sufficient to protect the donors, but the lower concentrations make it difficult to share antibody for the protection of others. Given that the concentrations of antibodies are lower, the post-exposure prophylaxis IG doses may need to be revised to provide adequate protection. Another effect of the long-term elimination of measles is that women giving birth in the US have lower concentrations of measles antibody. Again, these women have sufficient antibody for their own protection. But they provide lower concentrations of antibody to their infants, which results in early susceptibility to measles among infants born in the US. The current ACIP recommendations state that infants less than 6 months of age are likely to be immune and not need PEP; however, this may need to be revised. Recommendations regarding the type of exposure for which IG PEP is indicated may need to be clarified. IGIV products have been available since 1981, and 9 products are currently licensed. The major label indication is for prevention of common infectious diseases in the approximately 50,000 US patients with primary immunodeficiency disorders, but there are many off-label uses. The dosages range from 200 to 800 mg/kg given every 3 to 4 weeks. The IGIV label recommends measles PEP in patients with primary humoral immunodeficiency at a dosage of 400 mg/kg. The average cost in 2007 of 6 products was about $55 per gram.* Calculated out, the cost estimate for a 400 mg/kg dose for a 10 kg child is $220 and for a 70 kg adult is $1540 [*Sorenson R, et al. Expert Opinion Regarding Clinical and Other Outcome Considerations in the Formulary Review of Immune Globulin JMCP April 2007 Vol. 13, No. 3; +Leong H, et al Unlabeled uses of Immune Globulin. AM J Health System Pharm 65:1815-1824 2008].

IGSC products have been available since 2006, and 4 products are currently licensed. The major indication is the same as IGIV. IGSC infusion avoids the need for venous access. However, IGSC administration requires a pump and advanced training. The recommended dosage ranges from 100 to 200 mg/kg, given weekly by subcutaneous infusion at 15 mL/hr with separate sites for volumes >15 mL. Multiple, consecutive weekly doses are needed to establish steady-state, protective antibody levels. IGSC is recommended only for patients already on IGIV and are having difficulty with venous access.

Information regarding the current ACIP MMR recommendations for immunocompromised persons for IGIV and IGSC follows:

- For patients receiving IGIV therapy, a standard dose of 100–400 mg/kg should be sufficient to prevent measles infection after exposures occurring within 3 weeks after administration of IGIV; for patients exposed to measles >3 weeks after receiving a standard IGIV dose, an additional dose should be considered.
- IGIV is not specifically recommended by ACIP for PEP in patients not already receiving IGIV therapy.
- Anecdotal reports suggest IGIV is commonly used when IGIM is not readily available, for immunocompentent as well as immunocompromised patients.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- IGSC is not mentioned in ACIP recommendations.

Information regarding the current ACIP MMR recommendations for PEP IG is as follows:

- Administration of IGIM to susceptible household contacts who are not vaccinated within 72 hours of initial exposure is recommended. Throughout the recommendations, exposure is listed as "household exposure," which needs to be addressed because there is no mention of other types of exposures.
- The usual recommended dose of IGIM is 0.25 mL/kg (0.11 mL/lb) of body weight to a maximum dose of 15 mL. However, the recommended dose of IGIM for immunocompromised persons is 0.5 mL/kg of body weight with a maximum dose of 15 mL). The maximum dose of 15mL is one of the major limitations of using IGIM because it limits the amount of antibody that can be administered.
- IGIM is indicated for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged < 12 months, pregnant women, or immunocompromised persons).

The current ACIP MMR recommendations for PEP IG for infants state the following:

- Infants < 6 months of age are usually immune because of passively acquired maternal antibodies. However, if measles is diagnosed in a mother, unvaccinated children of all ages in the household who lack other evidence of measles immunity should receive IG. IG prophylaxis is not indicated for household contacts who have received a dose of measles vaccine on or after the first birthday, unless they are immunocompromised.

There are very few studies of PEP efficacy in the US in the vaccine era. Following an exposure in a neonatal intensive care unit (NICU) in 1990 in Ohio*, 21 infants had pre-PEP measles antibody titers tested by ELISA, PEP with Gamastan 0.25 ml/kg, and a second blood sample drawn 48 hours later. Of the 15 infants who were seronegative initially, only 2 were seropositive at 48 hours post-PEP, and 2 who had initial equivocal titers became seropositive. In another study during the measles resurgence from 1989 through 1991 in California+, a retrospective secondary attack rate (AR) study was conducted of unvaccinated household contacts <1 month to 22 months of age. There was an attack rate of 15/23 (66%) in children who did not receive IGIM, and 3/5 (60%) in children who received IGIM within 6 days post-exposure (PE 8%). The IGIM doses were not recorded in this study [*Subbarao EK, et al. Post-exposure prophylaxis for measles in a neonatal intensive care unit. J Pediatr. 1990 Nov;117(5):782-5; +King GE,et al.. Clinical efficacy of measles vaccine during the 1990 measles epidemic. Pediatr Infect Dis J. 1991 Dec;10(12):883-8].

One of the most interesting studies was conducted in Japan (1999-2000) by Endo et al* in which the investigators assessed 33 unvaccinated infants (mean age 1.5 years) who were given Japan's recommended IGIM dose of 0.33 mL/kg within 5 days of measles exposure. Their exposure was >1 hour in the same room with an infectious patient. After the fact, neutralizing antibody concentrations were determined in IGIM lots used for the PEP. The measles attack rates varied according to the titer in the lots, with 8/14 (57%) among infants given IGIM from lots with 16 IU/mL, (5.28 IU/kg); 1/6 (17%) among infants given IGIM with 33 IU/mL, (10.89 IU/kg); and 0/13 (0%) among those given IGIM with 40 or 45 IU/mL (13.2 IU/kg). Dr. Papania tried to translate this into IU/kg, given that there are so many formats of the dose. Protected children received a mean dose of 10.9 IU/kg (SD 3.4) compared to 5.7 IU/kg (SD 1.6) for whom PEP failed.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

In 2006, a study was conducted in New South Wales following a measles outbreak that identified 553 exposed individuals. These investigators used a very loose definition of exposure that included being in the same room as a case even up to 2 hours after the case had left. They were defined as susceptible by Australian guidelines, which also included children >4 years of age and adults who had received one dose of measles vaccine. In Australia, the recommended dose is 0.2 ml/kg IGIM (no maximum volume listed), with an estimated concentration of 32 IUml. This would be a dose of 6.4 IU/kg. They showed a very high protective efficacy of 75% overall, and if the PEP was delivered within 6 days, protection was 100%. The numbers are small [*Endo A, et al. Current efficacy of postexposure prophylaxis against measles with immunoglobulin. J Pediatr. 2001 Jun;138(6):926-8; +Sheppeard V, et al. The effectiveness of prophylaxis for measles contacts in NSW. N S W Public Health Bull. 2009 May-Jun;20(5-6):81-5].

In the US, the FDA requires that all US licensed IGs contain a measles antibody level (neutralizing or HAI) of adequate potency as compared with the US standard.* Plasma from donor populations with predominantly vaccine-induced immunity yields IG with lower measles antibody concentrations.+ Lower antibody concentrations in donor plasma made meeting minimum measles antibody concentration requirements difficult for IGIV and IGSC lots. Much higher volumes of IG can be given by IV and SC routes compared to IM, so the bulk of production is focused on IGIV and IGSC [*Department of Health and Human Services, Food and Drug Administration. Additional Standards for Human Blood and Blood Products (21 CFR Part 640 Subpart J-Immune Globulin (Human). Code of Federal Regulations, Title 21, Volume 7, Revised April 1, 2005. Online at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=640&showFR=1&subpartNode=21:7.0.1.1.7.10; +Audet S, et al. Measles-virus-neutralizing antibodies in intravenous immunoglobulins. J Infect Dis. 2006 Sep 15;194(6):781-9].

In 2007, the FDA Blood Products Advisory Committee lowered the measles antibody concentration requirement for IGIV and IGSC. FDA calculations estimated that products released at minimum potency and given at minimum label recommended dose 200 mg/kg would provide a measles antibody concentration of ≥120 mIU/mL for 28-30 days.* The IGIM minimum measles antibody concentration was not changed [*Department of Health and Human Services, Food and Drug Administration, Blood Products Advisory Committee Meeting Minutes August 16, 2007. Measles Antibody Levels in U.S. Immune Globulin Products Online. Available at: http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4317M.htm Accessed April 28, 2011].

CDC repeated the FDA pharmacokinetics calculations for IGIM at the currently recommended doses, which are reflected in the following table:

Estimates of US Minimum Measles Antibody Dose for Various IG Products

IG Product	Minimum Measles Antibody Potency / mL	Measles Antibody Dose Current Recommendation	Measles Antibody Dose 70kg person
IGIM (0.25 ml/kg)	25.2 IU/mL	6.3 IU/kg	5.4 IU/kg
IGIM (0.5 ml/kg)	25.2 IU/mL	12.6 IU/kg	5.4 IU/kg
IGIV (100 mg/kg)	12.3 IU/mL	12 IU/kg	12 IU/kg
IGIV (200 mg/kg)	12.3 IU/mL	24 IU/kg	24 IU/kg
IGIV (400 mg/kg)	12.3 IU/mL	48 IU/kg	48 IU/kg

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

For IGIM of 0.25 ml/kg, the currently recommended dose, the measles antibody dose would be 6.3 IU/kg, which is very close to the dose in the Endo study that was shown not to be protective. The other difficulty is that these estimates are only for people up to the threshold limit of 15 ml/kg. A 70 kilogram person would still be receiving 15 ml/kg, and their antibody dose would be 5.4 IU/kg. Because the IGIV does are not limited in volume, much higher quantifies of measles antibody can be given.

Again, using the pharmacokinetic calculations from the FDA, CDC tried to assess what titers might be expected in people given the products at the recommended doses. The FDA indicated to Dr. Papania that it is not fair to estimate the peak concentration for IGIM because their formulas are based and validated on IGIV delivery. However, the equilibrium concentration should be valid. At the recommended dose of 0.25 ml/kg, an equilibrium titer at 4 to 5 days after administration would be expected at approximately 63 mIU/mL, dropping to 32 mIU/mL within 30 days. The higher recommended dose for immunocompromised patients of 0.50 ml/kg gives a titer of 126 mIU/mL, just over the 120 mIU/mL defined protective titer. However, this drops to 63 mIU/mL within 30 days. The lower end of the current ACIP recommendation for IGIV of 100 mg/kg also has somewhat lower titers. The label recommendation for IGIV of 400 mg/kg offers a sustained high titer for the duration. In terms of the effect of the IGIM administration dose of 0.5 ml/kg (15 ml maximum dose) on the expected titers by age, once the 30 kg cutoff is reached for a 0.5 ml/kg dose, the titers are progressively lower for people who weigh more.

With regard to the evidence for increased susceptibility to measles among infants in the US, there is epidemiologic evidence that from 2001-2008, infants <12 months of age had the highest incidence of measles among US residents. There were 59 cases with an incidence of 3.5 cases/million. In 2011, there was some increase in measles cases with 29 (13%) of the US measles cases in infants <12 months of age, and 3 in infants < 6 months of age. These represent a fairly high percentage of the US cases even though the numbers are still very low. In 2009, 99.9% of women giving birth in the US were born after 1963, the year measles vaccination began in the US. These women would be expected not to have been exposed to measles and to have either vaccine-induced antibodies or no antibodies. From 2006 through 2008, a study was conducted among infants of vaccinated mothers in Belgium. This was one of the most thorough studies assessing antibody titers in infants. In this study, Leuridan et al found measles antibody titers of < 300 mIU/ml in 30% of infants at birth, which increased to 97% by 6 months of age.* In 2004, Gans et al detected transplacentally derived measles neutralizing antibodies in only 52% (15/29) of 6-month-olds,which decreased to 19% (4/21) by 9 months of age, and no neutralizing antibodies in 12-month-olds (0/83) infants.+ [*Leuridan E, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ. 2010 May 18;340:c1626; +Gans HA, et al. Humoral and cell-mediated immune responses to an early 2-dose measles vaccination regimen in the United States. J Infect Dis. 2004 Jul 1;190(1):83-90].

A quick survey was conducted of state immunization programs in 2011 regarding their use of IGIM PEP to understand what issues they were concerned about, and what was actually being done in the states. This was a convenience sample that included California, New York, New York City, New Jersey, Pennsylvania, Utah, Florida, Virginia, Massachusetts, Texas, and Washington. The state immunization programs have variable roles in IGIM PEP. The estimated IGIM measles PEP doses in 2011 was less than 5 for all states except Pennsylvania (N=93 doses) and New York City (N=74 doses). Pennsylvania spent roughly $30,000 and had many doses remaining. Pennsylvania reported no problems with IGIM supply, while other states said that it is generally available, but distribution can be difficult. At that time, IGIM was

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

on back order, with no doses expected for the rest of 2011. States are not involved in pre-exposure prophylaxis with IGIV and IGSC, and do not recommend IGIV in place of IGIM. All states give IGIM to exposed infants < 6 months of age, and some attempted to determine mother's immunity first. All states give IGIM to persons exposed in any setting, and some assess the duration and setting to make a decision. In terms of issues reported, states asked for clarification on recommendations for infants < 6 months of age and infants 6 through 12 months as to whether there would be a preference for IG versus vaccine PEP and for exposure other than household. States asked for data on the protective efficacy of PEP with IG or vaccine.

Discussion Points

Dr. Baker indicated that the presentation made her wonder whether the recommendation for timing of MMR vaccine in US children may change.

Dr. Marcy noted that in the New South Wales outbreak, 6.4 IU/kg was adequate to suppress measles development, and IGIV was given at 100 mg/kg, 200 mg/kg, and 400 mg/kg, resulting in levels that appeared to be far higher. He was confused that there would be a 3-week interval for 100 mg/kg to 400 mg/kg. In other words, 400 mg/kg would be 200 mg/kg 20 days later given the half-life of IgG. Thus, 100 mg/kg and 400 mg/kg both at 3 weeks made no sense. If willing to tolerate 100 mg/kg good for only 3 weeks, then 200 mg/kg good for 6 weeks and 400 mg/kg good for 12 weeks would have to be tolerated. To say that after 3 weeks this would have to be repeated if exposed to measles does not make sense for all three concentrations.

Dr. Papania responded that one of the recommendations from Judy A. Beeler and the folks at FDA was that the goal is to establish titers of ≥120 IU/mL for healthy patients. The basic dose of 0.25ml/kg for IGIM does not achieve that titer, except potentially as a peak titer. The higher level dose only achieves this titer for as long as 4 to 5 days. The titers said to be protective are really for healthy people. The protective titer for an immunocompromised person is unknown. The IGIV is typically recommended for immunocompromised people. The FDA suggested that it would be best to err on the side of caution and keep their titers much higher for as long as possible.

Dr. Meissner inquired as to whether thought had been given to a hyper-immune globulin for measles, which is used for a number of infectious diseases. However, because demand might not be high, it may be difficult to convince manufacturers that it would be worthwhile.

Dr. Papania agreed that this could help to solve some of the problems, and that the FDA is currently working with a manufacturer to try to boost the concentrations available in the current product. There is not currently a licensed hyper-immune globulin for measles, and the market is very thin so it may be difficult to develop one.

Dr. Pickering said he thought that for IGIV the requirements for titers were only for hepatitis B, polio, and diphtheria and that the measles titers were estimates. There is a major amount of variability among products and among lots from the same companies, so when IGIV is administered, it is not really clear how much antibody is being given for measles.

Dr. Papania replied that the FDA tests lots for measles antibody titers and they have to meet a measles antibody requirement for IGIV and all IG products.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Baker reported that she controls IGIV use in the largest children's hospital in the US, most of which is for Kawasaki Disease, Guillain–Barré Syndrome (GBS), and neurologic conditions. Nobody uses a lower dose than 400 mg/kg because they want to err on the side of caution. However, this drives the costs up considerably. This is a very expensive product. Compared to 5 or 6 years ago when it was on short supply due to some of the military requirements for IGIV, it is quite expensive to choose between these doses.

Ms. Stinchfield (NAPNAP) found this presentation to be very interesting and helpful, especially given that in 2011 Minnesota had the most measles cases. She was in the undesirable position of having to call 35 families of the 788 who were exposed to inform them that they were exposed to measles in the emergency department, and to request that they return for IG. The two hours afterwards in the room is a fairly typical exposure definition. She thought step one should address what constitutes an exposure, because that is going to determine whether someone will need prophylaxis products. Once the exposure is defined, a decision can be made about what to do for the exposed population. Having other products at the time would have been nice, and being able to clarify ACIP's recommendations on this would be very good. IGIM and IGIV are two very different procedures. IGIV requires admission, observation, and a good day in a short stay unit. Therefore, it is important to give consideration to these differences as well.

Dr. Baker emphasized the importance of this area for enlightenment through further evidence, especially with pockets of measles. The US immunization rates may be very high, but there are pockets of susceptibles who seem to live in closed communities.

Review of Policy Considerations Pertaining to MMR Vaccine

Huong McLean, PhD, MPH
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. McLean summarized the proposed policy considerations pertaining to the prevention of measles, mumps, and rubella, in preparation for an ACIP vote in October. For acceptable presumptive evidence of immunity, the propose changes are to include "laboratory confirmation of disease," remove "physician diagnoses of disease" as a criteria for measles and mumps, and to clarify that age-appropriate vaccination supersedes serologic testing. The rationale behind these changes is that the validity of disease history is low, especially over the last 30 years; there are challenges with documenting history from physician records for adults; and to be consistent with the recently published recommendations for health-care personnel.

For consistency with recommendations for healthcare personnel, as evidence of immunity the working group proposed to include laboratory confirmation of disease for all three diseases for completeness, and remove documentation of physician diagnosis for measles and mumps. The same changes are proposed for students at post-high school education and international travelers:

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Acceptable Evidence of Immunity
Routine

	Current	Proposed
Measles	(1) documentation of adequate vaccination: - preschool-aged-children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed measles~~	(1) documentation of age-appropriate vaccination with a live measles virus-containing vaccine: -children age 1-4 years: 1 dose -school-aged children (grades K-12, age 5-18 years): 2 doses -adults not at high risk: 1 dose, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957 (except women of childbearing age who could become pregnant)
Mumps	(1) documentation of adequate vaccination with live mumps virus vaccine: - preschool-aged children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed mumps~~	(1) documentation of age-appropriate vaccination with a live mumps virus-containing vaccine: -children age 1-4 years: 1 dose -school-aged children (grades K-12, age 5-18 years): 2 doses -adults not at high risk: 1 dose, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957

4

Acceptable Evidence of Immunity
Students at Post-High School Educational Institutions and International Travelers

	Current	Proposed
Measles	(1) documented administration of 2 doses of live measles virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed measles~~	(1) documentation of vaccination with 2 doses of live measles virus-containing vaccine, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus, vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957 (except women of childbearing age who could become pregnant)
Mumps	(1) documented administration of two doses of live mumps virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed mumps~~	(1) documentation of vaccination with 2 doses of live mumps virus-containing vaccine, or (2) laboratory evidence of immunity, or (3) **laboratory confirmation of disease**, or (4) born before 1957

5

For measles and mumps, it is not recommended that persons who have two documented doses of vaccine receive an additional dose of MMR vaccine if their subsequent serologic results are negative or equivocal.

For rubella, the same is true if a person has one documented dose of rubella containing vaccine, except for women of childbearing age. For vaccinated women of childbearing age, 1 additional MMR vaccine dose can be given if subsequent serologic test results are not positive.

For persons with HIV infection, the proposed changes are to remove the distinction between asymptomatic and symptomatic HIV infection, change the timing of the two doses to 12 through 15 months and 4 through 6 years; include recommendations for revaccination of persons with perinatal HIV infection who were vaccinated prior to effective Highly Active Antiretroviral Treatment (HAART); and expand the current recommendation to vaccinate close contacts of HIV-infected persons to all immunocompromised persons with 2 doses of MMR vaccine. Reasons for these changes are that with "symptomatic" staging, one cannot be restaged to a less severe stage; availability of HAART has improved immune status of patients; and immunocompromised persons are also at high risk for severe complications if infected with measles through their close contacts.

As a reminder, the current recommendations for persons with HIV infection is shown here, which distinguishes between asymptomatic and symptomatic infection:

- ❑ MMR vaccination is recommended for all asymptomatic HIV- infected persons who do not have evidence of severe immunosuppression and for whom measles vaccination would otherwise be indicated.
- ❑ MMR vaccination should also be considered for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression.
- ❑ Measles vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression.

The proposed recommendations would be based on the current status:

- ❑ Two doses of MMR vaccine is recommended for all persons aged ≥12 months with HIV infection who do not have evidence of current severe immunosuppression (i.e., must have CD4≥15% in the prior 6 months) or other current evidence of measles, rubella, and mumps immunity.
- ❑ MMR vaccine is not recommended for HIV-infected persons with current evidence of severe immunosuppression.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

With regard to timing, the current recommendations recommends the first dose as soon as possible upon reaching the first birthday and consideration to administering the second as soon as 28 days after the first dose:

- HIV-infected infants without severe immunosuppression should routinely receive MMR vaccine as soon as possible upon reaching the first birthday (i.e., at age 12 months).
- Consideration should be given to administering the second dose of MMR vaccine as soon as 28 days (i.e., 1 month) after the first dose rather than waiting until the child is ready to enter kindergarten or first grade.

The proposed recommendation would be to have the first dose administered at age 12 through 15 months and the second dose at age 4 through 6 years, the same schedule as uninfected children:

- The first dose of MMR vaccine should be administered at age 12 through 15 months and the second dose at age 4 through 6 years, or as early as 28 days after the first dose.

For children and adolescents with perinatal HIV infection who were vaccinated prior to effective HAART, the work group recommends that these children and adolescents be revaccinated with two doses of MMR vaccine once effective HAART has been established:

- Children and adolescents with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine prior to establishment of effective HAART should be considered unvaccinated and should be revaccinated with two doses of MMR vaccine once effective HAART has been established (≥6 months with CD4≥15%), unless they have other acceptable current evidence of measles, rubella, and mumps immunity.

As follows are the current and proposed recommendations for vaccination of household and close contacts of immunocompromised persons. The current recommendations only specifies contacts of HIV-infected persons, so the proposed recommendation is to include all family and close contacts of all immunocompromised persons and specifies two doses of MMR vaccine:

Current Recommendation

- All family and other close contacts of HIV-infected persons should be vaccinated with MMR vaccine, unless they have acceptable evidence of measles immunity.

Proposed Recommendation

- All family and other close contacts of immunocompromised persons should receive two doses of MMR vaccine unless they have other evidence of measles immunity.

Discussion Points

Dr. Baker emphasized the importance of using the word “through” or “to” in recommendations, depending upon the intent, instead of dashes.

Regarding women of childbearing age and proposed evidence of rubella immunity and subsequent testing, Dr. Hahn (CSTE) said she would interpret the first bullet to mean that women of childbearing age who have had one dose might be recommended to receive the vaccine, but it is stated as a double-negative, “In the event that a person (except women of

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

childbearing age) who has one dose of rubella-containing vaccine is tested serologically and is determined to have negative or equivocal rubella titer results, it is not recommended that the person receive an additional dose of MMR vaccine. Such persons should be considered to have presumptive evidence of immunity." The second bullet states that "vaccinated women of childbearing age can be administered," which is a soft recommendation. To be clear that women who have only one dose should receive the vaccine, that needs to be pulled out as a separate bullet and clearly stated.

Dr. Wallace (SME) said that the thinking behind this was that even though there is a routine two-dose MMR recommendation, for rubella the evidence of immunity is based on one dose. Much of this has to do with women who receive routine prenatal screening and are negative. This raises questions about how many times they should be revaccinated for rubella before stopping. He agreed that the statement could be made clearer.

Regarding the proposed recommendations for timing of the second dose for persons with HIV infection, Dr. Sawyer requested clarity about the rationale for moving the second dose to 4 through 6 years of age with a permissive recommendation to give it at 28 days.

Dr. McLean replied that since there is very low risk of exposure to measles in the US, the working group thought that giving both doses to HIV-infected persons within the first year may set them up for failure later. If the second dose is delayed to 4 through 6 years, HIV-infected persons would be on HAART longer and would be more likely to respond to a second dose. Those at risk of exposure due to travel would follow the travel recommendations.

Dr. Wallace added that the working group had some discussion with HIV experts, who said that with effective HAART, HIV-infected individuals should be treated more like a non-immunocompromised person. The HIV experts expressed concern about giving those two doses and the potential for waning immunity issues with mumps or other diseases. This is the recommendation for immune competent individuals, who can receive the second dose of vaccine 28 days after the first dose. Those who are immunocompromised who plan to travel are recommended to receive vaccine like anyone else.

Dr. Keitel requested information regarding how these recommendations would be made to HIV-infected adults and the definition of "immune suppression" in adult patients with HIV.

Dr. McLean responded that the working group has not discussed these recommendations in adults. The data show that for adults who were vaccinated and had antibody prior to developing HIV, susceptibility is not increased.

Dr. Marcy pointed out that "can be administered" implies that there is a criterion for administering the vaccine, and he asked what the criterion was. Without making a statement about this, physicians would be left not knowing what to do. He also wondered whether there would be a separate recommendation for bone marrow transplant patients.

Dr. Wallace replied that this was not stipulated, given that the conversation occurs between the doctor and the patient. He said he would not be uncomfortable if it was agreeable with others to state "should be." He indicated that the working group had not discussed having a separate recommendation for bone marrow transplant patients.

Dr. Keyserling (SHEA) indicated that the recommendation for bone marrow transplants is addressed. He thought it was to wait two years and then to give two doses.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Currently, there are no recommendations for a third dose of MMR vaccine for mumps outbreaks. The working group proposed a permissive recommendation because large mumps outbreaks have occurred among highly 2-dose vaccinated populations, standard outbreak control measures have not prevented some very large outbreaks, and a permissive recommendation would provide an additional tool for outbreak control. The proposed recommendation would be as follows:

- ❑ During mumps outbreaks, authorities may consider administering a third dose of MMR vaccine.

- ❑ Criteria to be considered include:
  - High 2-dose vaccination coverage (i.e., >90%)
  - Intense exposure settings (e.g., schools, colleges, correctional facilities, or congregate living facilities)
  - High attack rates (e.g., > 5 cases per 1,000 population)
  - On-going transmission for at least two weeks in the target population (i.e., population with the high attack rates)

A third dose of MMR vaccine may be considered for health-care personnel; however, routine use of a third dose of MMR vaccine is not recommended. This proposed recommendation is as follows:

- ❑ A third dose of MMR vaccine may also be considered for health-care personnel during mumps outbreaks given the higher risk of exposure to disease and those at higher risk of complications.

- ❑ Routine use of a third dose of MMR vaccine is not recommended.

Discussion Points

Dr. Sawyer recalled that based on the presentations from the February ACIP meeting, there was not convincing evidence that a third dose helped. Therefore, he wondered why consideration was being made for this recommendation.

Dr. Temte indicated that the two situations in question were Orange County and Guam, and by the time the third dose was initiated, it seemed as though the outbreaks had peaked. He thought the working group's response was due to requests from public health for the possibility of intervening in such situations. The working group was also cognizant of an apparent lack of any significant safety signal, though there were small sample sizes in both cases. The third dose seemed to be at least a tool that could be used to intervene. Dr. Temte stressed that this recommendation is made on the basis of expert opinion at the very best.

Dr. Wallace (SME) added that no evidence was found that was compelling enough to make a statement that a third dose "should" be given in all situations that have these criteria. However, they are receiving many requests and a third dose has been used in some situations. Offering this opportunity may have some impact, so CDC wants to provide some criteria for those considering this option.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Campos-Outcalt pointed out that based on the new wording, this would be a Category B recommendation. It was not clear whether GRADE criteria would be used, given that this was an older recommendation, but he reminded everyone of the effort not to use permissive language.

Dr. McLean responded that this issue could be reviewed.

Dr. Sawyer asked Dr. Duchin and Ms. Ehresmann to comment on whether they would interpret this to mean that a third dose should be administered, or whether they would feel some liability if their health departments decided not to do so and someone subsequently developed disease.

Dr. Duchin said it was unclear to him whether doing so would be helpful. Health departments may feel pressure from people to use the vaccine in the absence of strong evidence that it is effective. The use of vaccine during an outbreak situation is not trivial, given that it requires the mustering of resources and cost. He requested a reminder of the rationale suggesting that it would be helpful. He did not recall any data that was presented to suggest that this could be a useful intervention.

Ms. Ehresmann took a different perspective. She thought that the perspective Minnesota would take of this recommendation is that it would allow them to use this as a potential tool, and they would most likely be interested in collecting data to determine what effect, if any, this may have had on an outbreak. However, she did not want to discount what Dr. Duchin pointed out about the effort involved in a vaccination program. In a difficult situation such as an outbreak, this may not be the perfect tool, but at least it would be an option. In the absence of a recommendation such as this, that would be much more challenging.

Dr. Duchin inquired as to whether it was necessary to have a permissive recommendation in order to use a third dose and evaluate it in a field setting.

Dr. Hahn (CSTE) remembered from the presentations that one of the challenges is the length of time to get an outbreak vaccination program running, because there is no recommendation. While she understood the possible pressure to use vaccine when there is very weak evidence, but if they planned to try administering a third dose, it needed to be observed a few times during outbreaks and then there would be data. The recommendations could always be changed later.

Dr. Wallace (SME) said this is why the working group tried to bring some criteria into this issue. There was significant discussion during the last meeting regarding whether there should be strict criteria. They wanted to try to provide guidance so that this strategy would not be used every time three mumps cases were observed, but rather would be applied in sustained outbreak situations.

Dr. Baker asked whether HAART had been replaced with ART.

Dr. Zahn (NACCHO) agreed with Dr. Hahn that a statement would be useful. From a public health standpoint, people are aware that these events have occurred, particularly the New York event. If there is a long-term outbreak, the question about whether to administer a third dose of MMR is going to arise. The pressure exists to some degree already, so some guidance and a statement about that from ACIP would be useful.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Dr. Zucker (NYC Immunization Program) indicated that as the site with the largest number of cases during the outbreak, they would not need to have permissive recommendations and it would make the decision process much more difficult within the health department. The issue is in regard to when to administer the third dose. Once there is sustained transmission and an outbreak is on-going, by the time mobilization begins, the outbreak is likely to be near or at its peak and vaccination will be less efficacious. She thought that was the issue with some of the data that were presented. She was concerned that the recommendation would create pressure to institute a vaccination campaign. The discussion at the local level in New York City was that because the outbreak was nearing its peak, there seemed to be no point in implementing a large scale vaccination campaign. Therefore, she would not be in favor of this recommendation.

Dr. Baker expressed confusion. It seemed to her that this recommendation would allow health departments to move ahead with a third dose campaign and mobilize resources without having to engage in long discussions about it.

Regarding the issue of third doses for healthcare workers during a mumps outbreak versus routinely, Dr. Keyserling (SHEA) pointed out that the way the recommendation was written, it states during an outbreak not universally for all cases. The idea is to prevent transmission to immunocompromised patients in the hospital by healthcare personnel. He suggested that consideration be given to changing the recommendation to “healthcare workers exposed to a documented case of mumps should be immunized” rather than “during an outbreak.”

Dr. McLean said that this was more of a PEP question, but mumps vaccine has not been found to be as effective as PEP. A statement is included that offers facilities an option to give a third dose of MMR vaccine to healthcare personnel during an outbreak.

Dr. Campos-Outcalt said that this was an instance in which a description of the evidence would be helpful because different people will react differently, as will various jurisdictions. Describing the evidence would help people to understand what went into the thinking behind the recommendation and what the evidence behind it really is.

Dr. Duchin expressed concern about the precedent of issuing a recommendation before there is evidence that the intervention is useful. There are also implications for pertussis vaccine. What he would be thinking about with a recommendation like this would be the consideration of using pertussis vaccine during a pertussis outbreak. It was not clear to him where the line should be drawn and how much data would be needed before empirically administering extra doses of vaccines.

Dr. Elward (HICPAC) thought the current wording of the recommendation offered flexibility in the absence of data that this is effective for PEP.

Dr. Temte looked at some previous slides showing several epi-curves from Orange County, various colleges in Iowa, and so forth. Using the threshold that had been mentioned, he pointed out that this did not mean an outbreak was almost over. Actually, it is at the beginning. In Orange County, the outbreak continued for another 8 weeks after the threshold was reached. In some of the other cases, the outbreaks continued for 2 to 3 weeks after the threshold was reached. Many of these cases occurred in the confines of college campuses. He thought the recommendation offered a tool that may be beneficial. He thought there had also been some discussion about the limitation in Guam of going outside of protocol in terms of collecting data and having to seek IRB approval, which slowed progress down such that the peak had occurred.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Ms. Ehresmann added that off-label use for an individual clinician for an individual patient is very different from an off-label use in a public health setting. This recommendation allows for that use without the need for IRB approval, and allows for a much speedier response. She valued the recommendation because of its permissive nature.

Dr. Marcy suggested that since the permissive recommendation appeared to put pressure on some people, adding what was stated for healthcare workers, "Routine use of a third dose is not recommended." That would protect those who do not want to use it, but offers permission to those who do.

Dr. McLean indicated that the statement regarding routine use would be included in the section about administering a third dose, which will address use during outbreaks and for healthcare workers.

Dr. Moore (AIM) thought this seemed like the perfect opportunity for Epi-Aids. She encouraged CDC to continue to send Epidemic Intelligence Service (EIS) officers to investigate where the third dose option is used in order to collect the data needed to make a real recommendation. She recognized that the issue of IRB obstructs the ability to respond effectively when contending with an outbreak, and that this needs to be implemented, so perhaps something other than a permission recommendation is the way to handle that issue while collecting the information needed to make a recommendation based on real data showing whether administering a third dose works or does not.

Regarding measles post exposure prophylaxis, Dr. McLean reported that the proposed changes were to remove wording that limits use to exposure settings, increase the recommended dose of IGIM, include use of IGIV, and recommend the use of IG for all infants aged <12 months. The changes will simplify recommendations, and account for changes in measles antibody concentrations in IG due to changes in donor demographics and the availability of multiple IG preparations, and increased measles susceptibility at younger ages in infants.

The current recommendations for use of IG as post-exposure prophylaxis limits use to household contacts, and states that infants less than 6 months of age are usually immune:

- IG is indicated for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged <12 months, pregnant women, or immunocompromised persons).

- Infants <6 months of age are usually immune because of passively acquired maternal antibodies. However, if measles is diagnosed in a mother, unvaccinated children of all ages in the household who lack other evidence of measles immunity should receive IG.

The proposed recommendations would remove the wording that limits use to "household contacts," and a statement would be added to include consideration if exposure to measles is likely to result in infection:

- IG is indicated for close contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged <12 months, pregnant women, or immunocompromised persons).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

- Administration of IG to unvaccinated close contacts who do not have other evidence of measles immunity may be considered if their exposure to measles is likely to result in infection (e.g., household, daycare, classroom, etc.).
  - Use of vaccine within 72 hours of initial exposure is also acceptable.

Specific recommendations are given regarding which type of immune globulin should be used for those at higher risk for complications. For infants aged <12 months, IGIM should be given, but MMR vaccine is an acceptable alternative for infants over 6 months of age if given within 72 hours of exposure. The proposed language for the recommendation is as follows:

- IGIM should be given to infants <12 months of age who have been exposed to measles.

- For infants 6 through 11 months of age, MMR vaccine is an acceptable alternative to IG, if given within 72 hours of exposure.

For pregnant women, either IGIM or IGIV can be used. However, there was not a majority opinion in the working group: 50% thought that there should be no preference for IGIM or IGIV, 30% thought that there should be a preference for IGIV; and 20% thought that there should be a preference for IGIM.. The proposed language for the recommendation is as follows:

- IG should be given to pregnant women without evidence of measles immunity who have been exposed. Either IGIM or IGIV can be used.

For immunocompromised patients, IGIV is recommended. Also, a statement will be included for patients who are currently receiving subcutaneous immune globulin therapy. The proposed language for this recommendation is as follows:

- Severely immunocompromised patients* who are exposed to measles should receive IG prophylaxis regardless of vaccination status because they may not be protected by the vaccine. For these patients, IGIV is recommended.

- For exposed immunocompromised patients receiving subcutaneous immune globulin (IGSC) therapy, administration of at least 200 mg/kg body weight for two consecutive weeks before measles exposure should be sufficient.

  *Including HIV-infected persons with CD4<15% and those who have not received MMR vaccine since receiving effective HAART. Some experts would include all HIV-infected persons, regardless of immunologic status or MMR vaccine history.

With regard to the dose of IGIM, the current recommendation has different recommendations depending on immune status. The proposed dose will be 0.5 mL/kg of body weight for everyone, the maximum dose according to the label:

- **Current Recommendations**
  The usual recommended dose of IG is 0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL). The recommended dose of IG for immunocompromised persons is 0.5 mL/kg of body weight (maximum dose = 15 mL).

- **Proposed Recommendations**
  The recommended dose of IGIM is 0.5 mL/kg of body weight (maximum dose = 15 mL).

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

For IGIV, the current recommendation states that a dose of 100-400 mg/kg should be sufficient. To simplify, the proposed recommended dose for IGIV is 400 mg/kg, the typical dose of most immunocompromised patients, instead of a range. The current and proposed language are as follows:

Current Recommendations

- For patients receiving IGIV therapy, a standard dose of 100-400 mg/kg should be sufficient to prevent measles infection after exposure occurring within 3 weeks after administration of IGIV.

Proposed Recommendations

- The recommended dose of IGIV is 400 mg/kg.

Similar to the IG recommendations, the current recommendations for vaccine as post-exposure prophylaxis includes exposure setting, so to simplify, the proposed recommendation for use of post exposure prophylaxis would not include exposure setting:

Current Recommendations

- For most persons aged ≥12 months who are exposed to measles in most settings (e.g., day care facilities, schools, colleges, health-care facilities), administration of MMR or measles vaccine is preferable to using immune globulin (IG).

Proposed Recommendations

- For persons aged ≥12 months who are exposed to measles, MMR vaccine is preferable to using immune globulin (IG).

Discussion Points

Referring to slide 23 and the phrase “may be considered,” Dr. Marcy inquired as to what considerations would warrant the administration of IG to these unvaccinated close contacts. The basis on which IG can be given is not indicated, which leaves the question hanging without giving the considerations. “May be considered” is deadly for clinicians.

Dr. McLean responded that currently, states vary. Some states give IG to everyone who is exposed who they are not able to vaccinate. The goal is to have a priority list so that those who are at the highest risk for complications receive IG. For those who are very close contacts who are not vaccinated within 72 hours, IG can be considered. They were trying to give some flexibility because sometimes IGIM may not be available, and there are other considerations such as cost.

Dr. Marcy pointed out that if IGIM was not available, there would be nothing to consider. He strongly objected to “may be considered,” and suggested that it be removed or that criteria be included.

Dr. Wallace (SME) clarified that the consideration is really the exposure setting. He thought changing the language of “may be considered” would be doable. Unfortunately, as with mumps, what has been observed is that some health departments give IG indiscriminately, which is not believed to be necessary. Others need the ability to prioritize. The goal has always been to focus on those who are at the highest risk of complications in the first bullet, and that has always been the emphasis. However, there is a need to recognize that there will be some situations, such as the homeless shelters in Minnesota in which many people were not

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

vaccinated and they needed to ability to give IG because that was what was sustaining their outbreak. A specific reason and specific setting for giving IG was the thinking behind these recommendations.

Dr. Hahn (CSTE) pointed out that while Dr. Marcy read the recommendation as being geared toward clinicians, she read it as being for public health to consider on a population level. She suggested rewording the recommendation to make this more clear.

Dr. Schuchat thought the second bullet meant that this group may be considered if the exposure was likely to result in transmission, not in infection. Anyone without immunity who is exposed will be infected, so the focus would be on where there would be on-going public health issues.

Ms. Ehresmann said she interpreted the recommendation as being directed toward public health as well.

Ms. Stinchfield (NAPNAP) pointed out that infection control departments would look to these recommendations as well to determine who is defined, what should be done, et cetera. Because this would be the guidance in a hospital setting as well, she did not favor stating that the recommendation was for public health. She thought leaving the recommendation more generic would be helpful.

Dr. Sawyer said he was seeking a clear distinction between the two bullets. If he understood the recommendation, the first bullet was intended to state that this population “should” receive immune globulin and the examples were all people who could not receive vaccine. He wondered whether the first bullet was meant to relate only to people who could not receive vaccine, and if not, he wondered where a group who could receive vaccine would fit. The second bullet appeared to be a permissive recommendation for those not in that category.

Dr. McLean replied that Dr. Sawyer’s interpretation was correct for the most part. Immunocompromised persons could also include those with HIV infection who would technically be able to receive vaccine routinely if they are not severely immunocompromised.

Dr. Sawyer asked whether the document would stipulate when and where vaccine plays a role versus immune globulin, or both.

Dr. McLean responded that this would be included.

Dr. Campos-Outcalt requested further clarification about whether the first bullet meant regardless of vaccine status.

Dr. McLean responded that for pregnant women it would be those without evidence of immunity, so they would be susceptible essentially. Pregnant women with an adequate vaccine history would not need IG. For immunocompromised persons, it would be regardless of vaccine status.

Regarding exposure in healthcare facilities, Dr. Elward (HICPAC) pointed out that there is some variability in how people define exposure and they usually work with the state health department to determine what constitutes an exposure.

Dr. McLean replied that there is guidance in the CDC Vaccine-Preventable Disease Manual that would help states.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Regarding the recommendation for immunocompromised persons who have been exposed, to Dr. Duchin the second bullet read like a recommendation for any susceptible person to receive IG. He thought the recommendation needed further clarification.

Ms. Ehresmann said she viewed the examples as being more about closed settings with close, intense exposures versus the Mall of America.

Dr. Temte thought the distinction was between those individuals known to have a high likelihood of bad outcomes from measles and those individuals who may have some disease from measles, but do not tend to be the people who are hospitalized or die due to measles. He thought the language could be revised to read, "Immune globulin may be administered to unvaccinated . . ." He agreed that the recommendation should not be to think about something. It needs to be a recommendation to do something.

Dr. Jenkins wondered whether any of this was covered in the *Red Book*. It seemed as though they were trying to give direction to the public health community, but she wondered whether clinicians were aligned with this as well.

Dr. Pickering replied that generally, harmony is achieved, so changes would be placed in the *Red Book* Online and would automatically be sent to all members.

Dr. Moore (AIM) pointed out that the use of vaccine seemed to be an afterthought in the recommendation. She wondered whether the intent was for IG to be preferred in these situations. From a health department immunization program perspective, if they could reach someone within 72 hours, it would be preferable to administer the vaccine due to expense and the long-term benefit of protection.

Dr. McLean replied that for the general population, vaccine would be preferred over IG. The sub-bullet was included because household members are typically exposed for 4 days before there is a rash or measles is diagnosed.

Dr. Moore (AIM) thought it should be made clear that if someone could be reached within 72 hours, vaccine use would be preferable, understanding the time limitations.

Dr. Schaffner (NFID) supported harmonization with the *Red Book*, but the second bullet of the recommendation applies to adults, so regardless of what is in the *Red Book*, it should be made clear in ACIP's document.

Dr. Baker agreed, emphasizing that pregnant women are in a class by themselves.

Ms. Stinchfield (NAPNAP) suggested including definitions for close contacts, settings, immunosuppressed, et cetera. If examples are to be included, she suggested listing healthcare settings because they are a common setting for transmission and are full of immunocompromised people.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Day 2: Public Comment

No public comments were offered on the second day of the June 2012 meeting.

Dr. Pickering noted that at the close of the June ACIP meeting, 13 ACIP members and 5 *ex officio* members were present.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Certification

Upon reviewing the foregoing version of the June 20-21, 2012 ACIP meeting minutes, Dr. Carol Baker, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

ACIP Membership Roster

CHAIR
BAKER, Carol J., M.D.
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX
Term: 07/01/06 - 06/30/12

EXECUTIVE SECRETARY
PICKERING, Larry K., M.D.
Executive Secretary
ACIP
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

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Chapel Hill, NC
Term: 10/04/10-06/30/14

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

EHRESMANN, Kristen R., R.N., M.P.H.
Director
Infectious Disease Epidemiology, Prevention and Control Division
Minnesota Department of Health
St. Paul, MN
Term: 07/01/2008 – 06/30/12

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

KEITEL, Wendy A, M.D.
Professor
Molecular Virology and Microbiology and Medicine
Baylor College of Medicine
Houston, TX
Term: 07/01/09-06/30/13

MARCY, S Michael, M.D.
Clinical Professor of Pediatrics
University of Southern California
University of California Los Angeles
Schools of Medicine
Los Angeles, CA
Term: 07/01/2008 – 06/30/12

MEISSNER, H. Cody, M.D.
Professor of Pediatrics
Tufts Medical Center
Boston, MA
Term: 07/01/2008 – 06/30/12

ROSENBAUM, Sara, J.D.
Harold and Jane Hirsh Professor of Health Law and Policy
Department of Health Policy
George Washington University

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Washington, DC
Term: 01/01/10-06/30/13

SAWYER, Mark H., M.D.
Professor of Pediatrics
University of California, San Diego School of Medicine
San Diego, CA
Term: 04/23/08-06/30/12

TEMTE, Jonathan, 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

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)
Mary Beth Hance
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

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Food and Drug Administration
Rockville, MD

Health Resources and Services Administration (HRSA)
EVANS, Geoffrey, M.D.
Director
Division of Vaccine Injury Compensation
Healthcare Systems Bureau
Health Resources and Services Administration
Rockville, MD

Indian Health Service (IHS)
Amy Groom, 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

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, M.P.H., PA-C
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
Clinical 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)
LITJEN (L.J) Tan, M.S., Ph.D.
Director, Medicine and Public Health
American Medical Association
Chicago, IL

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

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., F.A.Ph.A.
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

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

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

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, M.D., M.P.H.
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., CPNP
Director
Pediatric Infectious Disease and Immunology Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

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
RICHARDSON, Vesta, M.D.
Director, National Center for Child and Adolescent Health
Ministry of Health - Mexico
Colonia Merced Gomez

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf

Mexico, D.F., Mexico

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, M.D.
Professor and Interim 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

This document has been archived for historical purposes. (7/1/2012)
https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun12.pdf