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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 21, 2015
Atlanta, Georgia

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329

October 21, 2015 (1-day meeting)

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, October 21st			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Ray Strikas (Acting ACIP Executive Secretary; CDC)
8:30	**Agency Updates** CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	CDC and *ex officio* members
8:45	**Child and Adolescent Immunization Schedule**		
	Introduction	Information, Discussion	Dr. Jose Romero (ACIP, WG Chair)
	2016 child and adolescent immunization schedule	**Vote**	Dr. Candice Robinson (CDC/NCIRD)
9:30	**Adult Immunization Schedule**		
	Introduction	Information & Discussion	Dr. Kathleen Harriman (ACIP, WG Chair)
	Erratum in 2015 adult immunization schedule		Dr. David Kim (CDC/NCIRD)
	2016 adult immunization schedule update	**Vote**	
10:00	***Break***		
10:30	**Meningococcal Vaccines**		
	Introduction	Information & Discussion	Dr. Lorry Rubin (ACIP, WG Chair)
	Serogroup C outbreak among men who have sex with men (MSM), Chicago, 2015		Dr. Sarah Kemble (Chicago DPH)
11:15	**Influenza**		
	Introduction		Dr. Ruth Karron (ACIP, WG Chair)
	Epidemiology and surveillance Update		Ms. Lynnette Brammer (CDC/NCIRD)
	Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older	Information & Discussion	Dr. Ayman Chit (Sanofi Pasteur)
	Adjuvanted trivalent influenza vaccine		Dr. Kelly Lindert (NVS Influenza Vaccines)

12:15	**Vaccine Supply**		Dr. Jeanne Santoli (CDC/NCIRD)
12:20	***Lunch***		
1:35	**Human Papillomavirus (HPV) Vaccines**		
	Introduction		Dr. Allison Kempe (ACIP, WG Chair)
	HPV vaccine coverage in the US, NIS-Teen 2014		Dr. Sarah Reagan-Steiner (CDC/NCIRD)
	Programmatic strategies to increase HPV vaccine coverage	Information	Dr. Robin Curtis (CDC/NCIRD)
	Update on HPV vaccine safety	& Discussion	Dr. Lakshmi Sukumaran, (CDC/NCEZID)
	Monitoring impact of the HPV vaccination program		Dr. Lauri Markowitz (CDC/NCHHSTP)
	HPV Vaccines Work Group plans		Dr. Lauri Markowitz (CDC/NCHHSTP)
2:35	**Japanese Encephalitis (JE) Vaccine**		
	Introduction		Dr. Lorry Rubin (ACIP, WG Chair)
	Change in JE vaccine distributor; immunogenicity in older adults; co-administration with rabies vaccine; alternative dosing schedule	Information & Discussion	Dr. Katrin Dubischar (Valneva)
	JE Vaccine Work Group plans		Dr. Susan Hills (CDC/NCEZID)
3:25	***Break***		
3:50	**Combination Vaccine**		
	Introduction		Dr. Art Reingold (ACIP, WG Chair)
	Pediatric hexavalent vaccine (DTaP-IPV-Hib-HepB), Merck/Sanofi	Information & Discussion	Dr. Andrew Lee (Merck)
4:35	**Cholera Vaccine**		
	Introduction	Information & Discussion	Dr. Art Reingold (ACIP, WG Chair)
	Cholera in U.S. travelers		Dr. Karen Wong (CDC/NCEZID)
5:10	**Ebola Vaccine Trial Update**	Information	Dr. Susan Goldstein, CDC Ebola Response Team
5:45	**Public Comment**		
6:00	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DTaP-IPV-Hib-HepB	Diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenzae type B and hepatitis B
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
MSM	Men who have sex with men
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	CDC National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIH	National Institutes of Health
NIS	National Immunization Survey
NVPO	National Vaccine Program Office
VFC	Vaccines for Children
WG	Work Group

Acronyms Used in This Document

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACA	Affordable Care Act
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ACS	American Cancer Society
AE	Adverse Events
AFIX	Assessment, Feedback, Incentives, and eXchange
AFP	American Family Physicians
aHCST	Autologous Hematopoietic Stem Cell Transplant
AMA	American Medical Association
ANA	American Nurses Association
APA	Academic Pediatric Association
APD	Adequate Provider Data
ASTHO	Association of State and Territorial Health Officials
aTIV	Adjuvanted Trivalent Inactivated Influenza Viral Vaccine
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Industry Organization
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CBO	Community-Based Organization
CCH	Center for Community Health (URMC)
CDC	Centers for Disease Control and Prevention
CDPH	Chicago Department of Public Health
ChAd3-EBO Z	Chimpanzee Adenovirus 3-Based Vaccine
CICP	Countermeasures Injury Compensation Program
CID	*Clinical Infectious Diseases*
CIN	Cervical Intraepithelial Neoplasia
CISA Project	Clinical Immunization Safety Assessment Project
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
COMAHS	College of Medicine and Allied Health Sciences
CRPS	Complex Regional Pain Syndrome
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CTSI	Clinical & Translational Science Institute (URMC)
CVD	Cardiovascular Disease
DC	District of Columbia
DCPC	Division of Cancer Prevention and Control
DM	Diabetes Mellitus
DNA	deoxyribonucleic acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
EBR	Evidence-Based Recommendations
ED	Emergency Department
EHR	Electronic Health Record
EIP	Emerging Infections Program

EIS	Epidemic Intelligence Service
EMA	European Medicines Agency
ENT	Ear, Nose, and Throat
Epi-X	Epidemic Information Exchange
ETEC	Enterotoxigenic *E. coli*
EU	European Union
EVD	Ebola Virus Disease
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
FLU VE	Influenza Vaccine Effectiveness Network
FOA	Funding Opportunity Announcement
FY	Fiscal Year
GBS	Guillain-Barré Syndrome
GDPH	Georgia Department of Public Health
GEVIT	Global Ebola Vaccine Implementation Team
GMC	Geometric Mean Concentrations
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAN	Health Alert Network
HBsAG	Hepatitis B Surface Antigen
HCP	Healthcare Personnel
HCW	Healthcare Workers
HCV	Hepatitis C Virus
HD-IIV	High-Dose Inactivated Influenza Vaccine
HEDIS	Healthcare Effectiveness Data and Information Set
HI	Hemagglutination Inhibition
Hib	*Haemophilus influenzae* type b
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplantation
HV	Hexavalent
IDSA	Infectious Disease Society of America
IgA	Immunoglobulin A
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IM	Intramuscularly
IMD	Invasive Meningococcal Disease
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
IT	Information Technology
JE	Japanese Encephalitis
JE-MB	Inactivated Mouse Brain–Derived Japanese Encephalitis Vaccine
JE-VC	Vero Cell Culture-Derived Japanese Encephalitis Vaccine
LAIV	Live Attenuated Influenza Vaccine
LCI	Laboratory-Confirmed Influenza
LGBT	Lesbian, Gay, Bisexual, and Transgender

LIVE	Lombardia Influenza Vaccine Effectiveness Study
LMP	Last Menstrual Period
LPS	Lipopolysaccharide
LY	Life Years
MCHS	Marshfield Clinic Health System
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MLST	Multi-Locus Sequence Type
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MOHS	Ministry of Health and Sanitation
MPSV4	Meningococcal Polysaccharide Vaccine
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NAO	National Area Health Education Center Organization
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center for Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHRC	Naval Health Research Center
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Influenza Centre
NIH	National Institutes of Health
NIP	National Immunization Program
NIPH	Norwegian Institute of Public Health
NIS	National Immunization Survey
NMA	National Medical Association
NMA	National Meningitis Association
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NYC	New York City
NYU	New York University
OPHSS	Office of Public Health Scientific Services
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PFGE	Pulsed-Field Gel Electrophoresis
PHAC	Public Health Agency of Canada
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Principal Investigator
PIDS	Pediatric Infectious Diseases Society
POI	Primary Ovarian Insufficiency
PPHF	Prevention and Public Health Funds
PRNT	Plaque Reduction Neutralization Test
PRP-OMPC	Polyribosylribitol Phosphate Polysaccharide linked to Outer Membrane Protein Complex
PRP-T	Polyribosylribitol Phosphate Polysaccharide Conjugated to Tetanus Toxoid (Haemophilus B Conjugate)
QALYs	Quality Adjusted Life Years
RCA	Rapid Cycle Analysis

RCT	Randomized Controlled Trial
RDD	Random Digit Dial
RSV	Respiratory Syncytial Virus
rVSV-ZEBOV	Recombinant Vesicular Stomatitis Virus Vaccine Expressing the Glycoprotein of Zaire Ebola Virus
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SAHM	Society for Adolescent Health and Medicine
SCR	Seroconversion Rate
SD-IIV	Standard-Dose Inactivated Influenza Vaccine
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Experts
SNP	Single Nucleotide Polymorphism
STI	Sexually Transmitted Infection
STRIVE	Sierra Leone Trial to Introduce a Vaccine against Ebola
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
TIV-HD	Trivalent, Inactivated Influenza Vaccine
UK	United Kingdom
UNICEF	United Nations International Children's Emergency Fund
URMC	University of Rochester Medical Center
US	United States
USAID	United States Agency for International Development
USPHS	United States Public Health Service
VAERS	Vaccine Adverse Event Reporting System
VBYG	Vaccinate Before You Graduate
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VHA	Veterans Health Administration
VICP	(National) Vaccine Injury Compensation Program
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VSVdeltaG-ZEBOV	Vesicular Stomatitis Virus-Based Vaccine
VTE	Venous Thromboembolism
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WNV	West Nile Virus
YF	Yellow Fever

Welcome, Introductions, & Greetings from Dr. Schuchat

Welcome and Introductions

Nancy Bennett, MD, MS
ACIP Chair

Raymond A. Strikas, MD, MPH, FACP
Acting Executive Secretary, ACIP / CDC

Following Dr. Bennett's greeting and call to order, Dr. Strikas welcomed everyone to the October 2015 Advisory Committee on Immunization Practices (ACIP) meeting. He indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and 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 meeting to assist with various meeting functions: Stephanie Thomas, Natalie Greene, and Chris Caraway.

Regarding staffing changes, Dr. Strikas announced that Dr. Anne Schuchat, formerly Director of the National Center for Immunization and Respiratory Diseases (NCIRD) and a fixture of the ACIP meetings for the last 10 or more years, had been appointed Principal Deputy Director of CDC. Dr. Rima Khabbaz is now Acting Director of NCIRD. Dr. Khabbaz and Dr. Nancy Messonnier were both present during this meeting. Key staff member of the ACIP Secretariat, Dr. Jean Smith, was not present as she was tending to an ill family member.

Dr. Strikas noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following this meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Ian Branam, located at the Press table, for assistance in arranging interviews.

The next ACIP meeting will convene at CDC on Wednesday and Thursday, February 24-25, 2016. Registration for all meeting attendees is required and will be open Wednesday, October 21, 2015 on the ACIP website. The registration deadline for Non-US citizens is February 3, 2016 and for US citizens registration closes February 10, 2016. Registration is not required for webcast viewing. As a reminder for non-US citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms be submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to help with any questions about the process.

Dr. Nancy Bennett

Dr. Strikas then introduced the new ACIP Chair, Dr. Nancy Bennett. Dr. Bennett will serve as Chair from this meeting through June 2018. Dr. Bennett is Professor of Medicine and Public Health Sciences at the Center for Community Health (CCH) and Co-Director of the Clinical & Translational Science Institute (CTSI) within the University of Rochester Medical Center (URMC) School of Medicine and Dentistry (SMD). She graduated from New York University (NYU) School of Medicine, and completed her Internal Medicine Residency and Chief Residency at Bellevue Hospital in New York City (NYC). She also completed a fellowship in general medicine, including a Master's Degree in Epidemiology, and served on the faculty at Columbia University College of Physicians and Surgeons before moving to Rochester. She served as Deputy Health Director of Monroe County Department of Public Health for 16 years before returning to URMC where she is currently the Director of the CCH and a Principal Investigator (PI) of the URMC CTSI. Since 1997, she has been the PI for the Rochester Emerging Infections Program (EIP) Region, and has led a variety of supplemental projects related to pneumococcal and influenza surveillance and prevention. Dr. Bennett served as the National Association of County and City Health Officials (NACCHO) liaison member to ACIP from 2004 through 2007, and has been a voting member of ACIP since 2011. For the past two years, she has served as the unofficial Vice-Chair of ACIP.

Dr. Bennett emphasized what a pleasure it was to serve as ACIP Chair. She has been attending ACIP meetings for many years, and participating as a voting member for the last few years and said that it is probably the most interesting and challenging work that she does. It has been a great honor and privilege, and she is very happy to be the new Chair. She said she thought the most important words she could convey is that she is available at all times to address the needs of the ACIP and its members . She invited input regarding ways to make ACIP run more smoothly, be more accountable, and make the best possible recommendations. She tends to believe in "servant leadership," which means making it possible for everyone to do their very best, which she perceives to be her job as the ACIP Chair—to help the members lead the committee rather than to lead them. She thanked everyone for this honor. Dr. Bennett then introduced and welcomed the following new ACIP members:

- Dr. Echezona Ezeanolue
  Professor of Pediatrics and Public Health
  Director, Global Health and Implementation Research Initiatives
  School of Community Health Sciences
  University of Nevada, Las Vegas

- Dr. Kelly Moore
  Director, Tennessee Immunization Program
  Tennessee Department of Health
  Assistant Clinical Professor, Department of Health Policy
  Vanderbilt University School of Medicine

- Dr. Emmanuel (Chip) Walter
  Professor of Pediatrics
  Duke University School of Medicine

- Dr. David Stephens
  Professor of Medicine, Division of Infectious Diseases
  Chair, Department of Medicine
  Emory University School of Medicine

Dr. Strikas made the following announcements regarding *Ex Officio* members:

- Dr. Narayan Nair, representing the Health Resources and Services Administration (HRSA), was in attendance

- Dr. Linda Kinsinger, Veterans Health Administration (VHA), was unable to attend

He made the following announcements regarding Liaison Representatives in attendance:

- Dr. Leonard Friedland, GlaxoSmithKline (GSK), representing the Biotechnology Industry Organization (BIO)

- Dr. Kimberly Martin, representing the Association of State & Territorial Health Officials (ASTHO)

- Dr. David Johnson from Sanofi Pasteur, representing the Pharmaceutical Research and Manufacturers of America (PhRMA), who will now serve as the regular PhRMA liaison member

Regarding public comments, Dr. Strikas indicated that topics presented during ACIP meetings include open discussion with time reserved for public comment. He explained that time for public comment pertaining to topics on the agenda was scheduled following the end of the day's sessions, and that time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before the vote. During this meeting, there was one public comment opportunity at 5:45 PM. People who planned to make public comments were instructed to visit the registration table at the rear of the auditorium where Ms. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide 3 pieces of information: name, organization if applicable, and any conflicts of interest (COI). Registration for public comment also was solicited in advance of this meeting through the *Federal Register*. Given time constraints, each comment was limited to 3 minutes. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

Regarding recommendations, ACIP uses a standard process to systematically collect and evaluate evidence behind each recommendation. More information about the Grading of Recommendation Assessment, Development and Evaluation (GRADE) process can be found on the ACIP website. Key factors for developing recommendations include the balance of benefits and harms, type or quality of evidence, values and preferences, and health economic analyses. The ACIP recommendation categories are:

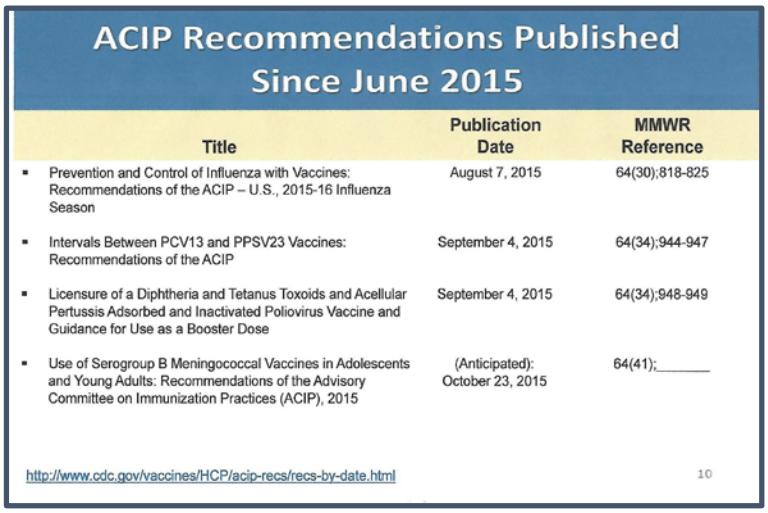
- Category A: A recommendation that applies to all persons in an age- or risk-based group.

- ❑ Category B: A recommendation for individual clinical decision making.
- ❑ No recommendation for an unresolved issue.

Vaccine safety issues will continue to be presented at every ACIP meeting. During this meeting, these issues were included as part of specific topic presentations.

Regarding ACIP implications of the Affordable Care Act (ACA), ACIP recommendations become policy following approval by the CDC Director and publication in the *Morbidity and Mortality Weekly Report* (*MMWR*). The ACA was enacted in 2010, and requires insurance coverage for recommended immunizations without copays/deductibles when provided by an in-network provider. Health plans have one plan year from *MMWR* publication to implement recommendations according to CDC immunization schedules, including recommendations illustrated in the graphics and those described in footnotes.

During every meeting, an update is provided on the status of ACIP recommendations. There have been three ACIP publications since June 2015, with one additional publication to be published this week, which are reflected in the following table:



ACIP Recommendations Published Since June 2015

Title	Publication Date	MMWR Reference
▪ Prevention and Control of Influenza with Vaccines: Recommendations of the ACIP – U.S., 2015-16 Influenza Season	August 7, 2015	64(30);818-825
▪ Intervals Between PCV13 and PPSV23 Vaccines: Recommendations of the ACIP	September 4, 2015	64(34);944-947
▪ Licensure of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine and Guidance for Use as a Booster Dose	September 4, 2015	64(34);948-949
▪ Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2015	(Anticipated): October 23, 2015	64(41);_____

http://www.cdc.gov/vaccines/HCP/acip-recs/recs-by-date.html 10

Recommendations and immunization schedules can be downloaded from the ACIP website. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, revised, or retired.

Applications for ACIP membership are due no later than November 13, 2015 for the 4-year term beginning July 1, 2016. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

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

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

A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submitted as e-mail attachments to Dr. Jean Clare Smith at jsmith2@cdc.gov

To summarize COI provisions applicable to the ACIP, as noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo 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 COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the proviso that he/she abstains on all votes related to the vaccines of that company. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

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

- Dr. Belongia: Receives research support from Medimmune and has a conflict for influenza.
- Dr. Walter: Receives research support from Merck for a rotavirus vaccine study, which is an investigator-initiated project.
- The remainder of the ACIP members declared no conflicts.

Dr. Bennett then introduced the *ex officio* members, and requested that the liaison and *ex officio* members introduce themselves.

Greetings from Dr. Schuchat

Anne Schuchat, MD (RADM, USPHS)
Principal Deputy Director
Centers for Disease Control and Prevention and
Agency for Toxic Substances and Disease Registry

Dr. Schuchat said it was such a pleasure to welcome everyone to the October 2015 ACIP meeting. Since February 2006 three times a year, she has participated in the extraordinary work of ACIP. She particularly welcomed new members, Drs. Ezeanolue, Moore, Stephens, and Walter. She thanked them in advance for the extraordinary effort they would put into ACIP. She also thanked the existing members for their hard work and the wisdom and expertise that they bring to this role. She was thinking about ACIP now that she is in the nostalgic phase of her CDC career, and realized that ACIP is the exact opposite of Las Vegas. What happens in this room does not stay in this room. In fact, it is being webcast all over the world and has impact in every family in America and in many communities around the world. The way ACIP reviews the evidence and deliberates on highly difficult issues has an impact for every practice, and on immunization policies in America and many other countries. She knows how much work it is to serve on ACIP and for CDC staff to support the work groups (WGs) and ACIP in general. She thanked everyone for what they do, and encouraged them to be serious, deliberate, and continue their extraordinary work for this nation.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Khabbaz said that it was a privilege to be serving as Acting Director of NCIRD with an outstanding Deputy Director, Dr. Nancy Messonier, and a great leadership team. NCIRD has established a search committee for a permanent Director that is chaired by Dr. Chesley Richards, Deputy Director of the Office of Public Health Scientific Services (OPHSS). Also serving on the search committee are Dr. Walter Orenstein and Dr. William Schaffner. The hope is to have the position vacancy posted soon. This is a great center for a good slate of highly qualified candidates. Dr. Khabbaz also announced that the National Immunization Conference is scheduled for September 13-15, 2016 in Atlanta, Georgia. This is a key conference of immunization partners to discuss science, policy, education, and other aspects related to vaccine-preventable diseases. She expressed gratitude to Dr. Strikas for serving as Acting Executive Secretary for ACIP, and noted that CDC would soon be announcing a permanent Executive Secretary.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance announced that CMS has developed a toolkit of outreach materials focused on preventive services for adults. CMS realized that as the number of adults in the Medicaid program has expanded, there are limited materials focused on adults. The materials in the toolkit emphasize the need to obtain basic preventive services, including immunizations. The toolkit has been very well-received. Again this year, CMS is working with the National Vaccine Program Office (NVPO) to track the prevalence of Medicare influenza vaccines this season. The interactive mapping tool on NVPO's website provides information on the number of fee-for-service Medicare beneficiaries who have obtained an influenza vaccine using claims data. The data are obtained weekly.

Department of Defense (DoD)

Dr. Sergienko reported that the Department of Defense (DoD) has begun its seasonal influenza vaccination program. Influenza vaccine is mandatory for all uniformed personnel, including Active Duty, Coast Guard, Reserve, and National Guardsmen. DoD's immunization goal is 90% by mid-December. In addition, influenza vaccination is mandatory for all healthcare personnel (HCP) who provide direct patient care in military facilities and is also recommended for all other HCP within the military healthcare system. To meet this demand, DoD ordered more than 3.6 million doses of vaccine to be distributed throughout its locations in the United States (US) and overseas and to ships afloat. The first meeting of the Vaccine Hesitancy Working Group was convened on August 26, 2015. That group is working to identify topics to increase uptake of vaccines among DoD beneficiaries. DoD is conducting a carriage study of most military personnel for meningococcal disease. That is being conducted through the Naval Health Research Center (NHRC) with the intent to identify DoD's baseline carriage and the impact potential vaccinations in that population. Dr. Sergienko thanked ACIP for allowing participation of DoD subject matter experts (SMEs) within the Maternal Immunization, Cholera, Meningitis, and Smallpox WGs. Since the June 2015 meeting, the bid was announced for the electronic health record (EHR) that the DoD will be adopting. DoD will be working with CDC to ensure that, as best possible, state registry data can be captured within the EHR and vice versa.

Food and Drug Administration (FDA)

Dr. Sun reported that the Food and Drug Administration (FDA) convened a Vaccine Advisory Committee meeting on September 15, 2015 to discuss the safety and effectiveness of the adjuvanted seasonal influenza vaccine that is under review currently at FDA. Another Vaccine Advisory Committee meeting will be convened on November 13, 2015 specifically devoted to the topic of maternal immunization, given the full range of vaccines that are being used and being considered for use during pregnancy: influenza, pertussis, respiratory syncytial virus (RSV), Group B streptococcus, and others. The Center for Biologics Evaluation and Research (CBER) is in a transition phase as the Center Director announced her plans to retire and a search for a new Center Director is underway.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that the National Vaccine Injury Compensation Program (VICP) had a very busy fiscal year (FY) 2015 with 802 claims filed and 526 claims adjudicated, of which 449 were compensable and 77 were dismissed. $204 million in awards were paid to petitioners, and over $20.6 million was paid in attorney fees. More data about this program can be obtained on the website. Development was completed of proposed recommendations to make several changes to the Vaccine Injury Table. The Notice of Proposed Rulemaking was posted for public comment on July 29, 2015 to be available for 180 days. A Final Rule proposing to add intussusception as an injury associated with rotavirus vaccine was published in the *Federal Registry* in June 2015. In August 2015, the Pandemic Influenza Injury Table Final Rule was published in the *Federal Registry*. In FY 2015, the Countermeasures Injury Table Compensation Program (CICP) has compensated 4 claims totaling $2.3 million. VICP and CICP are focused on outreach efforts to make providers and the public aware of these safety net programs.

Indian Health Services (IHS)

Ms. Groom reported that after several seasons of a voluntary comprehensive influenza vaccination program for Indian Health Services (IHS) HCP and stagnant rates among HCP, IHS has moved forward with a mandatory influenza vaccination policy. This policy is currently implemented for IHS's non-bargaining union employees, and the IHS is working with its unions now and hope to have this fully implemented this influenza season. In terms of maternal immunization, IHS has developed a performance measure for the agency to start tracking Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) and influenza vaccination of pregnant women, and are hoping this will help them with a reminder in the IHS EHR.

National Institutes of Health (NIH)

Dr. Bennett read the following National Institutes of Health (NIH) update into the record, given that Dr. Gorman was unable to attend:

The 2015 Nobel Prize in Chemistry has been awarded to NIH grantees Paul Modrich, PhD of the Howard Hughes Medical Institute and Duke University School of Medicine in Durham, North Carolina and Aziz Sancar of the University of North Carolina, Chapel Hill, North Carolina for having mapped, at a molecular level, how cells repair damaged deoxyribonucleic acid (DNA) and safeguard the genetic information. They share the award with Tomas Lindahl of the Francis

Crick Institute and Clare Hall Laboratory, Hertfordshire, United Kingdom (UK). The Royal Swedish Academy of Sciences said their work on DNA repair "has provided fundamental knowledge of how a living cell functions." From the National Institute of Allergy and Infectious Diseases (NIAID), funded researchers at Tulane University developed an experimental aerosol vaccine with a modified form of *Mycobacterium tuberculosis* (*Mtb*) that was genetically engineered to exclude a gene thought necessary for successful lung infection in Maccabees. This has been published by Kaushal et al in *Nature Communications*. Related to RSV, NIAID has recently begun testing an RSV challenge study. The strain is a molecularly cloned challenge virus, meaning the RSV A2 study virus originates from a single clone of the virus strain and has been tested to ensure that it is not contaminated with other infection-causing pathogens. NIAID investigators, in collaboration with Hopkins, will analyze participant samples to measure levels of virus shedding and immune protection. In addition, FDA and NIAID held a workshop in June 2015 that covered constructs, paths forward, obstacles, lessons learned, and potential endpoints for RSV candidate vaccines. The agenda and video are available on the NIAID website. Related to HIV, an article written about a preventive HIV vaccine has some thoughts that are generalizable to the entire field of vaccinology. Since efforts to develop a preventive HIV vaccine began in the 1980s, tension has existed between advocates for quickly moving vaccine candidates into human testing and those seeking more basic research on HIV and immune responses. In a new commentary, scientists from NIH have offered a historic perspective on the search for a safe and effective HIV vaccine through the lens of these two vaccine development strategies. That article is by Fauci and Marston and can be found in *Science*. A Phase I/II randomized placebo controlled trial in intravenous drug users of an hepatitis C virus (HCV) candidate vaccine continues. There is a Phase I trial dose escalating trail placebo controlled trial in healthy adults to assess a West Nile Virus (WNV) candidate vaccine, for which the primary objectives are to assess safety, reactogenicity, tolerability, and immunogencity. There is also a study of a candidate H7N9 vaccine underway.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that the National Vaccine Advisory Committee (NVAC) is also working on issues of maternal immunization, and has issued a report on how to improve uptake of current recommendations. The second phase of that is to assess the obstacles and barriers to developing vaccines intended for vaccination of pregnant women, and how to overcome those. NVAC has a workgroup and hopes to have a first set of recommendations focused on overcoming obstacles at its February 2016 meeting. McKenzie & Company is performing a landscape analysis of vaccine innovation challenges and opportunities. They asked for NVAC members to cooperate and potentially be interviewed as they try to develop an analysis and potential recommendations to incentivize vaccine innovation. In June 2015, NVAC approved the report on the role of vaccines in combating antimicrobial resistant bacteria. Hopefully, that report will be published soon in *Public Health Reports*. NVAC is attempting to develop a liaison relationship with the committee that is dealing with combating antimicrobial resistant bacteria, having one of them on the NVAC committee and an NVAC member on that committee.

National Vaccine Program Office (NVPO)

Dr. Gellin noted that the National Vaccine Program Office (NVPO) is now 5 years into the 10-year National Vaccine Plan (NVP), and is in the process of conducting a mid-course review. There is a survey on the NVPO website, and there will be conversations about it as well. He invited input. He shared a copy of a review on the progress on the NVP last year, indicating that a few hardcopies were published. Angela Shen has returned to NVPO after a stint at the United

States Agency for International Development (USAID). Among other efforts, Ms. Shen will head NVPO's adult immunization efforts.

Child and Adolescent Immunization Schedule

Introduction

Dr. José R Romero
Chair, Child and Adolescent Immunization Work Group

Dr. Romero introduced this session on behalf of Child and Adolescent Immunization WG. He reminded everyone that the schedule is presented for vote every fall, given that the ACIP's approval is necessary prior to publication of the schedule in January or February of the following year. ACIP's approval is also necessary before its partners, the American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and American Congress of Obstetricians and Gynecologists (ACOG) review and approve the schedule. No new policy is established by the schedule; rather, it reflects a summary of published ACIP recommendations. These edits are intended to improve the readability and utility of the schedule, and hence translate the respective ACIP recommendations into language that is easy to interpret for the busy provider.

This year, only a few of the vaccines on the schedule required attention. The proposed schedule and the full set of footnotes are posted on the ACIP members' background website. The most significant changes are in Figure 1, which is a reconfiguration of the order in which the vaccines are presented. They are listed in order from earliest to latest administration. In addition, meningococcal B vaccine (MenB) vaccine has been added to the figure and the footnotes. Also, clarifications were made to diphtheria, tetanus, acellular pertussis (DTaP), polio, and human papillomavirus (HPV).

Child and Adolescent Immunization Schedule 2015

Candice L. Robinson, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Robinson indicated that there were proposed changes for Figures 1 and 2, as well as the footnotes. On the cover page, only the year was changed. Proposed Figure 1 changes for the 2016 schedule include the following:

- A purple bar, which represents the range of recommended ages for certain high-risk groups, has been added to Hib line and extends from 5 years through 18 years. This was added to correspond with text in the footnotes and published recommendation for administration of Hib in this age group for unvaccinated persons with high-risk conditions.

- In the 2015 schedule, this bar (half green/half purple bar) within the Hep A line was represented in the key below figure 2. However, since each color is already present in the key, this bar has been removed from the key in the proposed 2016 figure.

- The Tdap line has been moved down, given a desire to have the vaccines routinely recommended by age group (gold bars) aligned from the earliest age (hepatitis B) to older ages (Tdap, HPV, and meningococcal vaccines in adolescence).

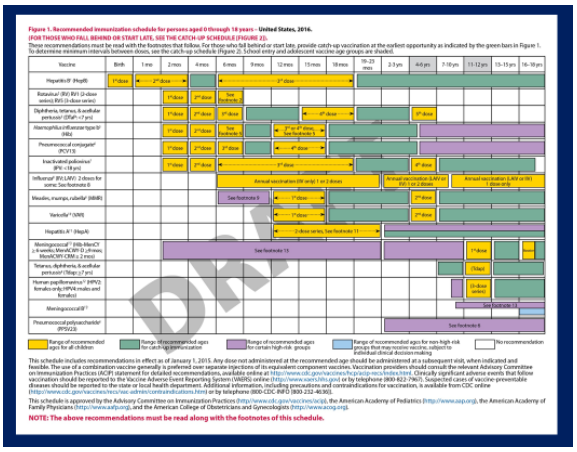
- The HPV nomenclature will be changed to reflect the new HPV nomenclature format. For example, HPV4 is now referred to as 4vHPV.

- In the HPV line, a purple bar has been added from age 9 through 10 years, for children at high-risk due to history of sexual abuse. This is in line with currently published HPV guidelines. Additional information has been added to the footnotes which will be discussed later.

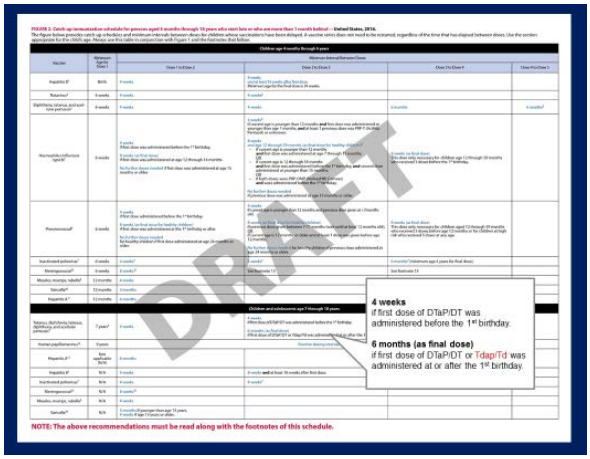
- A line for meningococcal B vaccine has been added to the schedule, with both a purple bar denoting high risk vaccination beginning at age 10 years, and a blue bar beginning at 16 years denoting non-high risk groups that may receive this vaccine, subject to individual clinical decision making. The blue bar is appropriate here given that the recommended ages for permissive use of meningococcal B vaccine is between 16 and 18 years.

- The pneumococcal polysaccharide bar has been moved to the bottom of the figure, because this vaccine is not routinely recommended for any population.

This is the resulting proposed figure 1:



There is a minor proposed change for Figure 2, the catch-up schedule. In the Tdap line, the dose 2 to dose 3 column, Tdap/Td was added to the list of possible previous vaccines:



Proposed changes within the footnotes include the following:

- The Red Book reference in the additional information section has been updated to the 30th edition.

- Footnote 3, the DTaP vaccine footnotes, has been revised to add Quadracel® to the minimum age exception line. The instructions were clarified regarding administration of an inadvertent dose of DTaP. It now reads "If the fourth dose of DTaP was administered at least 4 months, but less than 6 months, after the third dose of DTaP, it need not be repeated. The 4-day grace period may not be used for a fourth dose given less than 6 months after the third dose of DTaP". The description of "inadvertent dose" was used to indicate that this shortened interval between doses should not be used prospectively; however, the dose could be counted as valid after the fact.

- For footnote 7, inactivated polio, in response to questions from providers, guidance was added for inactivated polio vaccine (IPV) use in patients who have previously only received oral polio vaccine (OPV), and did not receive any doses after their 4th birthday. The addition reads "If only OPV were administered, and all doses were given prior to 4 years of age, one dose of IPV should be given at 4 years or older, at least 4 weeks after the last OPV dose." This is consistent with guidance provided by the SMEs.

- In the influenza footnote, the *MMWR* references were updated to those for the 2015-2016 influenza season. No other changes have been made to this footnote.

- HPV vaccination recommendations now include the 9-valent HPV vaccine, in addition to the bivalent and quadrivalent HPV vaccines. The footnote also contains the nomenclature change for HPV vaccines. The intervals between vaccine doses were clarified by restructuring the sentence without adding to or deleting any of the previous words. Text was also added regarding HPV vaccine use in high-risk children to correspond with the added purple bar discussed earlier. It reads "Administer HPV vaccination beginning at age 9 years to children and youth with any history of sexual abuse or assault who have not initiated or

completed the 3-dose series." This recommendation is part of the already published HPV guidelines.

- For the Meningococcal vaccines, the following revisions were made:

  - → The word "conjugate" has been removed from the footnote title and the meningococcal B vaccines have been added.

  - → Guidance regarding administration on meningococcal B vaccine has been added to the routine vaccination section.

  - → A new "Clinical Discretion" section has been added with instructions for MenB administration that read "Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) may be vaccinated with either a 2-dose series of Bexsero® or a 3-dose series of Trumenba® vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses."

  - → Within the "Vaccination of persons with high-risk conditions" section, guidance for the administration of Bexsero® and Trumenba® as well as the schedule has been added. It reads "Persons 10 years or older who have not received a complete series: Administer either a 2-dose series of Bexsero®, at least 1 month apart or a 3-dose series of Trumenba®, with the second dose at least 2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses."

  - → Clarification was added on what constitutes a persistent complement component deficiency.

  - → For both sections, separate subsections were added for meningococcal conjugate vaccines and meningococcal b vaccines.

  - → The MenB vaccines Bexsero® and Trumenba® were added to the list of meningococcal vaccines to administer or complete an age- and formulation-appropriate series during community outbreaks attributable to the vaccine serogroup.

  - → The MenB vaccine policy note reference and associated web address will be added when available.

The WG will make revisions as necessary based on feedback from ACIP and CDC internal clearance. A cleared, edited copy will be submitted to AAP, AAFP, and ACOG by January 1, 2016. The final edited copy will be sent to partner organizations for preparation of publication in their journals or their on-line publications by January 2016. Publication on the CDC website will occur in January to February 2016. Dr. Robinson thanked all of the CDC SMEs for their support and endless patience with the rewrites.

Discussion Points

Dr. Kempe noted that 9vHPV vaccine did not appear to have been added to Figure 1.

Dr. Robinson indicated that it would be corrected before publication.

Dr. Walter noted that the DTaP vaccine grace period was mentioned only on the note and at the top of the schedule. It might be helpful to reference back to the top of the schedule for the reader who might just be reading for that particular vaccine.

Dr. Robinson replied that she would make a note of this.

Referring to the second footnote slide, Dr. Sawyer said he did not understand why the 4-day grace period needed to be referenced because it already said "if the vaccine is given more than 4 months after the previous dose, it need not be repeated." It was unclear to him how the grace period comment added additional information.

Dr. Robinson said they could clarify that the grace period would not relate to the 4 months. If it is given at 4 months, there is no 4-day grace period. That could be made clearer or be omitted in the future.

Since there is typically a 4-day grace period before 6 months and here it was say 2-month grace period in terms of an inadvertent dose given up to two months before it was due, Dr. Moore suggested that there was no need to re-reference an additional grace period. It should simple say if a dose is given up to 2 months early inadvertently, it does not have to be repeated. That is the grace period for that particular dose.

Dr. Walter concurred that this is very confusing to the reader.

Dr. Robinson agreed that the 4-day grace period line could be removed.

Regarding the blue bar for MenB vaccine, which meant a Category B recommendation for clinical decision-making, Dr. Harriman expressed concern that this might make it seem like a lesser recommendation to providers.

Dr. Messonier said this marked the first time that they had tried to portray on the infant schedule the idea of a permissive recommendation. They must move forward with the schedule due to the time limit, but CDC will commit to a more comprehensive assessment of these schedules and how providers interpret them. The primary audience is providers, and as more vaccines have been added, the schedule has become highly complicated. It is a good time to review it and consider how to take advantage of modern technology. Part of that assessment will be making sure that people understand the various bars and what they mean.

Vote: Child and Adolescent Immunization Schedule

Dr. Rubin made a motion to approve the Child and Adolescent Immunization Schedule. Dr. Romero seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Pellegrini, Romero, Reingold, Riley, Rubin, Stephens, Walter
0 Opposed: N/A
0 Abstained: N/A

Adult Immunization Schedule

Introduction

Harriman, Kathleen, PhD, MPH, RN
Chair, Adult Immunization Work Group

Dr. Harriman reminded everyone that ACIP updates the adult immunization schedule each year. The schedule represents current ACIP policy and also updates approved policy changes from ACIP meetings. The Adult Immunization WG meets monthly and engages in ongoing consultation with vaccine SMEs to recognize changes over time. Updates in adult immunization schedule are approved by the following:

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- American Congress of Obstetricians and Gynecologists (ACOG)
- American College of Nurse Midwives (ACNM)

The adult immunization schedule is published in the *MMWR* and the *Annals of Internal Medicine.*

The 2016 adult immunization schedule updates are primarily based on 2015 updates in HPV, meningococcal, and pneumococcal vaccine recommendations. They reflect the ACIP policy changes associated with the recommended use of 9-valent HPV vaccine, serogroup B meningococcal vaccines, and the intervals between 13-valent pneumococcal conjugate (PCV13) and 23-valent pneumococcal polysaccharide (PPSV23) vaccines.

Adult Immunization Schedule 2015

Dr. David Kim
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In this presentation, Dr. Kim described the proposed changes to the 2016 adult immunization schedule. HPV vaccine recommendations now include three vaccines for females (2vHPV, 4vHPV, 9vHPV) and two vaccines for males (4vHPV, 9vHPV). There has been a nomenclature

change for HPV vaccines. For example, HPV4 is now referred to as 4vHPV. Females aged 19 through 26 years are routinely recommended to have a 3-dose series of 2vHPV, 4vHPV, or 9vHPV unless they have been vaccinated previously. Males aged 19 through 21 years are routinely recommended to have a 3-dose series of 4vHPV or 9vHPV unless they have been vaccinated previously. Men who have sex with men (MSM) and immunocompromised persons, including those with HIV infection, are recommended to have a 3-dose series of 4vHPV or 9vHPV through age 26 years if not vaccinated previously. The 2016 adult immunization schedule also contains a minor word change with the generic term "HPV vaccination" replacing specific HPV vaccine types.

The 2016 adult immunization schedule contains updates in the intervals between PCV13 and PPSV23. For immunocompetent adults ≥65 years, PPSV23 should be given at least 1 year following PCV13. The "at least 1-year interval" in the 2016 schedule replaces the "6 to 12 months interval" in the 2015 schedule. Note that the interval from PCV13 to PPSV23 is now the same as the interval from PPSV23 to PCV13. Also worth noting is that in February 2015, CMS implemented revised regulations for pneumococcal vaccines that allow for Medicare coverage for the different second pneumococcal vaccine 1 year after the first vaccine. The change in the ACIP-recommended interval between PCV13 and PPSV23 makes ACIP recommendations consistent with the current Medicare policy. The 2016 schedule also corrects two errata contained in the 2015 schedule, which are as follows:

- "Adults aged ≥19 years" replaces "adults aged 19 through 64 years" as was in the Policy Note for pneumococcal vaccination of adults with immunocompromising conditions, functional or anatomical asplenia, CSF leaks, or cochlear implants

- "Adults aged 19 through 64 years who smoke cigarettes or reside in nursing homes or long-term care facilities:

    - → "Adults aged 19 through 64 years who… reside in nursing home" is removed from the group of adults routinely recommended to receive PPSV23; these adults "should be assessed for PPSV23"
    - → "Adults aged 19 through 64 years who smoke cigarettes" remains an indication for PPSV23

During the June 2015 ACIP meeting, recommendations for the use of MenB vaccination were made. As shown in the 2016 adult immunization schedule, MenB vaccination is featured separately from the quadrivalent meningococcal conjugate vaccine (MenACWY) and meningococcal polysaccharide vaccine (MPSV4). A 2-dose series of MenB-4C (Bexsero®) or a 3-dose series MenB-FHbp (Trumenba®) is recommended for adults with anatomical or functional asplenia, persistent complement component deficiencies, microbiologists who are routinely exposed to isolates of *Neisseria meningitides*, and those at risk because of meningococcal disease outbreaks attributable to serogroup B. MenB vaccination is not recommended for persons who travel or live in countries in which meningococcal disease is hyperendemic or epidemic, because meningococcal disease in these countries is generally not caused by serogroup B. The MenB recommendation for adults with asplenia and complement deficiencies is represented in yellow on the schedule, meaning that it is recommended. It is represented in purple for all other listed indications, which means it is recommended if another risk factor is present.

Young adults 16 through 23 years, with a preferred age range of 16 through 18 years, may be vaccinated with a MenB vaccine series to provide short-term protection against most strains of MenB disease. This Category B recommendation for MenB vaccination has not been fully laid out in the 2016 adult immunization schedule as there are issues that remain to be resolved, such as how to best align the new Category B recommendation with existing recommendations that may also be considered permissive. An example might be the recommendation that hepatitis A vaccine can be administered to any person seeking protection. The Adult Immunization WG plans to conduct focus group and other human factors testing to determine how to best present this information. In the interim, the WG proposes that the Category B recommendation for MenB vaccination for adults aged 19 through 23 be presented in the schedule footnotes but not included in the figures.

There are additional changes in the footnotes for meningococcal vaccination. One change was to add MenB to the statement on HIV to read, "HIV infection is not an indication for routine vaccination with MenACWY or MenB vaccine." Two additional pieces of notable information have been added. The first is that "MenB-4C or MenB-FHbp vaccine may be administered concomitantly with MenACWY vaccine, but at a different anatomic site if feasible" and the second is that "the two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses." Finally, MenB vaccine has been added to the Contraindications and Precautions Table with the same information as MenACWY:

- Contraindications: Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component
- Precautions: Moderate or severe acute illness with or without fever

The proposed changes to Figure 1 of the draft 2016 adult schedule include the following:

- For Tdap, the text in the yellow bar that formerly stated "substitute 1-time dose of Tdap for a Td booster" has been simplified to state "substitute Tdap for Td once"

- For measles, mumps, and rubella (MMR), the text in the yellow bar stating "1 or 2 doses" has been clarified to "1 or 2 doses depending on indication"

- For PCV13, the text "1-time dose" that straddles the purple and yellow segments of the bar has been changed to "1 dose," similar to zoster vaccination, so that it does not confuse the reader into thinking that PCV13 is the only once-in-a-lifetime vaccine

- The text for PPSV23 for adults younger than 65 years of age has been modified from "1 or 2 doses" to "1 or 2 doses depending on indication"

- The text for Hepatitis A has been changed from "2 doses" to "2 or 3 doses depending on vaccine" to account for hepatitis A and B combination vaccine that is administered in a 3-dose series

- Meningococcal has been moved to below Hepatitis B and now appears in two rows, one for MenACWY/MPSV4 and another for MenB; both vaccines have purple bars running across all age groups

- The text for MenACWY/MPSV4 states "1 or more doses depending on indication"

- The text for MenB states “2 or 3 doses depending on vaccine” to account for the two MenB vaccines with different dosing schedules

- The text in the purple bar for *Haemophilus influenzae type b* (Hib) was changed from “1 or 3 doses” to “1 or 3 doses depending on indication”; more on this in Figure 2

- The language in the legend for the yellow bar “recommended for all persons” and the purple bar “recommended for persons with a risk factor” has been modified slightly for consistency; the inclusion of age in the purple legend in Figure 1 may be redundant because Figure 1 lists recommendations by age groups, but it is needed in Figure 2 in which recommendations are organized by indication

The proposed changes to Figure 2 of the draft 2016 adult schedule include the following:

- Some of the changes in Figure 2 are the same as for Figure 1

- The text in the indication bar across the top for immunocompromising conditions and HIV infection has been simplified

- The segmented yellow boxes and the text that specifies which types of influenza vaccine can be administered for specific indications have been condensed to a single yellow bar containing the text “1 dose annually” across all indications; this simplification is consistent with the ACIP recommendation that all persons 6 months of age and older receive the influenza vaccine

- For PPSV23, the text “1 or 2 doses” has been changed to “1, 2, or 3 doses depending on indication” to reflect that the maximum number of doses of PPSV23 that an adult should receive is 3; that is, 2 for an immunocompromising condition and 1 for reaching the age of 65

- As in Figure 1, the former single row for meningococcal vaccine is now two rows for MenACWY/MPSV4 and MenB

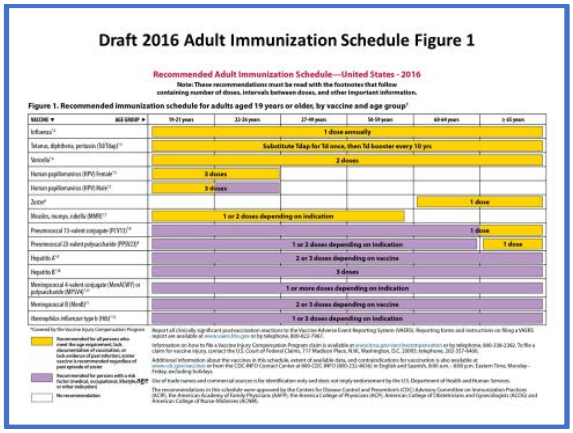
- The text for MenACWY/MPSV4 and Men B are the same as in Figure 1 but the text straddles the purple and yellow bars for Figure 2; the yellow reflects the recommendation for MenACWY and MenB for adults with asplenia and complement deficiencies

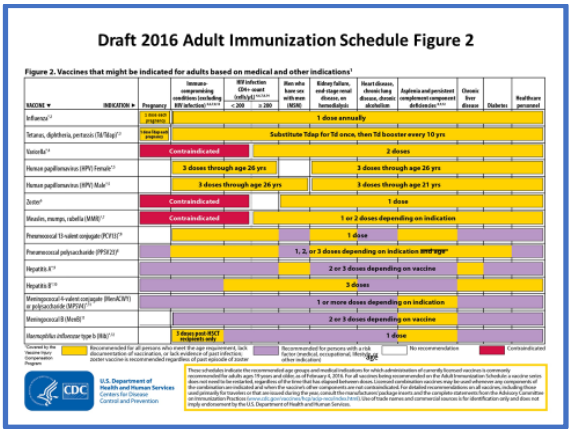
- MenB in pregnancy has been left white or blank, indicating that there is no recommendation for MenB vaccination during pregnancy

- For Hib, the 2015 text “1 or 3 doses” has been changed to state “3 doses post-hematopoietic stem cell transplantation (HSCT) recipients only” for the immunocompromising conditions column and “1 dose” for other conditions for which Hib vaccine is indicated

- “Contraindicated” was added, shown as a red box in the legend

Here are the drafts of proposed Figures 1 and 2 reflecting the changes as described for the 2016 adult immunization schedule:





Based on the discussion and recommendations by ACIP during this session, the draft 2016 adult immunization schedule will be revised and reviewed again by the WG and SMEs. Concurrence will then be obtained by the ACP, AAFP, ACOG, and ACNM. The revised adult immunization schedule, including figures and footnotes, will be submitted to CDC for clearance. The cleared adult immunization schedule will be submitted to the *MMWR* as a Notice to the Reader referring the reader to the CDC website to access the updated schedule, and published in the *Annals of Internal Medicine* in February 2016.

Discussion Points

Ms. Pellegrini recalled that when the MenB blue bar was added, there was discussion about coordinating with the adult schedule to carry the blue bar up to age 23 since the age recommendation straddles both schedules.

Dr. Romero replied that this was discussed originally, but then he and Dr. Strikas met with the group and decided to leave that off until further discussion.

Given the complexity of the schedule and the layout, Dr. Riley thought this was probably the best they could do. However, she emphasized how difficult it is to follow the columns. The MenB issue and the blue line highlight the confusion. If the schedules do not pair up, it makes it more confusing. There is no way to know currently if a 22 year old woman with no issues presents to a physician and asks for a MenB vaccine, just looking at the adult schedule and not reading the footnotes (which are blurry and too small to read), the assumption may be that the vaccine is unsafe. Her concern is that when information is not clearly laid out, there is a natural assumption that a vaccine is unsafe, cannot be given, or should not be given. This is the same comment for pregnancy in terms of understanding what can be given, what should be given, and what cannot be given.

Dr. Kempe shared Dr. Riley's concerns. At a minimum, the child and adult schedules should pair up. The decision for how to portray the blue bar for each should be the same. Realizing that they just voted on the childhood schedule, making a different decision for the adult schedule did not make sense to her. Family medicine will be looking at both schedules.

Dr. Bennett thought the problem was that the pediatric and adult schedules do not pair up in many ways. In addition, the adult schedule is difficult for providers because there is much information in the footnotes that is not in the schedule itself. The goal must be to develop an adult schedule that is more analogous to the pediatric schedule. That is more of an issue than presence or absence of the blue bar.

In reviewing the footnotes, Dr. Walter noted that "3 doses" referred only to 2vHPV and 4vHPV and not 9vHPV.

Dr. Stephens agreed that while it was routinely true that MenB need not be recommended for travelers, there are issues and settings in which group B outbreaks do occur. New Zealand is an example of that. "MenB is not routinely recommended for travelers" may be a better statement than "not recommended for travelers."

Dr. Fryhofer (AMA/ACP) expressed her gratitude for the time and effort that went into making a very difficult schedule somewhat more understandable through the graphics. Regarding footnote 8 for pneumococcal vaccination, it was not clear for those 65 and older who are immunocompetent and who are high risk because they have cochlear implants or a cerebrospinal fluid leak (CSF) leak whether the interval is 8 weeks or 1 year. Based on the two published recommendations that are posted on the ACIP website from October 12, 2012 and September 4, 2015 with the intervals, it appeared to her that for anyone age 19 and older who is immunocompetent, the interval would be 8 weeks.

Dr. Kim replied that for those who are immunocompromised who are 19 through 64 years of age and 65 years of age and older, the interval would be 8 weeks. For immunocompetent adults 65 years of age and older, the interval is 1 year. The interval is 8 weeks for immunocompetent adults 65 years of age and older who have cochlear implants or CSF leak.

Dr. Fryhofer (AMA/ACP) emphasized that the interval of 8 weeks for immunocompetent adults 65 years of age and older who have cochlear implants or a CSF leak needs to be reflected in the footnotes.

Vote: Adult Immunization Schedule

Dr. Reingold made a motion to approve the Adult Immunization Schedule. Dr. Rubin seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Pellegrini, Romero, Reingold, Riley, Rubin, Stephens, Walter
0 Opposed: N/A
0 Abstained: N/A

Meningococcal Vaccines

Introduction

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

Dr. Rubin reminded everyone that the following ACIP recommendation for use of serogroup B meningococcal vaccines in adolescents and young adults was voted on during the June 2015 ACIP meeting, for which a Policy Note is scheduled to be published in the MMWR on October 23, 2015:

> "A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. (Category B)"

The WG recognizes that there are ongoing challenges when considering routine use of MenB vaccines in adolescents. As a reminder, the proportion of serogroup B cases that could be prevented with MenB vaccines is unknown. The breadth of strain coverage is estimated, with actual breadth of strain coverage unclear. Available antibody persistence data suggests that there is limited duration of protection. Effectiveness data are not available, and licensure was based on bactericidal activity. Universal programs have not been implemented in any country to date. The impact on carriage is unknown, as is the potential impact of vaccine pressure on circulating strains.

Additional data for MenB vaccines that have been reviewed by the WG since June 2015 include some preliminary safety and immunogenicity data from two Phase 3 studies for the MenB-FHbp vaccine, including immunogenicity data on 10 secondary strains. Pfizer plans to present these data to ACIP in February 2016. The WG also reviewed an additional safety summary received from CDC's Immunization Safety Office (ISO). Relatively few reports have been received on MenB-FHbp (n=65) and MenB-4c (n=21) through the Vaccine Adverse Event Reporting System (VAERS) as of October 5, 2015. No safety signals have been detected to date. Few doses have been administered to the Vaccine Safety Datalink (VSD) population to date. Safety assessment can begin when a larger number of doses have been administered and data accumulated.

An ad hoc WG comprised of ACIP Meningococcal WG members, ACIP members, state public health officials, college health professionals, and CDC reconvened on September 3, 2015 with biweekly meetings. The objectives of this ad hoc WG are to: 1) review available data on the recent epidemiology of meningococcal disease and outbreaks; 2) review safety and immunogenicity of meningococcal vaccines; and 3) update and harmonize the current meningococcal outbreak guidelines for serogroups A, B, C, W, and Y. The Meningococcal Outbreak WG recommendations will be presented in an informational session during the

February 2016 or June 2016 ACIP meeting. Harmonized outbreak guidelines eventually will be published in the *MMWR*.

Immediate future Meningococcal WG activities are to reevaluate the policy options for use of MenACWY in MSM or HIV-infected MSM. This will include review of prior ACIP discussions which took place in February 2014; and evaluating recent data on outbreaks of serogroup C meningococcal disease occurring in MSM and sporadic cases, including results of an analysis to estimate risk for meningococcal disease among MSM.

The topic of today's session is a presentation regarding a serogroup C outbreak among MSM in Chicago in 2015.

Serogroup C Outbreak Among MSM, Chicago 2015

Sarah Kemble, MD
Chicago Department of Public Health

Dr. Kemble shared the Chicago Department of Public Health's (CDPH's) experience with a serogroup C meningococcal disease outbreak among Chicago-area MSM in 2015. She began by reviewing the epidemiology of the invasive meningococcal disease outbreak that occurred in the Chicago metropolitan area during the summer of 2015, and CDPH's response to the outbreak as it evolved. She also shared some details of CDPH's vaccination campaign, and discussed some of the challenges encountered in implementing the campaign and estimates of its cost.

CDPH became aware of the first case in this outbreak in mid-May. The case occurred in an HIV+ male who on initial interview reported being in a monogamous relationship with another male. There were a limited number of contacts, therefore, who required chemoprophylaxis. At that point, this seemed to be a single case. However, within two weeks, two additional cases were reported among MSM. At that point, CDPH became aware that an outbreak was likely occurring. They were not yet aware of the serogroup status of these cases, but when they were confirmed on June 2, 2015, a vaccination campaign was implemented on June 3, 2015. Press releases, an Epidemic Information Exchange (Epi-X), and a Health Alert Network (HAN) alerts were issued to local clinical partners to issue vaccination recommendations. The initial vaccination recommendations issued on June 3rd were focused on high-risk groups as defined by the epidemiology of the initial 3 cases of which the CDPH was aware. This meant HIV+ MSM, MSM regardless of HIV status who had close or intimate contact with anonymous partners, and those who sought sexual partners through use of on-line hook-up apps. On the day the recommendations were issued, a fourth case had illness onset and was reported to CDPH within the subsequent couple of days. Two additional cases occurred in the subsequent two weeks.

At this point, CDPH was dealing with 6 cases of invasive meningococcal disease (IMD) of the same serogroup occurring within a limited geographic area over a very short period of time. They knew that the ACIP-recommended threshold for initiation of a meningococcal vaccination campaign was an incidence of 10/100,000 among the at-risk population. ACIP guidelines also recommended consideration for a campaign when multiple cases occur within a short period of time, or when cases occur within a shared institution or in close geographic proximity. The initial recommendation for vaccination of HIV+ and high-risk MSM was based on the estimate that IMD incidence among Chicago HIV+ MSM had reached 19/100,000 as of June 3rd, well

exceeding the ACIP threshold. However, a number of challenges were encountered in implementing a vaccination campaign targeted at these more narrowly defined groups. The stigma associated with diagnosis of HIV and with admitting to anonymous sex and use of "hook-up" apps to identify sex partners complicated the vaccination message and limited vaccine acceptance. This was particularly a problem in the black community, which was a concern because the majority of cases were occurring among black MSM. CDPH reconsidered the recommendations as the case numbers continued to grow. They estimated that IMD incidence among all Chicago MSM regardless of HIV status had reached 10/100,000 as of June 18th, when the 6th case was also confirmed to be serogroup C [Bilukha OO, National Center for Infectious Diseases, Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR RecommRep 2005;54:1-21]. This was reaching a threshold that would define an outbreak more broadly in the MSM population in Chicago.

Consideration was also given to upcoming festivals and events that occur during the summers in Chicago, such as Pride Week and Black Pride. Many of the cases were of this demographic. This presented a risk for greater/broader transmission in the MSM population in Chicago, and for visitors from other states and countries. It also represented an opportunity to get vaccine out. With all of this in mind, CDPH issued expanded vaccination recommendation to all Chicago MSM as of June 18th. This was the day on which the 6th case was confirmed to be serogroup C. Following that expanded recommendation, one additional case was reported in the Chicago area at the end of June. Thankfully since then, no additional cases have been reported.

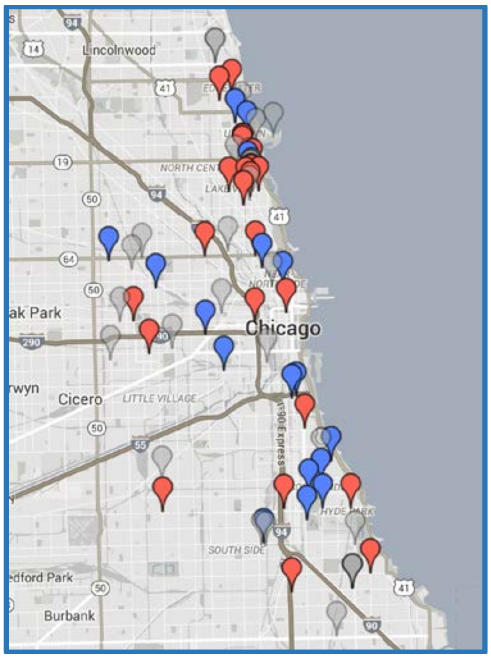
In summary of the case characteristics, 7 cases of serogroup C IMD were identified during this outbreak (6 in Chicago and 1 in a neighboring county). The age range of cases was from 29 to 54 years. One case was fatal. Of the 7 cases, 6 were African American and 5 were HIV+. CD4 counts of those for whom information was available ranged from 91 to 960. Only one case had a CD4 count less than 200, and the fatal case had the highest CD4 count of 960. Of the cases, 5 reported anonymous sex, including 1 sex worker, and 5 cases reported meeting partners using "hook-up" apps.

Extended case investigations were performed for all cases in this outbreak, meaning an attempt was made to trace all intimate contacts of cases going back 90 days prior to illness onset, by referencing the CDPH sexually transmitted infection (STI) partner services database and through in-person case interviews when possible. The primary goal of contact tracing was to make appropriate recommendations for chemoprophylaxis. Up to 9 contacts and a median of 4 contacts per case met indications for prophylaxis. Close or intimate contact with the case within 14 days of illness onset was considered to be an indication for chemoprophylaxis.

One goal of the extended investigations was to attempt to identify direct epidemiologic links between outbreak cases. This proved challenging because many contacts were anonymous or used aliases or temporary phone numbers. No direct epidemiologic links between cases were found; however, the extended investigations did serve some other important functions such as allowing CDPH to provide HIV partner services or to identify additional vaccination targets in the form of individual contacts, more extended friend networks, or venues frequented by cases and their social networks. For example, some cases agreed to post a message on their Facebook page urging other MSM in their friend networks to get vaccinated against meningitis. It was also through case interviews that several gyms were identified as being key venues for reaching African American MSM.

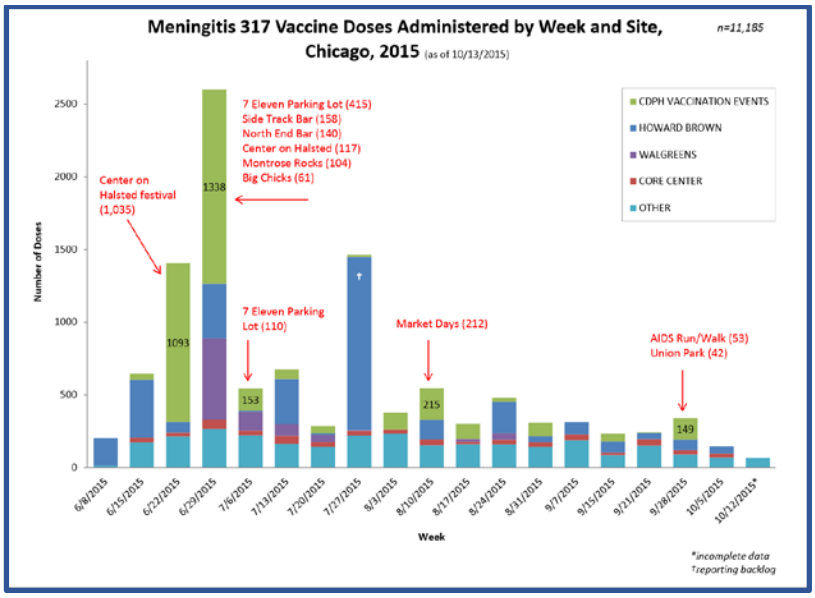
Laboratory testing performed at CDC revealed that all 7 Chicago-area case isolates shared an indistinguishable pulsed-field gel electrophoresis (PFGE) pattern and multi-locus sequence type (MLST). The isolates also had less than 12 single nucleotide polymorphism (SNP) differences by whole genome sequencing (WGS), meaning that they were also indistinguishable by this method. Approximately two weeks after the last case was reported in the Chicago area, a case was reported in Minnesota that was closely related by laboratory testing. Again, no direct epidemiologic links were found between this and the Chicago-area cases; however, concern that it could be related due to similar risk factors (HIV+ status and high-risk behaviors), in conjunction with Minnesota, CDPH issued an Epi-X that included a call for cases and reporting of MSM status for all meningococcal disease cases. Review of Chicago's meningococcal disease epidemiology over the past few years showed that since 2013 when Chicago has been more regularly tracking MSM status, the vast majority of Chicago's cases have been among MSM.

In terms of the CDPH meningococcal vaccination campaign components, the campaign began with federally funded 317 vaccine distribution. This was done through CDPH "pop-up" clinics, partner clinic sites, and pharmacies. Walgreens was a major partner with CDPH in these efforts. There was a communications and media component to the campaign, as well as community outreach through Ryan White grant recipients and other community partners. In terms of evaluation, CDPH attempted to track how it was doing as the response unfolded. The festival events were used as opportunities to establish pop-up clinics where vaccine could be offered in a mass-vaccination setting where people were already congregating. This was additionally folded into some of the "back to school" vaccination efforts as the summer wore on, and there were some broader community events that were brought to CDPH by community partners, at which vaccination staff and vaccine were provided. All of the pop-up clinic events and permanent clinic sites were mapped, and an interactive map was provided that could be accessed by the CDPH website so that people could identify locations where they could get vaccinated, as shown in the following illustration:



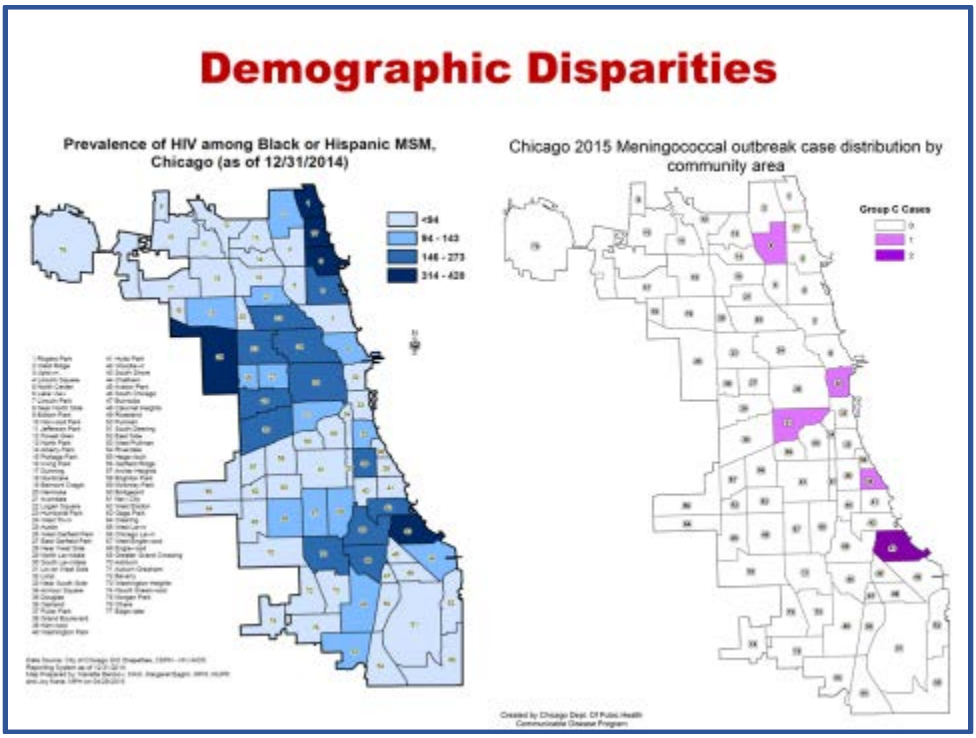
The media campaign included a standard press release to television, radio, and print media. Paper canvassing included posters, flyers, and palm cards. There were also billboards, Action Alerts to community partners, Twitter feeds, Facebook posts, push notifications on hook-up apps, and digital advertisements on Facebook, Twitter, and Google. CDPH engaged a number of community-based partner organizations, including HIV/MSM providers; STI clinics; non-clinical community-based organizations (CBOs); Lesbian, Gay, Bisexual, and Transgender (LGBT) Aldermen's Caucus; African American Aldermen's Caucus; gyms; bars/clubs; health fairs; community events; and House Ball networks. The House Ball network is a social phenomenon among black gay men in Chicago. This is akin to a fraternity system, which provides mentorship to young black men who are coming out and may not have role models and is like an alternate family structure. They have a number of parties as well monthly, throughout the summer, and throughout the year so this was an opportunity to work with some of those groups to incorporate the vaccination messages and possibly provide vaccine at some of their events.

Evaluation was primarily through reports back to CDPH from partners that received 317 vaccine, which are shown by week and site in the following graph:



The green bars represent CDPH-administered doses at pop-up clinic sites, the dark blue bars represent one of CDPH's highest volume clinical partners (Howard Brown Health Center), the red bars represent CDPH's other highest volume clinical partner (Core Center), and the purple bars represent Walgreens. There are some issues with reporting lags, so the large jump in the middle with the dark blue bars is primarily reporting lag of vaccine that was probably given in the earliest weeks of the campaign by Howard Brown Health Center. Overall, the highest number of vaccine doses were given out early on due to Pride Week and associated events. This was the biggest yield time to get vaccine out. The turquoise bars represent the amalgamation of other clinical partners, and it has been those clinical partner sites that have continued to get vaccine doses out after the initial push.

A number of challenges were encountered during this outbreak. One of the first challenges was deciding who was at risk. It can be difficult to determine who the denominator actually is. Most of the cases reported higher risk activities, but some did not and some identified as being in monogamous relationships. Many people use apps, but do not necessarily act on the partners they find there. Therefore, it is not clear whether app usage in and of itself is a risk factor or if it is what people do with the contacts they make through such apps. This is not a population who is stepping forward to indicate that they need to be vaccinated. Trying to find people who need to be vaccinated differs from a university setting in which there is a roster of students who belong to the university. One of the major challenges of this campaign pertained to demographics and disparities in access to care. The map on the left shows the prevalence of HIV among Black and Hispanic MSM in Chicago as of the end of 2014. The map on the right shows distribution of cases in the Chicago 2015 meningococcal outbreak by community area:



Cases in the outbreak were distributed in areas of the city where prevalence of HIV among minority populations is known to be high. However, clinical and outreach resources are concentrated in the Northeast neighborhoods, with much more limited access for populations on the south and west sides.

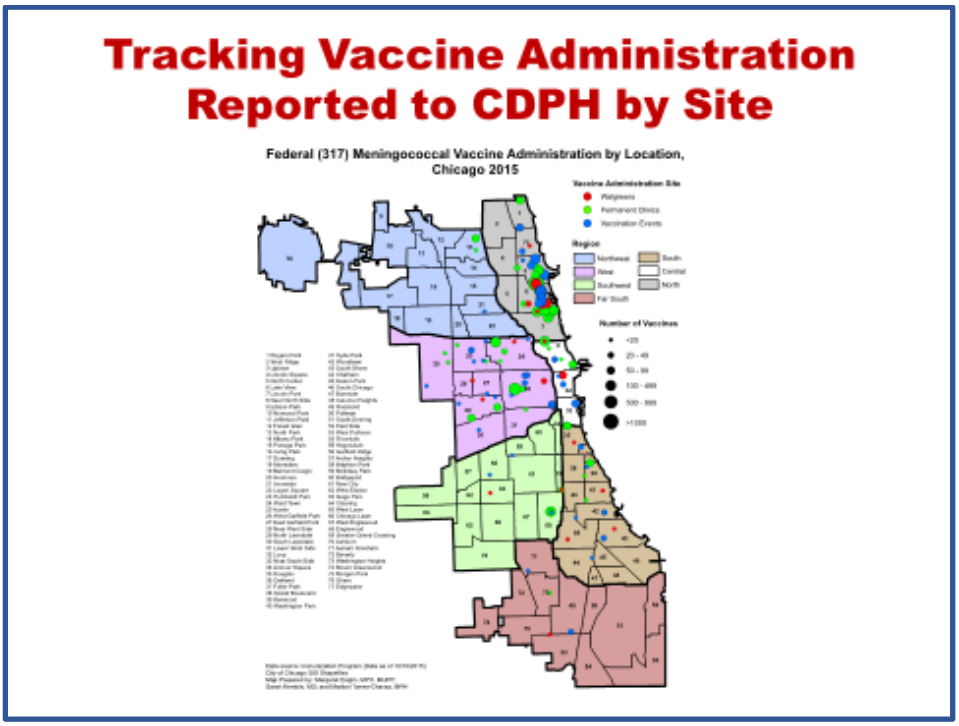
This was complicated by the fact that Black MSM were the least aware of the outbreak, based on data by Dr. Temi Folaranmi, an Epidemic Intelligence Service (EIS) Officer who joined CDPH for an Epi-Aid during this outbreak. Thanks to Dr. Folaranmi, CDPH was able to collect a lot of data on vaccine acceptance and demographics of those who were at sites where vaccines were made available [Temi Folaranmi MD, MPH, MPP, EIS Officer, MVPD Branch, NCIRD, Centers for Disease Control and Prevention, Epi-Aid 6/2015–10/2015, Survey of Clients at Vaccination Sites].

A number of community round table discussions were convened, particularly with Black MSM groups on the Southside and Westside, and some of the sentiment heard reflected the challenge of denial and stigma. Here are two examples of the comments made during the community round table discussions:

> "When we first heard about this [outbreak] we assumed, it's those white boys in Uptown bringing it in…We never thought it was happening in *our* community."

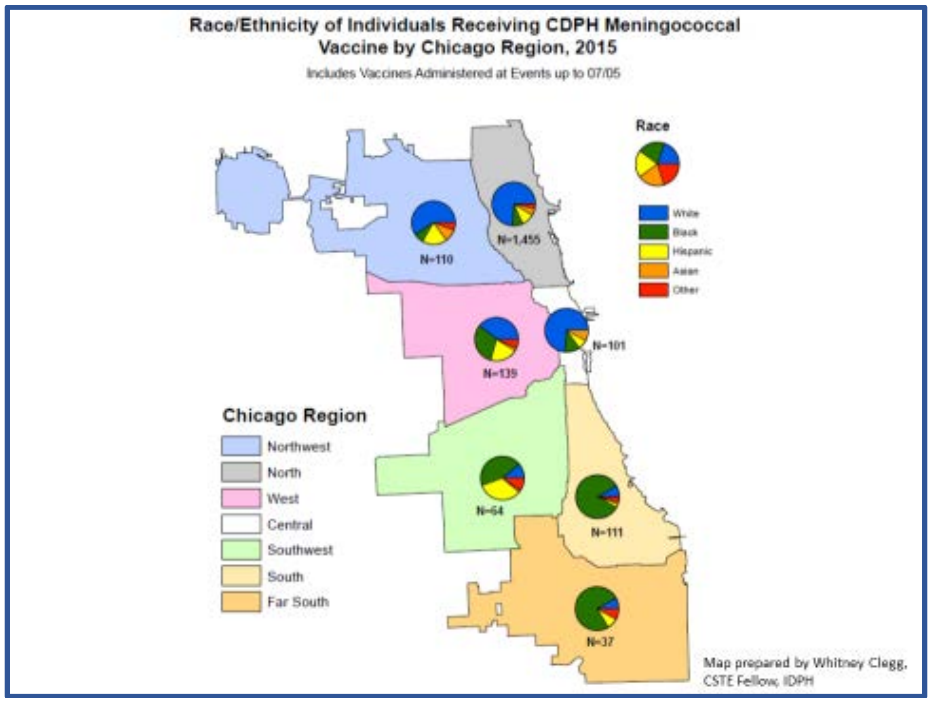
> "It feels like HIV all over again. Like, everything bad happens to [black gay men]."

Tracking vaccine administration was a challenge in and of itself. The highest risk groups were also the most difficult to reach, given that this includes Black gay men predominantly on the Southside and Westside of Chicago—the most underserved areas of Chicago. The nature of Pride Week and the festivals that occur is that they occur mostly on the Northeast side of the city, which is predominantly white and wealthier. The hope was that the demographic who needed to be reached would be attending these events. There are fewer opportunities on the Southside and Westside to get vaccine out in terms of festivals, events, and through standing clinics. Vaccine administration reported by site and area of town is shown in the following map:



Vaccine administration was also tracked by using the I-CARE vaccine registry and through several of the highest volume clinical sites that report into I-CARE. The initial weeks of the campaign showed most of the uptake in the Northeast corner of the city, again, the wealthier whiter areas. Over time, with the more targeted messaging developed and the work with community groups, uptake was increased in other areas of the city as well.

A preliminary assessment of the demographics of those who received vaccine reflected what would be expected based on the residential demographic distribution within Chicago, as shown in the following map:



CDPH felt confident that when they were vaccinating on the Southside, they were reaching much of the Black gay population.

There was also the challenge of HIV+ individuals requiring 2 doses of meningococcal vaccine given 8 weeks apart. A determination had to be made about how to identify those living with HIV, especially in a festival setting where it was not appropriate to ask people in front of others if they were HIV+. In addition, they had to ensure that those who were HIV+ returned for a second dose. Those challenges were met primarily by giving a generic message to all who approached the vaccination tables to let them know if they were HIV+, they would need a second dose.

In summary, the challenges encountered included how to reach members of social networks designed to preserve anonymity, how to facilitate communication and community participation to close knowledge gaps in underserved communities, and how to deliver vaccine in these areas despite the lack of infrastructure.

An effort is being made to estimate the cost of the campaign, which is in progress. Thus far, the total cost of the pop-up vaccine clinics is estimated to have been $51,672.76. This includes clinical staff (69%), outreach staff (20%), and medical supplies (11%). Virtually all of these clinics occurred during non-business hours, because that is when CDPH staff were available to vaccinate, and that is also when most of the events took place (e.g., weekends and after hours). The cost of vaccine is not included in this figure. The numbers of vaccines given by event type were not equal. Festivals had the highest yield in terms of the number of vaccines that could be administered with the fewest staff (n=2000), so the return on festival vaccinations was the highest. Bars were somewhat lower (N=607). Media costs are estimated to have been

$19,000. This includes Facebook/Twitter ($15,000), Grindr ($1500), and Radio ($2500). Free media channels included Jack'd, Scruff, and Manhunt. Advertisements on the digital billboard system supported by the city were at no cost to CDPH. At this point, the total expenditure by DCPH in terms of money is estimated to have been $70,000 from May through October 2015. Staff time during work hours is estimated to have been 3700 person-hours, which amounts to 466 8-hour work days. This is a significant opportunity cost to the health department in terms of not having time to work on some of its other usual activities.

In conclusion, the demographic most affected by the meningococcal outbreak in Chicago (e.g., African American, HIV+, and high-risk MSM) is also the most challenging demographic to reach. Pop-up clinics quickly boosted the numbers vaccinated, but permanent clinical sites were critical for a more sustained response. The vaccination campaign imposed a substantial burden on CDPH in terms of money and staff time.

Discussion Points

Dr. Harrison asked which vaccine CDPH used, whether WGS was done on the Minnesota case, and what the sequence type was.

Dr. Kemble replied that the vaccine provided through CDPH was Menactra®. The Walgreens sites predominantly gave Menactra®, but also used some private stocks and formulations. CDC performed WGS on the Minnesota case. It was closely related with greater than 99% similarity, but not less than a 12 SNP difference. It was more like a 74 to 84 SNP difference, but it was matched by PFGE; the PFGE sequence type was 428.

Dr. Stephens noted that there have been some reports of increased incidence of meningococcal urethritis among surveillance sites in the Midwest, and he wondered whether CDPH observed any increased reporting of meningococcal urethritis associated with the Chicago outbreak.

Dr. Kemble responded that CDPH was interested in this question because they were sharing the outbreak information with their clinical partners as it unfolded. Because of that, a couple of the partners brought cases to CDPH. Whether these were cases associated with the outbreak or just finders bias because they were talking about the outbreak was unclear, so two samples from these community clinical partners were sent to CDC. Neither of these samples could be typed and they were not matched by PFGE, so it is unlikely that they were related to the outbreak. However, it did raise the question of urethral carriage among these individuals and it would be interesting to see more data on that.

Dr. Duchin (NACCHO) asked what proportion of the vaccinated persons were in CDPH's high risk target population among those who had disease, and whether an assessment was done to determine which of the multiple outreach efforts were successful in driving those in who did come to get vaccinated.

Dr. Kemble indicated that it was difficult to assess who was in the demographic CDPH thought was at highest risk because many people are not willing to share certain information, such as information about finding partners on hook-up apps. The first case initially reported being in a monogamous relationship, but on repeat interview once other cases were discovered it came out that there were two or three anonymous partners during the incubation period. Through the Epi-Aid, there was a survey that asked about some of these risk factors among people who attended vaccination events, many of whom did get vaccinated, but not all. About 40% of Black

MSM reported use of apps, but there is likely to be underreporting. Data are lacking on HIV status because CDPH felt that asking people outright to share their HIV status when they came to get vaccinated would prevent people from coming to get vaccinated. The primary goal was to get vaccine out. The survey did ask about this, but not everyone chose to answer the question. She will review the survey data to determine what proportion reported being HIV+. It is certainly not as high for all-comers at these events as among the cases. In terms of which campaign components worked the best, looking at sheer numbers the festival events were the most successful. The subtext to that regards which events specifically reached Black MSM. That is the easiest component that could be assessed, other than parsing out risk factors. Some of the Ball Events and park events were the most successful at doing that, where most of the people vaccinated were Black MSM from the Southside or Westside. That was going into areas where they are known to hang out.

Dr. Gemmill (NACI) asked for the total number vaccinated in order to get an idea of cost per dose in this type of setting, whether only Chicago residents were immunized during events or if those from out of town were also included, and whether the vaccine campaign stopped the outbreak.

Dr. Kemble replied that the total number of vaccinated is not known because vaccination is ongoing with clinical partners providing vaccine. The current count is over 11,000 vaccinated and 15,000 doses distributed. With the reporting lag, the count will likely be 15,000 within the next couple of weeks. Immunization was not limited to Chicago residents. People were asked to fill in their address when they received the vaccine, but people were not told they could not get the vaccine if they were not from Chicago. About 9500 doses can be assessed through the I-CARE registry system, of whom 7500 provided a valid Chicago address. The rest is a combination of people who did not write down an address, wrote down a fake address, or were from other cities (a small number). A couple of thousand doses were administered between mid-June and the end of June when the last case was reported. It is difficult to know for certain whether the vaccination campaign stopped the outbreak, especially given that more of the highest risk demographic did not get vaccinated until somewhat later. Of course, CDPH hopes that this did stop the outbreak.

Dr. Reingold asked whether an attempt was made to try to ascertain risk factors for meningococcal disease in a case-control study in terms of sexual behaviors and so forth, and the extent to which CDPH worked with STI and HIV experts since this is a population with whom they work regularly. While it is true that there was a statistically significant relationship between awareness of the outbreak and race, all of these groups were about 80% to 90%, so he thought they achieved a pretty high level of awareness across the groups.

Dr. Kemble indicated that because the number of cases was so low, they did not pursue performing a case-control study. Risk factors were collected for all of the cases, but no attempt was made to assess controls and assess the same risk factors. That was done in New York City, and CDPH decided that their data were probably more valid given the numbers. Working with STI and HIV partners was brought to CDPH's attention early on by CDC colleagues, and CDPH did reach out to its own STI division. That was a large part of the impetus to perform the extended case investigations and case interviews. This was done through a partnership with CDPH's communicable disease staff who normally perform meningococcal investigations and an investigator from the STI-HIV division. Together, they conducted field visits and collected partner information from all of the cases. This was very helpful. Awareness was high among the younger demographic, but when parsed out to Black MSM below the age of 25, awareness

was about 50%. The concern was that some of the highest risk group was still not as aware of the campaign as CDPH would have liked.

Dr. Whitely-Williams (NMA) noted that HIV counseling and testing experts already are targeting a very high risk population and are able to do the HIV testing. To combine awareness and vaccinating with that group of individuals would have been very helpful. By doing testing, counseling, and vaccinating through this mechanism it would avoid anyone having to disclose whether they were HIV+.

Dr. Kemble responded that they did try to partner with community-based Ryan White-funded organizations to conduct HIV counseling and testing along with meningococcal vaccination. It would have been great to compile that type of partner counseling data with the demographics of those vaccinated, but the logistics of it were too complicated in terms of space and organization to combine them that seamlessly—though it is a great idea.

Influenza

Introduction

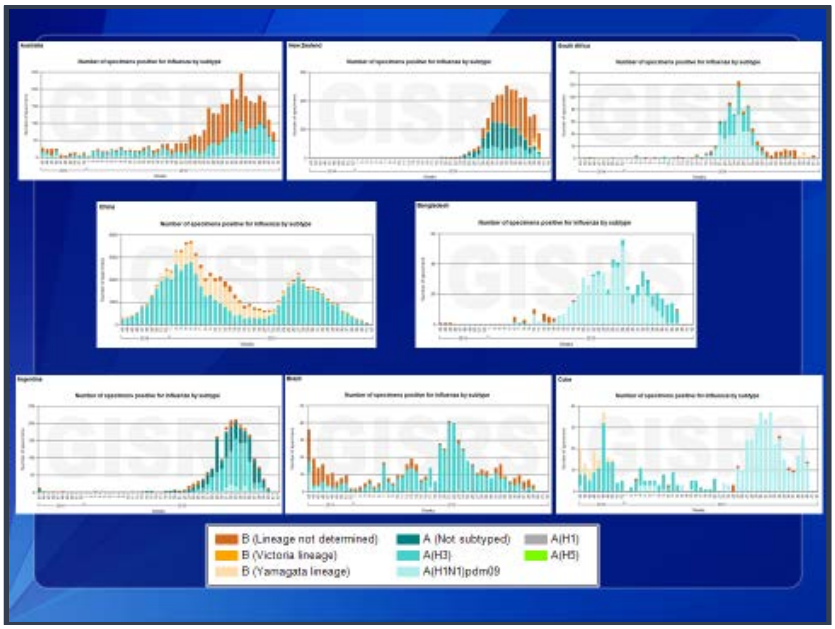
Ruth Karron, MD
Chair, Influenza Work Group

Dr. Karron reported that since the June 2015 ACIP meeting, the Influenza WG had considered the cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine (IIV) for persons ≥65 years, as well as clinical data for adjuvanted trivalent inactivated influenza vaccine (TIV). She indicated that during this session, the full ACIP membership would hear an update on influenza epidemiology and surveillance, and a report on the cost-effectiveness of high-dose versus standard-dose IIV for persons ≥65 years, and a report on the clinical data for adjuvanted TIV.

Epidemiology and Surveillance Update

Lynnette Brammer, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Brammer presented updates on international influenza activity, recent US influenza activity, and Southern Hemisphere vaccine recommendations. Based on an aggregation of influenza positives reported by the National Influenza Centres (NICs) in Southern Hemisphere countries, there was a mix of all viruses (H1N1pdm09, H3N2, A viruses not subtyped, B viruses). Information from individual countries reflects the variability observed in predominating viruses by countries, as illustrated by the following graphs of countries with recent activities:



The first two graphs on the top left are Australia and New Zealand, where there was a largely even distribution between H3N2 viruses and influenza B viruses. This is in contrast to what was observed in South Africa where there was predominantly H1N1pdm09 viruses, with some H3N2 viruses and an uptick in influenza B late in their season. Recent activity in China has been predominantly H3N2. Bangladesh had a predominantly H1N1 season, although they have had an increase in H3N2 viruses more recently. In the Americas, Argentina had predominantly H3N2 viruses and very little B viruses. Their outbreak was sharp and brief. Brazil has a much more prolonged outbreak, which was H3N2 predominant with some influenza B virus at the end of their season. In contrast, Cuba has had a lot of H1N1 activity recently.

For the US, several changes have been made in how surveillance data will be reported for the coming season. Laboratory data have been obtained from the US World Health Organization (WHO) Collaborating Laboratories and the National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories, and data from clinical laboratories and data from public health have been split out and will be reported separately. Each of these components will be used to offer the best representation of the data. Regarding influenza positive data from US clinical laboratories from May 24, 2015 through October 10, 2015, influenza B was predominant in the late spring. As the summer progressed, influenza A became predominant. During the week ending October 10th, 1.2% of the specimens tested and reported to CDC from clinical laboratories were positive for influenza, but influenza activity remained very low compared to the peak of the season last year. During the same timeframe, detailed data from US public health laboratories showed a predominance of influenza B coming out of last season, but over the summer there was a dramatic shift to influenza H3N2 viruses with a small number of H1N1pdm09 viruses. Overall, these data showed very low activity as well during this time period. Reported through the Influenza-Like Illness Surveillance Network (ILINet), 1.2% of patient visits were for influenza-like illness (ILI). Compared to other recent seasons, this is typical for this time of year.

Another major change for surveillance this year is that CDC is transitioning away from its traditional system for reporting pneumonia and influenza mortality from the 122 Cities system to the National Center for Health Statistics (NCHS) mortality surveillance system. These are the regular vital statistics data that NCHS collects, which are being made available to NCIRD in real time. The data will be presented the same as the 122 Cities data have been reported, showing the percent of death certificates that have pneumonia or influenza listed anyplace on the certificate and the seasonal baseline and epidemic thresholds, which are modeled using a robust regression procedure. One advantage of these data is that when all data are in, NCIRD will have virtually 100% of all deaths that occurred in the US within a year of the date of time of death. In addition, rather than being reported the week the death certificate is filed, it is possible to plot the data by the date of death, which offers a more accurate picture of the timing of influenza activity. As of October 15, 2015, through the week ending September 26, 2015, 5.5% of the deaths reported to this system had pneumonia or influenza reported someplace on the certificate. That is compared to a baseline of 6.2%.

The geographic distribution of influenza as of the week ending October 10, 2015 (Week 40) is basically as would be expected at this time of year, with the majority of states reporting either no activity or sporadic activity. However, Oklahoma reported local activity, Hawaii reported regional activity, and Guam reported widespread activity.

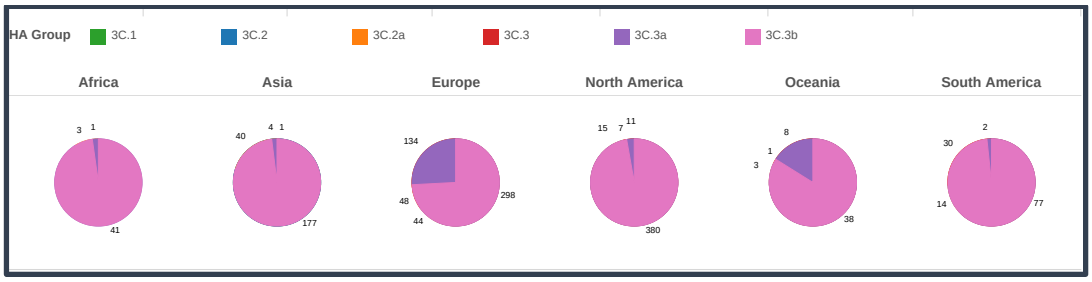
In terms of the Southern Hemisphere vaccine virus selection, the WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for the Southern Hemisphere 2015 was convened on September 22-24, 2015. During that meeting, it was recommended that the following viruses be used for trivalent influenza vaccines in the 2016 Southern Hemisphere influenza season:

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus

For quadrivalent vaccines containing two B components, it was recommended that the following viruses be used in the 2016 Southern Hemisphere influenza season:

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
- A B/Phuket/3073/2013-like virus

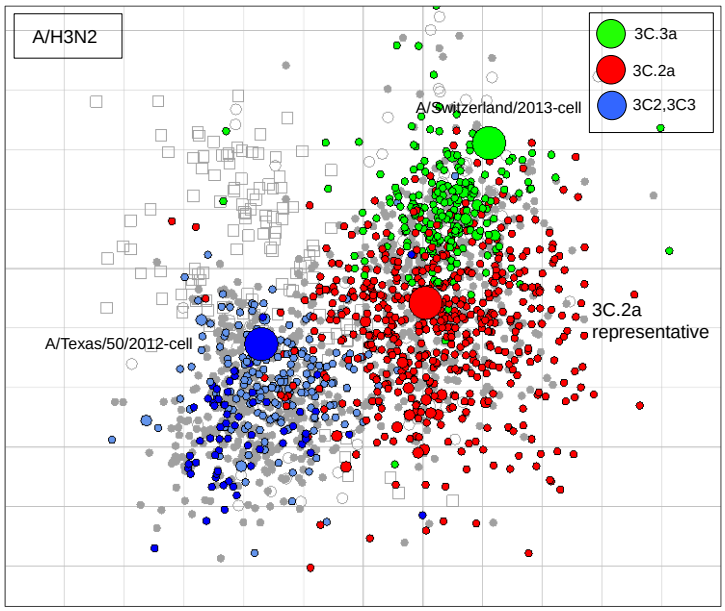
The Southern Hemisphere recommendation represents an update in the H3N2 component and a switch of influenza B virus lineage for the trivalent vaccine formulation. These updates are not the result of significant antigenic drift as was observed last season. Global laboratory data continue to indicate that most currently circulating viruses are antigenically similar to the vaccine viruses included in the 2015-2016 US vaccines. Considering the H3 viruses in more detail, recent H3N2 viruses can be divided into multiple genetic groups as illustrated in the following graphic:



The A/Switzerland/9715293/13 viruses which is in the Northern Hemisphere vaccine this year formulation belongs to the 3C.3a group. A/Hong Kong/4801/14 which was recommended for the Southern Hemisphere component belongs to the 3C.2a group. While there are 3C.3a viruses still circulating throughout the world, the majority of viruses are in the 3C.2a genetic group.

Antigenic characterization of A(H3N2) viruses remains technically difficult. Many of the 3C.2a viruses assessed had low or undetectable hemagglutination activity or could not be recovered in cell culture at all. This required the use of modified hemagglutination inhibition (HI) and virus neutralization assays for analysis. Egg propagation of these viruses can introduce changes in the viruses that may affect their antigenicity.

The following is antigenic cartography data produced from HI assays performed at CDC using reference ferret antisera raised to representative viruses from different antigenic groups:



There is a good bit of overlap between the two genetic groups 3C.3a (lime dots), the group to which A/Switzerland belongs, and the 3C.2a (red dots), the group to which A/Hong Kong belongs. This indicates that there is cross-reactivity between many of the viruses in this groups, and that the majority of viruses are antigenically related. However, there are viruses on the periphery that are antigenically distinguishable from one another. Comparing this to the older 3C.2a, 3C.3a, and last season's A/Texas vaccine viruses represented by the blue dots, there is

much less overlap between those viruses and the 3C.2a and 3C.3a viruses, indicating that those viruses were more antigenically distinct.

Genetic subgroup 3C.2a viruses are predominating globally. Antigenic characterization using reference ferret antisera indicate that 3C.3a and 3C.2a viruses are overall antigenically similar but are distinguishable in some cases. A suitable candidate vaccine virus for 3C.2a genetic subgroup viruses was not available last February when the Northern Hemisphere vaccine strain selection was made, but now there are several 3C.2a candidate vaccine viruses available.

The influenza B viruses recommended for quadrivalent influenza vaccines did not change. The influenza B lineage recommended for trivalent influenza vaccines switched from a B/Yamagata lineage to the B/Victoria lineage. B/Victoria and B/Yamagata lineage viruses continue to co-circulate, with B/Yamagata viruses predominating in many countries but the proportion of B/Victoria viruses increased in Australia and New Zealand from June 2015.

In summary, influenza A(H1N1)pdm09, A(H3N2), and both lineages of influenza B viruses continue to circulate worldwide. Activity in the US and other Northern Hemisphere countries remains low at this time. Recommended viruses for the 2016 Southern Hemisphere vaccine differ from the current Northern Hemisphere viruses, but changes represent minor updates and are not due to significant antigenic drift. Global laboratory data continue to indicate that most currently circulating viruses are antigenically similar to the vaccine viruses included in the 2015-2016 US vaccines. This suggests that vaccination with Northern Hemisphere influenza vaccine should offer protection against the majority of circulating viruses analyzed to date and may offer significantly more protection compared to last season's vaccine.

Discussion Points

Dr. Belongia requested information about whether there has been any antigenic testing of high growth reassortant viruses that are used for vaccine manufacturing and how those compare with the WHO reference viruses.

Dr. Jacqueline Katz (NCIRD) responded that the WHO Collaborating Centers routinely compare the candidate vaccine viruses with the reference ferret antisera that were produced against the parental wild type strains. In order for candidate vaccine viruses to be passed and approved for use by a manufacturer, they must be antigenically similar to the recommended strains. That has been done and a number of these are posted on the WHO website.

Ms. Stinchfield (NAPNAP) noted that the Influenza WG has discussed whether there is a time that is too early to start vaccinating and the duration of protection. She wondered whether anything was known about the vaccination status of the individual cases in the South African spring B outbreak and H1N1 in Cuba, and whether CDC had any plans to assess late season breakthrough disease in people who are vaccinated early in August and September.

Ms. Brammer replied that CDC does not have the vaccination status for the viruses submitted from South Africa, or from any of the viruses reported to the WHO system. CDC will be conducting vaccine effectiveness (VE) studies to understand VE in the US in the fall, and that will be done throughout the season. There will be early season estimates, which would represent people vaccinated earlier in the season. Because the plan is to assess the entire season, it will be possible to notice any changes that occur late in the season.

Cost-Effectiveness of High-Dose Versus Standard-Dose Inactivated Influenza Vaccine in Adults Aged 65 Years and Older

Ayman Chit, MBiotech, PhD (Via Teleconference)
Sanofi Pasteur
Lesli Dan School of Pharmacy
University of Toronto, Ontario, Canada

On behalf of the authors of the study and Sanofi Pasteur, Dr. Chit thanked ACIP and the CDC Influenza WG for the opportunity to present the results of Sanofi Pasteur's study during this session. In addition, he thanked the Office of the CDC Chief Economist for reviewing the study. The slides presented during this session were the result of the scientific exchange that they have had with the Office of the CDC Chief Economist. The study was published in September 2015 in *The Lancet Infectious Diseases*. During this presentation, Drs. Chit and Greenberg reviewed the study methods, results, and limitations.

This study was an economic evaluation of High-Dose Fluzone® vaccine, which is an inactivated split virus influenza vaccine containing 4 times the antigen content of standard-dose vaccine. More specifically, a cost-effectiveness analysis was conducted that compared Fluzone® High-Dose vaccine versus standard-dose Fluzone® vaccine. This analysis primarily used data from the randomized control study FIM12, an efficacy study that has been presented to ACIP in the past that has been published in the *New England Journal of Medicine (NEJM)* and elsewhere. *At this point, Dr. Chit was breaking up and could not be understood, so Dr. David Greenberg delivered the remainder of the presentation.*

David P. Greenberg, MD
Vice President, Scientific & Medical Affairs
Chief Medical Officer, Sanofi Pasteur US

Dr. Greenberg apologized for the technical issues, and completed the remainder of Dr. Chit's presentation. He explained that the analysis was primarily from the randomized controlled study, which Sanofi Pasteur termed FIM12, which Dr. Chit had mentioned has been presented previously to ACIP and to the CDC Influenza WG. The results were published in the *NEJM* last year, and follow-up reports were subsequently published in other journals. Dr. Greenberg emphasized that the key feature of the analysis that Dr. Chit performed was from the randomized controlled trial of FIM12, so very little modeling or extrapolation of the data was required because it was all contained within that efficacy trial. This was a study of nearly 32,000 seniors who participated in the two-year study. The results are reported from both the healthcare payer and societal perspectives, and the latter encompasses the former and adds costs associated with workplace productivity. A single influenza season was used as the time horizon for assessing healthcare resource utilization and changes in quality of life due to clinical events. Lost life years (LY) and lost quality-adjusted life years (QALYs) due to deaths were considered up to the life expectancy age. A 3% annual discount rate was used and was applied to outcomes that occurred after the first year.

In terms of the basic design of the FIM12 randomized controlled trial (RCT), and how the economic evaluation was added on, FIM12 spanned two influenza seasons: 2011-2012 and 2012-2013. The 2011-2012 season was mild and had a good match between the vaccine and circulating strains, while the 2012-2013 season was more severe and had a mismatch between the circulating and vaccine H3N2 strains. Participants were enrolled and randomized at the

beginning of each season. Study centers collected data on clinical events and health care resource utilization from the participants. Data on clinical events experienced by study participants were then mapped to corresponding costs and quality of life data. All costs were reported in 2014 dollars. To estimate cost-effectiveness, costs and outcomes were compared between the two groups. Unlike most cost-effectiveness studies which rely heavily on mathematical modeling of the relationship between the vaccine and clinical outcomes, this analysis relied on the FIM12 head-to-head RCT to directly inform the impact of these vaccines on the clinical outcomes. As noted earlier, little mathematical modeling was needed for this analysis.

Two sets of analyses were performed, and subgroup analyses were conducted within each. The first set, identified as Scenario 1, involved assessing all of the outcomes collected in the study regardless of their relation to influenza. More specifically, this included the cost of vaccine, medication, hospitalization for any reason, and emergency department (ED) non-routine urgent care visits following a new respiratory illness. Lost life due to death was considered regardless of the cause of death. To emphasize, Scenario 1 involves assessing all of the outcomes collected in the study regardless of their relation to influenza. So for example, if a study participant was hospitalized due to an accident, that outcome was included in Scenario 1 despite its unlikely relationship to influenza. The upside of that strategy is that it provides insight into the relative impact of Fluzone® High-Dose in the total cost and the overall health of the study population. The downside of this strategy is that it may miss the impact of vaccine due to noise generated by the non-influenza related medical events, and there are many of those in this population.

To address the downside, a second analysis was conducted and is referred to as Scenario 2. Scenario 2 considered only cardio-respiratory clinical outcomes that were considered plausibly related to influenza. The feature allowed for the removal of much of the noise generated by outcomes not likely related to influenza. For each of these two scenarios, two sub-group analyses were performed in subjects who had either one or more pre-specified high-risk comorbid conditions, typical high-risk conditions for complications due to influenza, and in subjects who were 75 years of age and older.

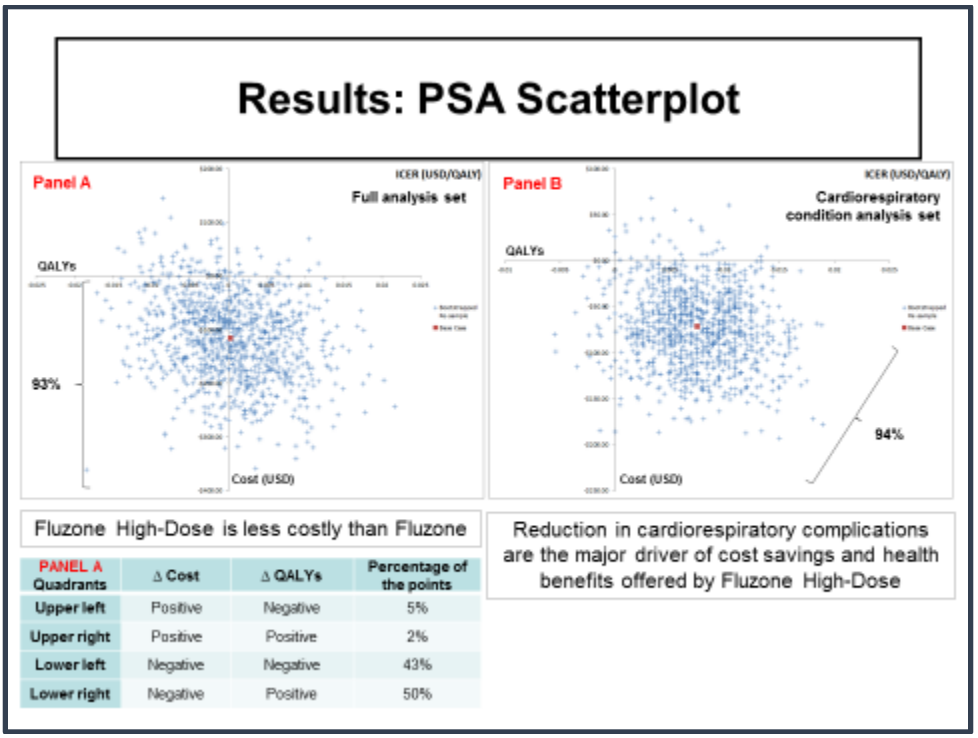
With regard to the key data collected and used in the economic analysis and evaluation to supplement the FIM12 clinical trial, the vaccine prices were provided from the CMS seasonal influenza vaccine pricing list: about $12 for Fluzone® vaccine and about $32 for Fluzone® High-Dose. The reason the other medications were listed is because the medications were restricted to antipyretics and antivirals. Healthcare visit and hospitalization costs were obtained from sources that represent Medicare costs. Most notably, it was estimated that the hospitalization costs varied from about $1200 per day to just over $9000 per day. That variation was driven by the various hospitalization diagnostic codes. Regarding the quality of life data used in the study, the investigators began with average utility scores of 0.802 and 0.771 for males and females, respectively. These were drawn from the literature. Various medical encounters would then reduce the quality of life by varying amounts. For example, the reduction from baseline associated with hospitalization equals 0.4272 for the first 3 days and 0.2832 for the remaining days until discharge.

Comparing the costs between the two arms of the study presented per participant; that is, the total costs for each cost category summed up for each study arm and then divided by the number of study participants enrolled in that arm of the study, the price difference between the two vaccines was about $20 per participant. In terms of whether there were any cost savings

that would offset the $19.75 investment in Fluzone® High-Dose, there was little difference with respect to the prescription medications, ED visits, or urgent care visits. However, hospitalization costs were $136 per participant lower in the Fluzone® High-Dose group compared to the Fluzone® group. This offset the incremental increase in the vaccine cost and resulted in a net savings of $116 per participant. This is the most important finding of this study. This considers only the cost burden to the healthcare system.

When the scope was widened to include costs from the rest of society, further savings were associated with anticipated improvements in the productivity of the Fluzone® High-Dose group for a total societal-wide savings of $128 per participant. Regarding the results from the cost-effectiveness calculations, Fluzone® High-Dose also generated a higher number of QALYs than the standard dose Fluzone® vaccine group. As such, Fluzone® High-Dose dominated Fluzone® in the cost-effective analysis. In other words, Fluzone® High-Dose was both less costly and more effective than Fluzone®. The primary conclusion applies to the other analyses conducted as well. Fluzone® High-Dose was both less costly and more effective than Fluzone® in the cardio-respiratory outcomes analysis Scenario 2 and in all of the subgroup analyses, which is a reminder that the subjects have comorbid conditions and are 75 years of age and over.

A probabilistic sensitivity analysis was performed to help understand the impact of the statistical uncertainty of the conclusions, illustrated by the following scatterplots:



PANEL A Quadrants	Δ Cost	Δ QALYs	Percentage of the points
Upper left	Positive	Negative	5%
Upper right	Positive	Positive	2%
Lower left	Negative	Negative	43%
Lower right	Negative	Positive	50%

Starting with the plot on the left, the horizontal axis represents the difference in the QALYs between the Fluzone® High-Dose and Fluzone® groups, so any positive findings (the right side of the graph) supports QALY benefits in favor of Fluzone® High-Dose. The vertical axis represents the difference in costs between the two vaccines, so any negative readings (the lower half of the graph) support cost savings in favor of Fluzone® High-Dose. The red square at the center of the dots represents the base case or average. The dots on this graph are the points of the statistical distribution of the effectiveness analysis, and that was the bootstrapping

with 1000 samples. The red square at the center of the dots represents that average case. The one on the left is just to the right of the vertical line and well below the horizontal, and the other one is on the right. The left panel represents results from the full analysis set.

Recall that this analysis contains high background noise, as all medical events were included. For example, hospitalizations due to injuries or accidents are also in this dataset. The striking finding of the dataset is that despite that heterogeneity, 93% of the statistical distribution shows that Fluzone® High-Dose provides cost savings, because 93% of the analysis is in the lower half of the plot, which represents cost savings in the High-Dose compared to Standard-Dose Fluzone®. The right panel represents results from the cardio-respiratory analysis. Here the signal to noise was improved, only focusing on the respiratory conditions plausibly related to influenza. In other words, the events that were not cardio-respiratory in nature and not likely to be related to influenza were stripped out. Now 94% of the statistical distribution falls in the bottom right corner region that supports the conclusion that Fluzone® High-Dose is both less costly and more effective than Fluzone® vaccine. This was the second most important finding from the study.

Hospitalization data were the primary driver of the analysis. Hospitalization event data were all collected in the head-to-head RCT, and they were not based on modeling. The costs were obtained from Medicare sources, and these represented 95% of the total costs to the healthcare payer and 87% of the total societal cost. After hospitalization costs, the vaccine costs and the indirect costs were the next two notable cost categories, respectively. However, their contribution was minor compared to the cost of hospitalization.

Like any study, this one has standard limitations. First, the evaluation was conducted on the FIM12 study population. Therefore, all limitations of an RCT apply. Most notably, the trial did not enroll bed-ridden seniors due to practical considerations of the study, and the trial did not collect data on indirect protection of vaccine to others in the household or community. Second, QALY data were not collected directly in the FIM trial. Instead, QALY data were acquired from the literature. Third, some diagnostic codes had to be grouped when estimating the hospitalization costs, which was primarily to simplify the exercise of costing the more than 3000 unique hospitalizations recorded in the FIM12 study. Fourth, disutilities and costs were limited to those experienced during the study period. If disutility was experienced by seniors due to a hospitalization after the study ended, that was not included.

Discussion Points

Dr. Moore requested clarification that the difference in QALYs, although it was dominated, was four ten thousandths.

Dr. Greenberg replied that all of the analyses were divided across all 32,000 participants. So, a reduction of QALY gained there of 0.0004 was averaged across all 32,000 participants.

Dr. Karron asked whether a difference was observed by season and within subgroups, high-risk groups, those over 75 years of age.

Dr. Greenberg replied that certainly any time data are cut in a different way, there will be slightly different results. He emphasized that they were just modest differences. All of the conclusions about Fluzone® High-Dose being less costly and of greater benefit applied in all of the subgroup analyses and by season. That conclusion was the same for the very mild 2011-2012 season,

as well for the more severe H3N2 season with some mismatch. The conclusions were the same by the comorbidity and cardio-respiratory subgroup analyses and by age. While there was some variation in the exact dollar amounts, this was not by a magnitude and they were all directionally the same.

Dr. Sun (FDA) asked whether any subgroup analyses were performed based on gender in terms of this cost-benefit analysis.

Dr. Greenberg replied that such analyses were not performed prospectively as far as he was aware, but this certainly could be done.

Dr. Weber (SHEA) asked whether there were any plans to perform this analysis of high-dose versus quadrivalent standard-dose.

Dr. Greenberg responded that an analysis was performed which was more of a modeling study based on the literature and what is known about Fluzone® High-Dose and quadrivalent vaccines. That analysis is published. In the senior population where influenza B occurs but H3N2 is clearly the more severe pathogen and results in more hospitalization, complications, and deaths, the analysis clearly showed that in terms of a cost per QALY, Fluzone® High-Dose was more cost-effective than quadrivalent vaccine.

Dr. Neuzil (IDSA) asked whether there will be a quadrivalent high-dose in the future and if so, whether the price differential between the high-dose and the standard-dose for quadrivalent would be similar.

Dr. Greenberg responded that the clinical development program for quadrivalent high-dose Fluzone® High-Dose is underway. Sanofi Pasteur is conducting a Phase II study this year, and that process is ongoing. Having a high-dose vaccine for the senior population was paramount, so that is where Sanofi Pasteur focused its efforts. The quadrivalent vaccines do not provide as much benefit in this population, but the process is underway for the high-dose quadrivalent vaccine. While he could not comment on price at the moment, he said he would provide it.

Dr. Messonier (CDC SME) asked whether Dr. Greenberg had data showing a sensitivity analysis of price to reflect at what point the comparative advantage would fall off.

Dr. Greenberg responded that while he did not have this information with him, his understanding of the data and Dr. Chit's analyses was that it would have to be a very expensive vaccine for the cost benefits to disappear or drift down to zero.

Dr. Duchin (NACCHO) recalled that in each of the categories in the QALY analyses, high-dose was preferred because it dominated in the analysis. But he also noticed that the difference was about four ten thousandths of a QALY between the two vaccines. He asked Dr. Greenberg to help him understand what four ten thousandths of a QALY meant.

Dr. Greenberg explained that if a person is hospitalized, there is a reduction of about a 0.4 QALY in the person's quality of life during early days of the hospitalization, somewhat less of a drop-off in their quality during the latter part of the hospitalization, and probably a little reduction occurs after that person goes home. But that is one hospitalization—one dramatic effect on that one person's quality of life. There were plenty of hospitalizations in the study, many of which were not related to influenza. When all of the hospitalizations and other medical events that

occurred in the high-dose group versus the standard-dose group are combined and averaged them among 32,000 people, the difference is small. The difference would be large when assessing only the cardio-respiratory events, but if a vaccine provided health benefits so that the quality of life was better, even marginally, but cost a lot, the discussion would be about how many dollars per QALY that benefit would cost the health system and society. This vaccine resulted in less cost. While the difference in the QALYs across 32,000 people who had all sorts of medical events occurring during the two years of the study was small, it actually cost the medical system less money to provide that vaccine than a standard-dose Fluzone®.

Dr. Duchin asked why the benefit was found only in hospitalization if it was so dominated by cardio-respiratory conditions in general.

Dr. Greenberg responded that this was somewhat due to the design. In this case, it was possible to identify all of the cardio-respiratory events that occurred in the trial. When including every office visit, ED visit, and non-urgent visit that occurred during the study, it just got diluted by all of the noise of everything that was not related to influenza or was not serious. So, that was why the cost savings were observed primarily for the serious events.

Adjuvanted Trivalent Influenza Vaccine

Kelly Lindert, MD
Head, Development
NVS Influenza Vaccines

Dr. Lindert provided an overview of NVS Influenza Vaccines' adjuvanted trivalent inactivated influenza viral vaccine (aTIV). She provided a brief overview of the development of aTIV, the mechanism of action of NVS Influenza Vaccines' adjuvant known as MF59, data on the immunogenicity and safety of aTIV in clinical trials, safety data from post-marketing experience, data from two observational trials evaluating the effectiveness, and additional data relating to the recent A(H3N2) mismatch.

The development program supporting aTIV spans more than 20 years, with the first clinical trials initiated in 1992. Since then, aTIV has been reviewed and approved by several health authorities. It was first approved for us in Europe in individuals 65 years of age and older in 1997. In 2011, aTIV was approved in Canada for use in older individuals. In 2015, it was approved in Canada for use in children. aTIV is currently approved in more than 30 countries worldwide, and to date, more than 76 million doses have been distributed across these countries for use in the prevention of influenza. In 2014, Novartis filed a Biologics License Application (BLA) seeking US licensure for the use of aTIV in individuals 65 years of age and older. These data were reviewed at Vaccines and Related Biological Products Advisory Committee (VRBPAC) in September, with a favorable vote by the members of that committee.

Regarding the rationale for development of an adjuvanted influenza vaccine, influenza-associated deaths remain high in those individuals 65 years of age and older despite recommendations for use and the use of influenza vaccines in this age group. This is in part due to immunosenescence, or the aging of the immune system. Immunosenescence is a deregulation of immune function, which not only increases the incidence and severity of infections, but also reduces a person's ability to respond to vaccination. These two issues create a particular unmet need in the older population that adjuvant use can help to address.

MF59, the adjuvant in aTIV, enhances the immune response to influenza vaccine and has an acceptable safety profile. MF59 is a stable oil and water emulsion in which droplets of squalene coated in surfactants are suspended in a citrate buffer. Squalene is a naturally occurring precursor to cholesterol and is present in the liver, adipose tissue, and skin. The surfactants, Tween® 80 and Span® 85, are commonly used for pharmaceutical products and are sourced from plants. Overall, it is the droplet structure that is critical for the adjuvant effect of MF59. Furthermore, no single component of MF59 individually enhances immunogenicity. Rather, it is the combination that is necessary.

The adjuvant's mechanism of action can be described in three basic steps. First, MF59 activates dendritic cells and macrophages, attracting monocytes and neutrophils to the site of injection. Second, the presence of MF59 leads to differentiation of these cell types. These cells transport more antigen from the injection site to the draining lymph node. Third, within the lymph node, MF59 leads to T-cell activation and an increased B-cell expansion, with the downstream result of increased production of neutralizing, influenza-specific antibodies.

With regard to how this mechanism of action translates into response in the clinical setting, MF59 has been evaluated extensively in clinical trials. Data from 58 interventional trials were included in the BLA filing. Of these, 39 were performed in individuals 65 years of age and older leading to a safety database of over 27,000 individuals. The large number of trials facilitated the review of the safety profile of aTIV. However, it is the large pivotal trial, V70_27, that represents the primary study evaluating the immunogenicity and safety of aTIV in older adults. Additional analyses of immunogenicity were conducted in a grouping of 15 randomized, controlled primary vaccination and in 7 revaccination trials. The latter included individuals receiving up to 3 annual doses of aTIV or TIV vaccine.

Pivotal study V70_27 was designed to evaluate the immunogenicity and safety of aTIV. This study was a randomized, controlled, observer-blinded multi-center trial enrolling 7104 study participants 65 years of age and older. The subjects included both healthy individuals and those with underlying comorbidities, and the subjects were assigned to 1 of 3 lots of aTIV or to non-adjuvanted seasonal TIV. The 3 lots of aTIV were confirmed equivalent and, therefore, data from the subjects receiving vaccine from any of these 3 lots were pooled into a single aTIV group for comparison with the non-adjuvanted TIV group for subsequent study objectives. Of note, the TIV comparator was a US-licensed vaccine with the same antigen content as the aTIV, and it is approved for use in older adults. In this trial, individuals received a single dose of vaccine on Day 1, representing the start of the treatment phase. The treatment phase lasted until Day 22 when the co-primary objectives were evaluated. Participants were followed for safety until one year after vaccination. Additional blood samples were taken at Day 181 and Day 366 to evaluate antibody responses at later intervals following vaccination. This is referred to as persistence.

The primary non-inferiority objective comparing aTIV to the US-licensed comparator was met in this pivotal trial. With respect to the comparison of the homologous antibody responses (e.g., the antibody responses against antigens included in the composition of the study vaccines), for all three homologous influenza strains, the lower bound of the 95% confidence interval for the geometric mean titer (GMT) ratio was above 0.67, which is the margin for non-inferiority in this study. The lower bound of the 95% confidence interval for differences in vaccine group seroconversion was greater than -10%. In this study, an additional objective evaluated antibody responses for superiority, defined as exceeding GMT ratios of 1.5 and seroconversion rate differences of 10%. Although the study objective was not met, aTIV met these thresholds for

the A(H3N2) strains and demonstrated overall a trend of higher antibody responses for the other two influenza strains. Antibody responses against unmatched or heterologous influenza strains were also evaluated in this trial. Both GMT ratio and seroconversion rates against these two heterologous A(H3N2) and one B strain met the non-inferiority criteria. Antibody responses were also consistently higher following vaccination with aTIV.

Safety data collected in this pivotal trial included solicited and unsolicited AEs that were monitored within the period immediately after vaccination. A subset of the unsolicited AEs were monitored for the full year in this older population. These safety assessments demonstrated no differences in unsolicited AEs. Of individuals within the aTIV and TIV groups, 1.5% and 1.3% died within the year of follow-up, 7% experienced serious adverse events (SAEs) within this interval, fewer than 1% of subjects in each vaccine group withdrew from the study due to AEs, 16% of individuals in both vaccine groups experienced unsolicited AEs within the first three weeks after vaccination. Somewhat of a difference between vaccine groups was an increase in solicited AEs within a week following vaccination. The most common solicited AEs overall included injection site pain, tenderness, myalgia, headache, and fatigue. In these 5 events, the events were more commonly reported in the aTIV group as compared to the TIV group. Nevertheless, the majority of the events were mild or moderate in severity and of similar duration in both vaccine groups.

Additional safety data are available beyond the clinical trial experience. As described earlier, aTIV has been licensed outside of the US for over 17 years. Spontaneous reporting of safety data are available following the distribution of over 76 million doses of the vaccine. As a general note, the ongoing routine surveillance of these spontaneously reported cases has demonstrated a safety profile consistent with other licensed influenza vaccines, and without detection of any novel safety signals. Furthermore, for the BLA filing, these data were further analyzed for reporting of potential adverse events of special interest and adverse events following immunization. An analysis comparing reporting in the aTIV database against reporting of these cases in the database of another non-adjuvanted influenza vaccine administered to older individuals demonstrated no disproportionality for either AEs of special interest or AEs following immunization. Of note, no narcolepsy cases have been reported to date with the aTIV vaccine.

Two effectiveness studies have been conducted with aTIV. The first trial is known as the Lombardia Influenza Vaccine Effectiveness (LIVE) study, which is a large, multi-season community-based observational study in Italy. In this study, older individuals received either aTIV or a non-adjuvanted influenza vaccine. These individuals were followed prospectively for pneumonia- or influenza-related hospitalizations. At baseline, the patients vaccinated with aTIV had more comorbidities, showed higher functional impairment, and were 17% more likely to be hospitalized prior to study enrollment. However, in spite of this imbalance and after adjusting for confounders, the risk of hospitalization for influenza and pneumonia for those receiving aTIV was reduced by 25% during the active influenza season.

The second effectiveness study was undertaken in British Columbia, Canada. In British Columbia, all influenza tests are analyzed by a central laboratory and positive tests are reported to health authorities by law. This lends itself well to a case-control test negative, community-based study evaluating RT-PCR-confirmed influenza cases. At the conclusion of this influenza season, in the community dwelling residents, aTIV was 73% effective versus 42% for TIV, leading to a 31% absolute difference between the two vaccines in the prevention of RT-PCR-confirmed influenza. In addition, in older patients with comorbidities in long-term care, aTIV effectiveness dropped to 60%, but TIV was reported as ineffective. As a result, the relative

benefit of aTIV over TIV was 63% in this population. Also of note, the prevalent influenza strain circulating in the year of this study was A(H3N2).

In earlier discussions with the ACIP WG, NVS Influenza Vaccines was requested to provide data on how aTIV performed against last year's mismatch. Prior to the 2014-2015 Northern Hemisphere influenza season, two parallel trials were conducted wherein older individuals were vaccinated with either aTIV or a non-adjuvanted seasonal influenza vaccine. The sera from these trials were re-evaluated using a microneutralization assay against the vaccine strain, A/Texas, and the strain most closely resembling the mismatched A/H3N2/Hong Kong. Higher percentages of individuals vaccinated with aTIV demonstrated seroconversion as compared to non-adjuvanted influenza vaccine. This was true for both the matched Texas and the mismatched Hong Kong strains.

In conclusion, the data gathered to date reflect a positive benefit-risk profile following vaccination with aTIV. aTIV was non-inferior to a US-licensed comparator in its pivotal trial. It also demonstrated higher homologous and heterologous titers, reduction of influenza-related disease in two effectiveness trials, a safety profile similar to both other licensed influenza vaccines and other vaccines administered commonly to older individuals, and higher antibody titers against a recent relevant mismatched A(H3N2) strain. If approved for use, aTIV will be an important additional option for prevention of influenza in adults 65 years of age and older.

Discussion Points

Dr. Belongia noted a couple of trials which assessed repeated vaccination two or three seasons in a row. A number of studies have shown evidence that the vaccines received in prior seasons may influence one's response to the current season. He wondered what had been learned about the effective prior season vaccination in terms of aTIV.

Dr. Lindert replied that in general, across the 7 revaccination trials conducted, higher antibody responses are consistently observed with aTIV. Of note, across those 7 different revaccination trials, there were 3 trials where one of the strains remained the same. In other words, they wanted to understand the impact if one was repeatedly exposed to the same strain. They continued to see still higher titers in the aTIV versus TIV recipients. That was the one instance where the strain did not change across the 7 revaccination studies.

Dr. Moore asked with repeated annual immunization what was known about any change in the AE rate among recipients who have received the vaccine several years in a row.

Dr. Lindert responded that they still note increased reactogenicity with the adjuvanted vaccine as compared to the TIV, but the clinical spectrum remains largely the same. The events remain mild to moderate, and do not increase in relative frequency relative to TIV. The overall trends in terms of the reactogenciity profile remain stable with revaccination, but reactogenicity such as pain remains still higher following vaccination with aTIV.

Dr. Paul Offit (Children's Hospital of Philadelphia) noted that narcolepsy appeared to be a consequence of the squalene adjuvant in the 2009 influenza vaccine, Pandemrix™. A recent *Science Translational Medicine* paper essentially implicated influenza nucleoprotein as having molecular mimicry between that and the hypocretin receptor 2. He wondered whether Dr. Lindert knew the quantity of influenza nucleoprotein in this vaccine and whether there is a nucleoprotein-specific antibody response to this vaccine.

Dr. Lindert indicated that she would have to follow up with precise estimates; however, by and large, the nucleoprotein levels are low to nearly undetectable in NVS's vaccines. The vaccines are subunit vaccines, so by nature they are more purified in terms of removal of nucleoprotein relative to, for example, split vaccines. She can come back with more precise estimates.

Dr. Paul Offit (Children's Hospital of Philadelphia) said he thought that in the *Science Translational Medicine* paper, there was a second squalene adjuvant in influenza vaccine, Focetria®, which did not have that response because it had much lesser quantities of nucleoprotein.

Dr. Karron wondered whether, now that MF59-adjuvanted vaccine had been licensed in many countries for many years, NVS had had an opportunity to assess effectiveness against drifted strains as well as antibody response specifically against the drifted strains. She also noted that NVS has the blood samples to be able to evaluate duration of protection of antibody response. In addition, she asked whether there were plans for a quadrivalent preparation of this vaccine.

Dr. Lindert indicated that to date, mismatched strains have not been evaluated. However, NVS presently has an ongoing efficacy study in children that started enrollment two years ago. With last year's mismatch, they expect to have data that should help to inform everyone about how well MF59 works against last year's mismatch in an efficacy setting. That study is in children ages 6 months to less than 6 years of age. For brevity, the data related to duration of antibody response were not included in this presentation. In the pivotal trial, antibody responses were assessed at Day 181 and Day 365. Particularly at Day 181, across all 3 influenza strains, the aTIV titers remained higher than the TIV. This trend remained significant at Day 365 only for A(H3N2). NVS does have plans for a quadrivalent preparation of this vaccine. The pediatric efficacy trial is being conducted with a quadrivalent formulation. In addition, in this quarter, the aQIV will be initiated as well, which is in the elderly.

Given that this vaccine has been used for a long time in the European Union (EU), Dr. Walter wondered whether there were any longer term surveillance data on repeated dosing.

Dr. Lindert replied that beyond the 7 revaccination trials she mentioned, they do not. The rest of the data rest in the post-marketing surveillance data in terms of understanding if there are any unusual patterns in the safety of revaccination, for example, of NVS's adjuvanted versus non-adjuvanted vaccines. Again, no meaningful trends have been observed with use of both vaccines over several years.

Ms. Pellegrini asked whether the BLA that is currently pending with FDA was for licensing only in the elderly at this point and, if so, whether NVS anticipated filing a BLA at some point in the future for children.

Dr. Lindert replied that the pending BLA is only for the elderly, but they do intend to file the quadrivalent vaccine for use in children after the completion of the efficacy study just mentioned. This was in discussion and agreement with FDA.

Because the vaccine has been used for so long in other parts of the world, Ms. Pellegrini asked whether Dr. Lindert could share any of the factors that went into the company's decision to delay seeking approval in the US for so long.

Dr. Lindert explained that this vaccine has been in the hands of a few different vaccine manufacturers through the years. When Novartis originally acquired the MF59-adjuvanted vaccine, they were very enthusiastic about seeking US licensure and started the conversations with the FDA. Prior to that, there were different strategic prerogatives for the predecessors.

Related to Dr. Karron's question, Dr. Duchin (NACCHO) asked whether there are any data on the relative effectiveness of adjuvanted versus non-adjuvanted looking at the time since vaccination over the course of one season.

Dr. Lindert responded that they do not have those data at this point. There will be further exploration in the efficacy trials to understand that. Because the immunogenicity data show some interesting trends, they would like to determine whether that translates into additional benefit.

Dr. Schaffner (NFID) asked whether it was correct that the comparator vaccine has been TIV in all of the clinical trials and that aTIV has not been compared with high-dose vaccine.

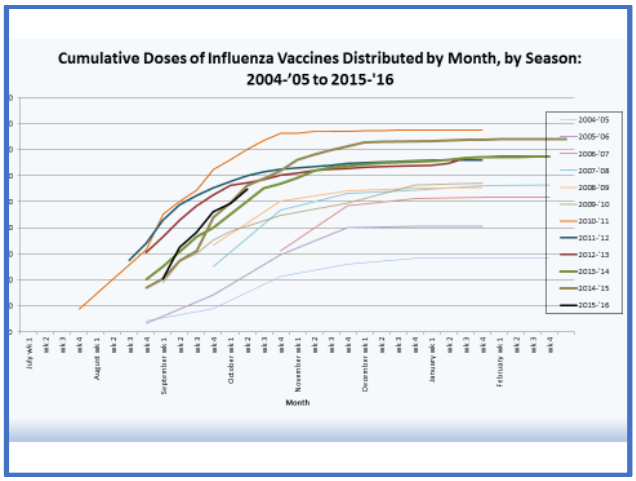
Dr. Lindert confirmed that this was correct.

Vaccine Supply

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

During this session, Dr. Santoli presented an update on the 2015-2016 US influenza vaccine supply. Manufacturers have estimated that as many as 171 to 179 million doses of influenza vaccine will be available this season, depending upon yield, lot release, and demand for product. To put that into perspective, 147.8 million doses were distributed last season. The highest number of doses distributed in a single season was 155.1 million doses, which was during the 2010-2011 season.

Distribution began in August 2015 and is anticipated to continue throughout December 2015. As of October 9, 109.4 million doses have been distributed, which is similar to this time last year. The following graphic depicts the cumulative doses of influenza vaccines distributed by month, by season for the 2004-2015 compared to the 2015-2016 season:



Some distribution delays are occurring for specific vaccines from MedImmune and Sanofi Pasteur. For MedImmune, all doses originally pre-booked will be produced to fill orders. Distribution of FluMist® Quadrivalent began in September and will continue throughout December. Partial shipments are being used to distribute vaccine. For Sanofi Pasteur, all doses originally pre-booked will be filled. Distribution of Fluzone® in unit dose vials, multi-dose vials, and Intradermal Fluzone® is complete. Multi-dose vials and intradermal vaccine supply remain available for immediate shipment. Distribution of pre-booked Fluzone® in prefilled syringes, including the pediatric 0.25mL syringes, is ongoing and will complete by the end of November. For older adults, Fluzone High-Dose® Vaccine will be complete in early November. Partial shipments are being used to distribute vaccine.

CDC's Vaccine Supply/Shortage Webpage can be found at:
http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Discussion Points

Dr. Karron requested that the manufacturers comment more specifically on the reasons for the delays, problems, and solutions where possible.

Dr. Phil Hosbach (Sanofi Pasteur) indicated that there are now many different "flavors" of Fluzone® vaccine, so the process for filling and packaging is much more extensive and complex. However, Sanofi Pasteur is only two to three weeks behind original projections with most of its vaccines. The good news is that Fluzone High-Dose® Vaccine orders have increased. The confidence in patients and providers has exceeded Sanofi Pasteur's expectations. This year it is anticipated that 50% of all seniors 65 years of age and older who receive an influenza vaccine will receive the high-dose vaccine. That is going very well. More than 50% of the pediatric syringes have been shipped. Of the estimated 65 million doses of vaccine Sanofi Pasteur anticipated shipping this season, 50 million have already been shipped. The remainder will be shipped by the end of November.

Dr. Allyn Bandell (MedIummune AstraZeneca Medical Affairs) reported that they had some unforeseen challenges in production of FluMist® this year. To date, 5 million doses have been shipped and 4 to 5 million doses are anticipated to be shipped by the end of November. Production of FluMist® will continue through the season to meet any late season needs, which is supported by CDC. Earlier this year, they had longer to develop the H1N1 strain that was

included in this year's vaccine. Recently, a number of lots had H3N2 potency that was outside of specifications. It is important to note that nothing that has entered or will enter the market has exceeded specifications. All products have passed internal quality assurance measures.

Dr. Sawyer (PIDS) pointed out that for the pediatric 0.25mL dose for young infants, there is a single manufacturer. California has a law that prohibits the use of thimerosal -containing vaccines, so they must wait for that vaccine to immunize infants. Since most infants need two doses of vaccine, he expressed his hope that the company would reprioritize the order of their doses and distribute the young pediatric dose first. Otherwise, an even better solution would be for another manufacturer to produce this vaccine as well for this age group so there would be some competition.

Dr. Phil Hosbach (Sanofi Pasteur) indicated that Sanofi Pasteur tries to balance its production amongst all of the varieties of influenza Fluzone®. The trivalent vaccine will no longer be produced, which will certainly be helpful. They cannot prioritize based upon laws of states, but do prioritize based upon the orders received. Fortunately, over 50% of the vaccine has been distributed across the country in a variety of healthcare settings. That should have gotten at least one dose for every child. Two doses are needed of the 0.25mL dose. Hopefully, there was enough for everyone to get started. He promised that the remainder of orders would be fulfilled before the end of November.

Dr. Leonard Friedland (GSK) reassured Dr. Sawyer that GSK is working on an influenza vaccine licensed down to 6 months of age. Information has been shared with the Influenza WG. GSK plans to proceed ahead, so hopefully there will soon be two manufacturers.

Dr. Duchin (NACCHO) asked whether there are any current vaccine effectiveness studies of high-dose vaccine.

Dr. David Greenberg (Sanofi Pasteur) replied that there is an ongoing trial by an independent investigator with funding from Sanofi Pasteur who specifically studied high-dose vaccine in nursing homes. That study was conducted over two seasons, and the preliminary results were recently presented in San Diego. His publications are pending the receipt of Medicare data, which is a struggle. As soon as he receives those data, he will be able to complete his analyses and publish the results. During the first season of the study, which was an H3N2 year, there was a 30% reduction in all-cause hospitalizations from nursing homes. During the second season, which was an H1N1 year, there was a 7% reduction in all-cause hospitalizations. There was also a recent presentation during a conference in San Francisco on another totally independent cost-effectiveness analysis of Fluzone High-Dose® Vaccine versus standard dose vaccines from the University of Pittsburg. An additional study, the CDC/FDA/CMS of vaccine effectiveness for outpatient and inpatient care for influenza that is published, showed a 22% reduction in outpatient and inpatient influenza cases among over 900,000 high-dose recipients compared to 1.6 million standard dose recipients.

Dr. Kelly Moore commented that the unfortunate complication of the MedImmune challenges this year has been particularly difficult for programs conducting school-located vaccination clinics. There are numerous challenges from the outset with scheduling with schools, which in themselves must be overcome. FluMist® is a popular product in those settings understandably with children who are unaccompanied. Unfortunately, the delay has resulted in varying degrees of cancellations or reductions in immunizations given in those settings. She suggested assessing the impact of delays operationally in terms of coverage rates among those age

groups later in the season to determine whether there is an actual impact in coverage rates due to changes in supply availability in the early part of the season.

Dr. David Weber (SHEA) indicated that the same problem occurred with immunization of their healthcare workers. When schedules are set up in August and then there are shortages, it is a major problem because they require all of their healthcare personnel to be immunized by December 1st. Late deliveries into November and December are well beyond the time for them to meet their requirements for immunization.

Human Papillomavirus (HPV) Vaccines

Introduction

Allison Kempe, MD, MPH
Chair, ACIP HPV Vaccines WG

Dr. Kempe said that she was very honored to be asked to Chair the HPV Vaccines WG. Dr. Kempe described some of the history of the work of the HPV Vaccines WG over the past one to two years regarding 9vHPV vaccine. ACIP reviewed data on the 9vHPV vaccine during 2014. The vaccine was then licensed at the end of that year. 9vHPV vaccine was recommended by ACIP during the February 2015 meeting. An *MMWR Policy Note* was published in March 2015.

The February 2015 ACIP meeting was abbreviated due to inclement weather and one issue, 9vHPV for persons who completed an HPV vaccination series with 2vHPV or 4vHPV, was not discussed. In June 2015, the WG reviewed additional 9vHPV vaccination information for those previously vaccinated, including the burden of disease, immunogenicity data from the trial of 9vHPV among persons who previously completed a 4vHPV series, and cost-effectiveness. Questions/answers were drafted to be posted on the CDC website regarding this issue were discussed. During that meeting, there was discussion of reviewing this issue again using GRADE and the WG was asked to re-discuss this subject. After the meeting, the questions/answers giving guidance to vaccine providers were posted and there was an announcement in the *MMWR* in July 2015 alerting readers about the posting.

The document "Supplemental Information and Guidance for Vaccination Providers Regarding Use of 9-Valent HPV Vaccine," links from the ACIP website, and the announcement in the *MMWR* state that there is no ACIP recommendation for routine additional 9vHPV vaccination of persons who previously completed a quadrivalent or bivalent vaccination series. Information is provided about the safety and immunogenicity of additional vaccination.

After the June 2015 meeting, the HPV Vaccine WG re-discussed 9vHPV vaccine for persons who completed an HPV vaccination series. There were discussions with other professional groups including AAP, Society for Adolescent Health and Medicine (SAHM), and the AAP Committee on Infectious Diseases (COID). The WG also reviewed additional transition issues. Almost all members felt that this issue should not be brought back to ACIP during the October 2015 meeting.

During this session, presentations were given on the following topics:

- ❑ HPV vaccination coverage in the US, National Immunization Survey (NIS)-Teen 2014
- ❑ Programmatic strategies to increase HPV vaccine coverage
- ❑ HPV vaccine safety
- ❑ Monitoring the impact of the HPV vaccination program and future WG plans

HPV Vaccine Coverage in the US, National Immunization Survey-Teen (NIS-Teen) 2014

Sarah Reagan-Steiner, MD, MPH
Medical Officer, Assessment Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Reagan-Steiner's presentation included an overview of the NIS-Teen, discussion of the revised definition of adequate provider data implemented in 2014, and an update on HPV vaccination coverage among adolescents in the US.

The NIS-Teen is an annual survey implemented in 2006. It is a random digit dial (RDD) telephone survey of landline and cell phone numbers. Parents of adolescents 13 through 17 years of age are interviewed to obtain sociodemographic information about the adolescent and the household. All estimates are based on provider reported vaccination histories from adolescents with adequate provider data (APD). The APD definition was revised for the survey conducted in 2014. This changed the criteria for inclusion in the analytic sample. The revised APD definition was applied retrospectively to the 2013 NIS-Teen data to assess its impact on coverage estimates and to inform the approach to the 2014 analyses.

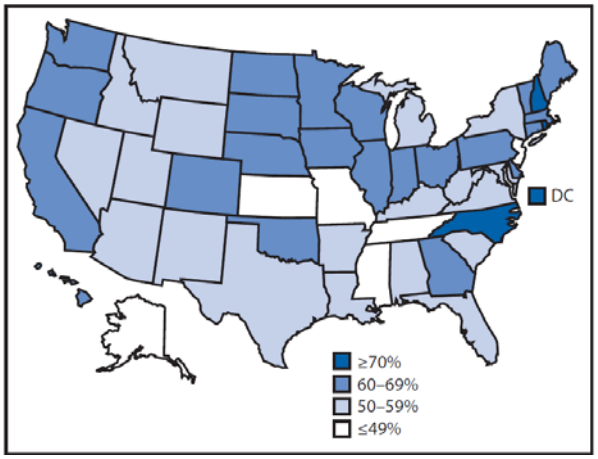
Regarding why this assessment was important, prior to 2014, determining whether an adolescent had APD was based on a comparison of household and provider reported vaccination history. In 2014, most vaccination history questions were removed from the household questions in an effort to shorten the questionnaire and improve survey response rates, so this comparison was no longer possible. To have APD prior to 2014, if an adolescent was not completely unvaccinated by household report, they had to meet a variety of criteria. In summary, if the adolescent was not up to date and there was disagreement between the household and provider reported history, they were excluded. For the definition implemented in 2014, which is the same definition that is currently used by the NIS, adolescents are included in the sample if they are either completely unvaccinated by household report or have one or more vaccine doses by provider report.

Revised 2013 estimates were calculated after applying the revised APD definition. These were lower than the original published estimates. Percentage point differences ranged from 0.6 for one or more doses of HPV vaccine in females, to 2.2 for two or more doses of MMR. Given these differences, it was determined that 2014 NIS-Teen estimates, which would use the revised APD definition, would not be comparable to those previously published. As a result, changes in coverage between the 2013 and 2014 NIS-Teen are best measured by comparing estimates that used the same revised APD definition. This was the approach used for the data presented during this session [http://www.cdc.gov/vaccines/imz-managers/coverage/nis/teen/apd-report.htm].

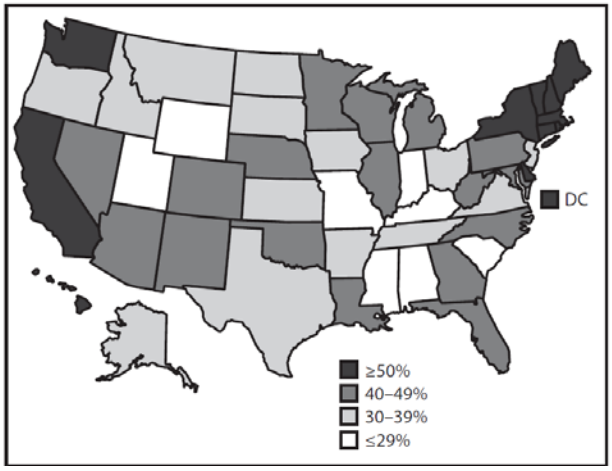
In the 2014 NIS-Teen, the national sample included 20,827 adolescents from the 50 states and the District of Columbia (DC). Of these, 54% were from the landline and 46% were from the cell phone sampling frames. Response rates were 60.3% for landline and 31.2% for cell phone frames, and 57.1% of adolescents from landline and 52.3% from cell phone sample had APD. In terms of the trends in vaccination coverage from 2006 through 2014, there were two estimates for 2013, the originally published and the revised estimates. In 2014, there were increases in coverage for all vaccines routinely recommended during adolescence versus the 2013 revised estimates. However, a notable gap remained between coverage with Tdap and MenACWY vaccination and HPV vaccination in females and males. In 2014, among females, coverage with one or more HPV vaccine doses was 60.0% and for three or more doses was 39.7%. These were increases of about 3 percentage points for each HPV vaccine dose from the 2013 revised estimates. This was the second consecutive year of increases in HPV vaccination coverage in females. Among males, coverage with one or more doses was 41.7%, and with 3 or more doses was 21.6%. These were larger increases at around 8 percentage points compared to 2013 [*MMWR* 64(29);784-792].

In 2014, there were differences in vaccine coverage by poverty status. Coverage with each HPV vaccine dose was higher among adolescents living below the poverty level compared with those living at or above the poverty level. The finding of higher coverage with three or more doses among females below the poverty level had not been observed since 2011. Note that coverage being higher among adolescents living below poverty is different from the pattern observed for many childhood vaccines where coverage is lower for children below the poverty level. Differences were also observed in HPV vaccine coverage levels by race/ethnicity. Coverage for each dose of HPV vaccine was higher among Hispanic as compared to white non-Hispanic adolescents. Coverage with one or more doses of in both females and males, and with two or more doses among females was higher in black non-Hispanic adolescents compared with their white non-Hispanic counterparts [*MMWR* 64(29);784-792].

The following map shows the considerable variation in coverage with one or more doses of HPV vaccine among females by state. States with higher coverage are in darker blue, while those with lower coverage are in white. Coverage ranged from 38% Kansas to 76% Rhode Island; while not shown here, Philadelphia had the highest local area coverage at 80%, and in Puerto Rico coverage was 76% [*MMWR* 64(29);784-792]:



Similarly, the following map shows that coverage with one or more doses of HPV vaccine among males also varied by state. Coverage ranged from 23% in IN to 69% in RI [*MMWR* 64(29);784-792]:



While nationally modest but significant improvement was observed in HPV vaccination coverage in females, seven jurisdictions (DC, Georgia, Illinois, Illinois-Chicago, Montana, North Carolina, Utah) achieved larger significant percentage point increases in coverage, 6 for 1 or more and 6 for 3 or more HPV vaccine doses. This included 5 jurisdictions (DC, Georgia, Illinois, Chicago, Utah) that benefited from 2013 federal funding to increase HPV vaccination coverage among adolescents. Project periods for this funding began in late September 2013. Activities were subsequently conducted in a timeframe that could have impacted 2014 coverage [*MMWR* 64(29);784-792].

HP2020 objectives include targets for coverage with three or more HPV vaccine doses among adolescents 13 through 15 years of age. In terms of trends in coverage with three or more doses in this age group by survey year, very gradual progress is observed over time. Compared with 2013 revised estimates, no improvement was observed among females in 2014. Coverage was low and far below the target at 34.4%. While coverage improved among males, it was still low at 20.6% [NIS-Teen 2008-2014].

A recommendation for HPV vaccination is important. Improving the provision of strong, age-appropriate recommendations for HPV vaccination by clinicians has been a key part of the efforts to improve vaccination coverage. In 2014, the percent of parents reporting receipt of provider recommendations increased for both girls and boys. Notably, however, this shows that approximately 30% of girls and 50% of boys did not receive a recommendation. This leaves room for improvement [Unpublished NIS-Teen 2013 (Revised) and 2014 data].

Parental attitudes toward HPV vaccination are also relevant. Among unvaccinated adolescents whose parents had no intention to vaccinate in the next 12 months, the top 5 reasons why included: not needed/necessary, safety concerns/side effects, lack of knowledge, not recommended, and not sexually active. Though there is no predominant reason, the most common reason was that the vaccine is not felt to be needed or necessary. There were some differences by gender in other reasons. A higher percentage of parents of girls cited safety concerns/side effects. A higher percentage of parents of boys indicated that it was not recommended. This may be due in part to there being some males in the sample who were 13

years or older when the routine recommendation for males was issued in 2011 [Unpublished NIS-Teen 2014 data].

Receipt of HPV vaccine at the recommended age of 11 through 12 years is best measured by examining coverage by age 13 years by birth cohort using NIS-Teen data that has been combined over multiple survey years. These data were published in 2014 for one or more HPV vaccine doses among females only, and include information from the 2007 through 2013 NIS-Teen survey years. Coverage with one or more doses by age 13 years increased on average 5.8% with each birth cohort, reaching 47% for females born in 2000 (those who turned 13 in 2013). This demonstrates the challenges associated with improving HPV vaccine series initiation at the recommended age. Part of this challenge has been missed opportunities. A missed opportunity is defined as a healthcare encounter where at least 1 vaccine is administered but not all indicated vaccines are given. Coverage with 1 or more HPV vaccine doses by 13 years of age could have reached 91% for females born in 2000 if these missed opportunities were eliminated [*MMWR*. 2014; 63:620-4].

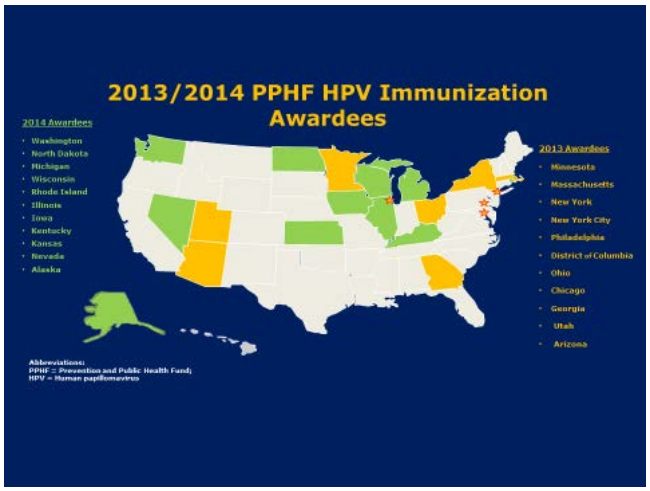
In summary, national HPV vaccination coverage increased in 2014, but remains lower than Tdap and MenACWY, suggesting persistent missed opportunities for HPV vaccination. Of note, the impact of recent interventions aimed at improving age-appropriate HPV vaccination at 11 through 12 years was not yet measurable by the 2014 NIS-Teen, given that the survey assesses coverage in adolescents aged 13 through 17 years. Coverage is higher for adolescents living below the poverty level and Hispanic and non-Hispanic Black adolescents. There was considerable variation in HPV vaccine coverage by state and local area. We continue to face challenges in HPV vaccination coverage among younger adolescents. However, seven public health jurisdictions achieved improvement in HPV vaccination coverage among females and strategies used can inform activities elsewhere.

Programmatic Strategies to Increase HPV Vaccine Coverage among U.S. Adolescents

C. Robinette Curtis, MD, MPH
Medical Officer, Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Curtis emphasized that improving HPV vaccination coverage among adolescents is an agency and division priority. During this session, she provided brief background information, reviewed what worked for the jurisdictions with increases in HPV vaccination coverage among females, shared some related highlights of a selected initiative, and discussed the challenges and opportunities moving forward.

Immunization Services Division (ISD) strategies to increase HPV vaccination coverage include supporting state and local immunization programs, mobilizing partners and stakeholders, strengthening provider commitment, improving and utilizing systems, and increasing public awareness. Consistent with these division strategies, CDC has provided technical assistance and Prevention and Public Health Funds (PPHF) to 22 awardees. On the following map, the 11 awardees that received funding in late 2013 are shown in gold and those funded in August 2014 are in green:



Of the seven public health jurisdictions that Dr. Reagan-Steiner mentioned with improvements in HPV vaccination coverage, five were PPHF HPV immunization awardees. The four 2013 awardees (DC, Chicago, Georgia, and Utah) with increases were able to conduct their activities in 2013 and 2014 in a timeframe and with activity target groups that could have impacted NIS-Teen estimates. Illinois and Chicago program leaders agree that Chicago activities likely account for the coverage increases observed for Illinois, which did not receive its award until August of 2014. Although the PPHF HPV Immunization awardees overall are in different stages with their implementation and evaluation activities, all have worked to increase HPV vaccination coverage through activities in the five areas specified in the Funding Opportunity Announcement (FOA). Dr. Curtis reviewed each of the activity areas below and provided a brief example for each to illustrate how awardees were implementing their activities. The activity areas are:

- ❑ Developing a jurisdiction-wide joint initiative with immunization stakeholders
- ❑ Implementing a comprehensive communication campaign targeted to the public
- ❑ Implementing Immunization Information System (IIS)-based reminder / recall for adolescents aged 11 through 18 years
- ❑ Using assessment and feedback to evaluate and improve the performance of immunization providers in administering the 3-dose HPV vaccine series consistent with current ACIP recommendations
- ❑ Implementing strategies targeted to immunization providers to:

    - ➢ Increase knowledge regarding: HPV-related diseases (including cancers), and HPV vaccination safety and effectiveness
    - ➢ Improve skills needed to deliver strong, effective HPV vaccination recommendations
    - ➢ Decrease missed opportunities for timely HPV vaccination and series completion
    - ➢ Increase administration of HPV vaccine doses consistent with current ACIP recommendations

In describing stakeholder engagement, Dr. Curtis showed a slide illustrating that stakeholders are varied and have included partners such as local chapters of the American Academy of Pediatrics, the American Academy of Family Physicians, the American Cancer Society, immunization coalitions, public school systems, insurers, pharmacies, and other organizations. In illustrating elements of communications campaigns, Dr. Curtis noted that the campaigns have typically included varied components, with the slide highlighting print and outdoor ads, radio and

television, public transportation ads, social media (including Twitter and Facebook), and digital media, including Pandora. With respect to reminder / recall, Dr. Curtis noted that reminder/recall involves informing members of a target population that one or more vaccinations are due (reminders) or late (recall).

In describing the AFIX activity area, Dr. Curtis noted assessment and feedback entails retrospectively assessing providers' performances in delivering one or more vaccinations to a client population and giving this information (feedback) to providers, so that providers can improve their performance and vaccination coverage within their practices. Assessment and feedback are two of four key strategies to a quality improvement program known as AFIX. This AFIX website (http://www.cdc.gov/vaccines/programs/afix/index.html) allows all immunization awardees to access CDC guidelines and materials as they seek to engage providers. In describing an example of strategies targeted to immunization providers, Dr. Curtis noted that the Minnesota Department of Health developed a series of videos on delivering effective HPV vaccination recommendations. These videos are being used by partners for teaching and talks across the country. (As of 1/8/16, these videos are currently available at: http://www.health.state.mn.us/divs/idepc/immunize/hcp/adol/hpvvideos.html)

Regarding what worked for the seven public health jurisdictions with improvements in HPV vaccination coverage, Dr. Curtis noted that some of what she would describe during her presentation was included in the July 2015 *MMWR* NIS-Teen article referenced in presentation slides (MMWR 64(29);784–792). Varied combinations of interventions were identified as important by six of the seven jurisdictions. Most of the identified activities are as follows:

Activities Specified in PPHF FOA

- ❑ Joint initiatives with cancer prevention and immunization stakeholders
- ❑ Public communication campaigns
- ❑ IIS-based reminder / recall
- ❑ Assessment and feedback
  - ➢ Conducting activities consistent with federal AFIX guidance
  - ➢ Ensuring clinical practice decision makers participate
  - ➢ Including a clinician-to-clinician educational component
- ❑ Provider and practice-focused strategies aimed at improving HPV vaccination administration consistent with ACIP recommendations

Other Activities

- ❑ Using all opportunities to educate parents and clinicians about the importance of routine HPV vaccination at ages 11 through 12 years
- ❑ Incorporating HPV vaccination into cancer control plans

Note that the first five activities listed here are activities specified in the PPHF FOA. While it was anticipated that these would be useful, it was helpful to confirm with the jurisdictions that the activities worked and resulted in increases. With the exception of large communication campaigns, these are all activities that can be undertaken as part of routine programmatic work. Dr. Curtis highlighted that "Assessment and Feedback" emerged as having been integral to the successful efforts in North Carolina and three of the 2013 HPV immunization awardees (with the characteristics of the most effective AFIX including conducting activities consistent with federal AFIX guidance, ensuring clinical practice decision makers participate, and including a clinician-to-clinician educational component). Provider and practice-focused strategies were identified as important by six jurisdictions, and these same jurisdictions also stressed the utility of using all

opportunities to educate parents and clinicians about the importance of routine HPV vaccination at age 11 through 12 years. An example of using all opportunities includes emphasizing HPV vaccination in communications about school vaccination requirements. Incorporating HPV vaccination into cancer control plans also appears to be a best practice that can bring together stakeholders and create an imperative for increasing HPV vaccination coverage.

A more recent initiative includes multiple partnership cooperative agreements focused on increasing HPV vaccination. These cooperative agreements were initially funded in late 2014 with the following national partners:

- ❑ American Academy of Pediatrics (AAP)
- ❑ American Cancer Society (ACS)
- ❑ Academic Pediatric Association (APA)
- ❑ National Area Health Education Center Organization (NAO)
- ❑ National Association of County and City Health Officials (NACCHO)

This map shows where funded partners are planning to target their activities, as well as locations of PPHF HPV Immunization awardees. In states with overlap, work is being done to ensure collaboration among funded partners and awardees:

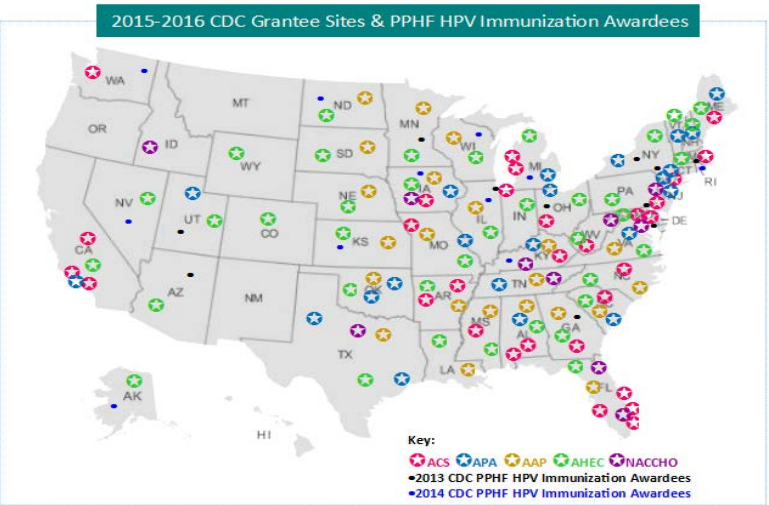


Image Courtesy of the American Cancer Society

In the context of the data and initiatives shared during this session, there are a number of opportunities and challenges moving forward. Evolving recommendations and related issues can make programmatic planning and execution difficult and might decrease interventions' impacts. For example, the transitions related to 9vHPV use likely affected vaccination delivery this year. Evaluating the impacts of interventions can be difficult, given that increases in immunization coverage are hard to achieve in short time horizons; other process and outcome measures may be difficult to interpret; and the impact of interventions promoting adherence to routine recommendations at age 11 through 12 years are not measurable by the 2014 NIS-Teen. The fact that five of the PPHF HPV immunization awardees had measurable improvements in vaccination coverage as an outcome measure so quickly was exciting, but unexpected, by evaluation experts. Some PPHF HPV immunization awardees are still in the process of both implementing and beginning to evaluate their activities, so the data that we

have available are early. Both implementation and evaluation are affected by competing demands. The establishment of partnership cooperative agreements has created more opportunities for collaboration in many arenas, including state and local jurisdictions.

From the early data and lessons learned so far, it is helpful from a strategic perspective to begin to define generalizable, promising practices that can be integrated into routine programmatic activities. These include leveraging opportunities for partnership engagement and collaboration; conducting Assessment, Feedback, Incentives, and eXchange (AFIX) consistent with CDC guidance and, when feasible, enhanced by clinician-to-clinician education; incorporating HPV vaccination into cancer control plans; and using all opportunities to educate parents and clinicians about the importance of routine HPV vaccination at ages 11 through 12 years. Based on the experiences of six of the seven jurisdictions with improvements in HPV vaccination coverage among females in 2014, these interventions appear to be most effective in combination, but recent experiences suggest that any one of them would be a useful place to start for any jurisdictions and stakeholders who would like to join in increasing HPV vaccination coverage among our nation's adolescents.

Discussion Points

Dr. Bennett asked whether any lessons could be learned from the fact that reverse disparities are observed with respect to HPV vaccination rates in different groups, and whether consideration has been given to why that might be the case. She also requested elaboration on integration with cancer control activities.

Dr. Reagan-Steiner responded that the reverse disparity patterns are important to explore. It is likely that multiple factors contribute to the patterns observed, potentially due to differential Vaccines for Children (VFC) eligibility in children below poverty and in particular racial and ethnic groups. This echoes back to an analysis of 2011-NIS Teen data, on which Dr. Curtis was the lead author, in which teens who were VFC-eligible and on Medicaid had higher 1- and 3-dose HPV vaccination coverage than privately insured teens. There are also likely differential patterns of parental acceptance and provider practices by poverty and by race/ethnicity, which definitely merit further exploration.

Regarding integration with cancer control programs, Dr. Curtis said it seemed like it would be intuitively obvious that these entities would work together. However, sometimes they are not historically working together because this might be their first opportunity beyond some hepatitis B work in which the topic of vaccination reaches into the cancer prevention realm. Sometimes it is as simple as just getting the discussions started between the different entities within the same health department, which can then lead to identification of synergies. The national partnership cooperative agreements are also very fortunate, and other organizations are interested in working together. The PPHF awards created impetus for bringing these organizations together, having stakeholder meetings, and identifying activities to work on together. Working on cancer control plans, for example, can bring partners together. However, it is important that cancer control plans are developed consistent with ACIP guidelines. That is sometimes a missing piece.

Dr. Bennett pointed out that in most places, there are breast and cervical cancer control programs. Yet, those programs have not thus far integrated HPV vaccination into their activities. She wondered whether consideration has been given to this.

Dr. Curtis replied that, for at least some of the PPHF HPV immunization awardees, there have been partnerships with local National Breast and Cervical Cancer Early Detection Programs [which are funded through CDC's Division of Cancer Prevention and Control (DCPC)]. For example, one of the National Breast and Cervical Cancer Early Detection Programs is paying for the printing of materials for dissemination by a PPHF HPV Immunization awardee. Most of the emphasis of HPV vaccination at this point is for those 11 through 18 years of age and the overlap in ages, given that the National Breast and Cervical Cancer Early Detection Program serves 18 years and older, is somewhat limited.

Dr. Belongia indicated that the Marshfield Clinic Health System (MCHS) receives some supplemental funding to allow them to work to improve HPV vaccination coverage within the MCHS system, at the same time the State of Wisconsin is engaged in its own initiative. MCHS engaged its quality improvement group. There is a Healthcare Effectiveness Data and Information Set (HEDIS) measure for this, given that it is considered important from a quality improvement perspective. They discovered that this was being considered to some extent, but limited efforts were being made. By working with the quality improvement group, MCHS was able to change much of what they were doing in terms of their recommendations to the clinics and reminder / recall, which they believe will lead to an increase coverage. Quality improvement is probably an area in which there can be synergy.

Dr. Curtis noted that the Georgia Department of Public Health (GDPH), as part of their PPHF HPV Immunization award activities, had worked with a major health system in the Georgia area to implement some quality improvement strategies as well. That seemed to be very helpful and has been featured on an AAP webinar by the Georgia chapter. If it is feasible from the MCHS's perspective to disseminate that information, that would be very powerful. There is a pending effort in North Dakota to do something similar. Having the benefit of lessons learned from other organizations would be tremendously valuable.

Dr. Reingold pointed out that countries as diverse as Brazil, Rwanda, and the UK conduct school-based HPV vaccination. There are a number of school-based influenza immunization programs in the US. He was curious to know which, if any, of the states have tried school-based HPV vaccination, and what their experience has been. If none of them have, he wondered why.

Dr. Curtis replied that the Rhode Island Department of Health is embarking on an expansion of their Vaccinate Before You Graduate (VBYG) program in middle schools. It is interesting that when they tried to share that plan with the area providers and invited them to refer their patients to these pending programs in middle schools, there was some push-back. That points to one challenge. Another challenge is with the administration of a series. With an influenza program, all-comers are presumable not vaccinated during a given season, which makes it somewhat less challenging than trying to figure out where children might be in terms of their completion of the HPV vaccination series.

Dr. Kempe indicated that Colorado conducted a fairly successful school-based vaccination program. The most difficult part was billing because this is an expensive vaccine that requires a full billing program, unlike with influenza vaccine programs in which vaccine has been donated. In her research, the two most rapid ways to increase rates have been centralized reminder / recall using an IIS and standing orders. She wondered whether any of these programs used those methods.

Dr. Curtis responded that centralized IIS-based reminder / recall was encouraged for the FOA. There are some jurisdictions in which there are political constraints in terms of conducting centralized reminder / recall. In those contexts, some jurisdictions have opted to pursue the provider-based approach. Some jurisdictions feel strongly that they want to build capacity for providers to perform their own reminder / recall, and have that become integrated into routine practice. One reason she did not mention IIS-based reminder / recall in general in her conclusions was because that has probably been the hardest of the five areas for grantees to implement, in part due to infrastructure challenges with their IIS systems. This is very much in the implementation and evaluation phase. Some jurisdictions already seem to have very promising data in terms of the effectiveness of their centralized reminder / recall, which is very exciting.

Dr. Moore offered the encouraging thought that perhaps the VFC program and the streamlining of access is a reason for the reverse disparity with the poverty level. It is a credit to the VFC program that it streamlines and simplifies access to vaccines immediately upon introduction to the VFC formulary. School-located clinics are easier done all or nothing. Trying to have some school-based and some private sector-based administration with this series is very challenging, particularly with regard to the cost of the vaccine and the complexity of VFC versus private insurance in the school setting. In her experience, the collaboration with cancer programs in Tennessee, where she Co-Chairs Cervical Cancer Free Tennessee activities along with the breast and cervical cancer program at the state level, awareness is raised jointly of the current screening guidelines for cervical within OBGYN and a talk that she gives on HPV vaccine. They find it to be very useful not only to work together, but also to raise awareness among each other's constituents about the importance of lifelong prevention activities, whether it is primary prevention with vaccination or secondary prevention through screening throughout a lifetime. Raising community-wide awareness through different advocacy groups is helping Tennessee, although the numbers do not quite yet show it.

Ms. Pellegrini noted that a few weeks back, she answered the phone and was very excited because it was NIS-Teen. At the end of the survey, she was invited to provide her pediatrician's name and address. She was told that, if authorized, they would check her parental recall against her children's actual records. She wondered what percentage of respondents authorize that check with their pediatricians, what type of concordance they see between the records of parental recall, and what is done when there are differences.

Dr. Reagan-Steiner replied that approximately 70% of parents who complete the household interview provide consent to contact their vaccination providers for records. All vaccination coverage estimates are based solely on provider-reported vaccination history, given that previous analyses have shown that there was discordance between parent recall and provider report.

Carol Hayes (ACNM) asked whether any attempt has been made to work directly with Title X programs. In the majority of states, the funds are allocated to FQHCs and sometimes other entities.

Dr. Curtis replied that from a broad perspective, FQHCs and community health centers were identified as stakeholders explicitly in the FOA. Most of the awardees have been working with those partners. The work that is occurring is primarily in local and state jurisdictions, and they have been encouraged to build ties there. FQHCs and community health centers have been extremely strong partners with some of the awardees.

Update on HPV Vaccine Safety

Dr. Lakshmi Sukumaran
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Sukumaran provided a brief background; reviewed HPV vaccine safety publications, which have predominantly been in quadrivalent HPV vaccine; discussed current HPV vaccine safety related activities at CDC; and discussed plans for 9vHPV vaccine safety monitoring. Three HPV vaccines are currently available, including: 1) 4vHPV (GARDASIL®), which was licensed in 2006 and of which 80 million doses have been distributed[1,2]; 2) 2vHPV (CERVARIX®), which was licensed in 2009 and of which 839,600 doses distributed[1,3]; and 3) 9vHPV (GARDASIL®9), which was licensed in 2014 and of which 5 million doses distributed[1,2] [[1]Doses distributed in the US through September 2015; [2]Kuter B, personal communication, 20 October 2015; and [3]Tofa A, personal communication, 14 October 2015].

There are three components to CDC's vaccine safety monitoring infrastructure, including the following: 1) VAERS, the frontline spontaneous reporting system to detect potential vaccine safety issues; 2) VSD, a large linked database system used for active surveillance and research; and 3) Clinical Immunization Safety Assessment Project (CISA), an expert collaboration that conducts individual clinical vaccine safety assessments and clinical research.

Regarding post-licensure HPV vaccine safety studies starting with quadrivalent vaccine and general safety, a VAERS post-licensure safety summary showed that the proportion of reports for venous thromboembolism (VTE) and syncope after quadrivalent vaccine were higher than expected[1]. Updated VAERS reviews were published in 2013 and 2014, and no new concerns were identified[2,3]. The VSD conducted near real time monitoring following over 600,000 quadrivalent vaccine doses and found no associations with the listed outcomes[4]. However, there was a non-significant elevated risk for VTE in females 9 through 17 years[5]. A general safety assessment from two large US health plans with almost 190,000 female vaccinees found that 4vHPV was associated with syncope on the day of vaccination and skin infections in the two weeks following vaccination[6]. [[1] Slade et al, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009; [2] Stokley et al, Human Papillomavirus vaccination coverage among adolescent girls, 2007-12, and postlicensure vaccine safety monitoring 2006-2013 – United States. MMWR 2013; [3] Stokley et al, Human Papillomavirus vaccination coverage among adolescents 2007-13 and postlicensure vaccine safety monitoring 2006-2014 – United States. MMWR 2014; [4] Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011; [5] Relative risk calculated using Poisson based maximized sequential probability ratio test (maxSRPT); and [6] Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012].

Because the VAERS study showed an increased proportion of reports of VTE and the VSD study showed a non-significant elevated risk in VTE following HPV vaccine, further studies evaluating VTE were conducted. In two national register-based cohort studies, no elevated risk for VTE was found following HPV vaccine. In addition, a VSD study using self-controlled case series method found no increased risk of VTE following quadrivalent vaccine in persons aged 9 through 26 years [Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013; Scheller et al, Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. JAMA 2014; and Naleway et al, Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008-2011. Vaccine (in press)].

Because Guillain-Barré Syndrome (GBS) is a rare outcome following immunization, the VSD extended surveillance for GBS from the previously mentioned study. The VSD did not observe an increased risk of GBS following quadrivalent vaccine among females ages 9 through 26 years. The surveillance period was 6 years, and over 1.4 million doses of quadrivalent vaccine were administered. After electronic data and medical records were reviewed, there were 0 incident cases of GBS within 42 days following quadrivalent vaccine.

There have also been concerns for potential associations with autoimmune and neurologic disease following 4vHPV. No evidence for a causal association has been observed between 4vHPV and autoimmune and neurologic conditions in 4 large epidemiologic studies. The first study examined 16 autoimmune conditions; the second study assessed 23 autoimmune and 5 neurologic conditions; the third study assessed 6 autoimmune conditions; and the last study considered multiple sclerosis and demyelinating diseases [[1]Chao et al, Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012; [2]Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013; [3]Grimaldi-Bensouda et al, Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2013; and [4]Scheller et al, Quadrivalent HPV vaccination and the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015].

In terms of the safety of HPV vaccines in pregnancy, there have been studies of both quadrivalent and bivalent vaccines. For 4vHPV, there was no increased risk of fetal loss, spontaneous abortion, or congenital anomalies in Phase III clinical trials[1]. In addition, the 4vHPV pregnancy registry identified no concerns [[1]Garland et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstetrics & Gynecology 2009; and [2]Goss et al. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine 2015].

For 2vHPVin pregnancies, although there was no overall increased risk of adverse pregnancy outcomes in pre-clinical trials, pooled analyses of these trials have shown a possible increased risk of spontaneous abortion in women 15 through 25 years of age who were vaccinated around the last menstrual period (LMP)[1,2]. However, a post-licensure study found no evidence of increased risk of spontaneous abortion or other adverse pregnancy outcomes in women inadvertently vaccinated around LMP[3] [[1]Descamps et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: A pooled analysis of 11

clinical trials. Human Vaccines 2009; [2]Wacholder et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ 2010; and [3]Baril et al. Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. Vaccine 2015].

In a review of the findings from a 2011 Institute of Medicine (IOM) report on AEs of vaccines with regard to HPV vaccine, for the outcome of syncope, the IOM concluded that "the injection of a vaccine was a contributing cause of syncope." This could be any injected vaccine and is not specific to HPV. For the outcome of anaphylaxis, the IOM concluded that "the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis." Again, this is similar to other vaccines [*Adverse Effects of Vaccines: Evidence and Causality*, Institute of Medicine, Aug 2011; http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx]. For example, a recent VSD study (McNeil) showed that anaphylaxis after vaccination occurred at a rate of 1.31/million vaccine doses. In this study, rates of anaphylaxis following HPV vaccine were similar to other vaccines.

Pertaining to some recent concerns in HPV vaccine safety, case reports in the media of Primary Ovarian Insufficiency (POI) following HPV vaccine led to public concern. Cases reported to VAERS were reviewed, and there were no safety findings[1]. Complex Regional Pain Syndrome (CRPS) is a syndrome of chronic pain and autonomic changes in extremity that can sometimes occur after trauma. Case reports in Japan of pain following HPV vaccination led to suspension of their HPV vaccine recommendation due to concerns of CRPS. Case reports were reviewed and adjudicated, and there was no evidence for a causal association observed between bivalent vaccine and CRPS[2]. In addition, there were no safety findings in VAERS. For Postural Orthostatic Tachycardia Syndrome (POTS), concerns in Europe lead to an EMA review of POTS and CRPS following vaccination[3]. This review is ongoing and the EMA has not recommended any change in vaccination [[1]http://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html; [2]Huygen et al. Investigating Reports of Complex Regional Pain Syndrome: An Analysis of HPV-16/18-Adjuvanted Vaccine Post-Licensure Data. EBioMedicine 2015; and [3] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/07/WC500189481.pdf].

Regarding current HPV vaccine safety related activities at CDC, within VAERS there is ongoing monitoring of US reports, clinical reviews of deaths and other pre-specified AE outcomes as needed (for example, there is an ongoing review of POTS following HPV vaccine), and FDA collaboration with CDC on HPV monitoring. Within CISA, there is a study assessing the feasibility and impact of implementing an oral water hydration strategy prior to vaccination to prevent post-vaccination pre-syncope and syncope in adolescents and young adults. There is also a POTS technical review that will be done in response to the spontaneous reports and public concern. Within VSD, there is a study addressing quadrivalent vaccine safety following inadvertent exposure during pregnancy. In addition, there are studies addressing safety concerns from case reports and/or the media including a study of the long-term risk of autoimmune disease following quadrivalent vaccine; POI following 4vHPV; and mortality following 4vHPV and other adolescent vaccines. The study of mortality following vaccination showed no increased risk of death during the 30 days after immunization.

With respect to 9vHPV safety, among seven pre-licensure studies[1,2], 9vHPV was found to be generally well-tolerated in over 15,000 subjects. The AE profile was similar to that of 4vHPV; however, there was more injection site swelling and erythema in the 9vHPV group. Among inadvertent pregnancies occurring during the clinical studies[3], the proportion of adverse outcomes observed was consistent with those observed in the general population. A post hoc analysis showed that pregnancies within 30 days of 9vHPV vaccination resulted in a spontaneous abortion more frequently than after 4vHPV. The rate was 27.4% in the 9vHPV group compared to 12.7% in the quadrivalent group. Both rates are within the spontaneous abortion background rates, which range from 10% to 31%[4,5] [[1]http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf; [2]https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3; [3]9vHPV is FDA Category B for pregnancy; [4]Gray RH, Wu LY. Subfertility and risk of spontaneous abortion. Am J Public Health 2000; [5]Wilcox A et al. Incidence of early loss of pregnancy. NEJM 1988].

For 9vHPV safety monitoring and evaluation at CDC, in VAERS there will be monitoring of US reports, clinical reviews of pre-specified outcomes as needed, and the FDA will be collaborating with CDC on 9vHPV monitoring. This table shows preliminary data from VAERS 9vHPV vaccine reports as of October 2, 2015. During this time period, 5 million doses of GARDASIL®9 had been distributed through September 2015 in the US. VAERS received 193 reports, with an age range from 5 through 72 years with a median of 14 years. The onset interval ranged from 0 to 20 days with a median of 0. There were 8 serious reports and 0 deaths. The most common terms found in reports were “no adverse event” in 52 reports, dizziness in 27 reports, and syncope in 25 reports. No AE is reported when there is a vaccination error without an AE, such as administration of the vaccine outside the recommended age range. In addition, there have been no new data mining findings for 9vHPV vaccine.

In VSD, there is near real time monitoring for several pre-specified outcomes through Rapid Cycle Analysis (RCA). The outcomes are similar to those evaluated in the original VSD study and include anaphylaxis, allergic reactions, appendicitis, GBS, seizure, stroke, syncope, VTE, pancreatitis, and injection site reaction. There will also be an epidemiologic study evaluating spontaneous abortion following inadvertent 9vHPV administration.

There are also 9vHPV post-marketing commitments to be conducted by the manufacturer including: 1) completion of two 10-year study extensions evaluating long-term safety, immunogenicity, and effectiveness in the licensed groups; 2) an observational study to further characterize the safety profile in 10,000 persons; and 3) a pregnancy registry of exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy. FDA’s sentinel initiative will be conducting a general safety study and a pregnancy outcomes study.

In conclusion, a large body of published and preliminary data from many sources demonstrate the safety of HPV vaccines. Safety monitoring and evaluation will continue for all HPV vaccines with enhanced monitoring for 9vHPV during the initial uptake phase.

Discussion Points

Regarding the series of studies that found no association between vaccination and the outcomes of interest, Dr. Duchin (NACCHO) said it would be very helpful to include the strength of association being rejected through a study. He can say that he has found no associations in his personal experience as well, which is not very meaningful. A study that is meaningful should include some measure of the level of risk being excluded.

Dr. Moore noticed that in the VAERS reporting, there was a very wide age range of 5 through 72 years of age. She asked whether there was any qualitative or significant and important difference in the nature of AEs reported among the ages for whom the vaccine is recommended as opposed to those for whom it was obviously administered but not recommended.

Dr. Sukumaran replied that these data are all preliminary, but most of the reports outside of the recommended age range were the "no AE" reports. The median age was 14 years, so the majority of reports were within or close to the recommended age range. There was no difference.

Dr. Plotkin (Vaccine Consultant) thought there was an important international aspect of this. Considering that this vaccine was invented by a US government laboratory, the US has some responsibility with regard to the use of the vaccine elsewhere. The Japanese withdrawal of government support for HPV vaccine was mentioned during this presentation. Recently, a French study was published that in effect blamed the vaccine for causing GBS. He strongly recommended that CDC publish a supplement in the *MMWR* on the safety of HPV, consider publishing a supplement in *Clinical Infectious Diseases* (*CID*) of all safety studies published, or at least publish a summary article in a journal with a large circulation in order to inform foreign users of HPV about the safety data from the US where the vaccine has been used in millions of individuals.

Dr. Sukumaran responded that there is currently an overview paper of the HPV vaccine safety studies that is almost complete.

Monitoring Impact of the HPV Vaccination Program / HPV Vaccine WG Plans

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

Dr. Markowitz briefly presented data on the impact of the HPV vaccination program in the US. Post-licensure monitoring is important to evaluate the real world effectiveness of HPV vaccines. Because the impact of HPV vaccines on cancers, the main target of vaccination programs, will not be observed for decades, more proximal outcomes are being evaluated. Population impact on early and mid HPV-related outcomes has been reported now from a variety of countries. These outcomes include prevalent HPV infection, genital warts, and cervical pre-cancer lesions.

This year, a review and meta-analysis of population level impact and herd effects following HPV vaccination programs was published. This was a review of 20 studies in 9 high-income countries conducted within four years of vaccine introduction. Among the findings were that in countries with 50% or greater coverage, among females younger than age 20, HPV 16/18 prevalence decreased by at least 60%. In countries using quadrivalent vaccine, anogenital warts decreased by about 60%. There was evidence of herd effects, including decreases in anogenital warts among older females and in males. There was some evidence of cross protection against other types. In countries with less than 50% coverage, there were also early but smaller decreases in prevalence and anogenital warts. There were no significant increases in non-vaccine types [Drolet et al. Lancet Infect Dis 2015;15:565-80].

Some of the first post-licensure vaccine impact data were reported from Australia, where high coverage was achieved through school-based vaccination programs in the target age groups and in catch-up age groups. As noted, a rapid decrease in genital warts was observed soon after vaccine introduction among females less than 21 years of age and 22 through 30 years of age. While the vaccination program was only targeting females during this time, a decline was also observed among heterosexual males less than 21 years of age and 21 through 30 years of age [Ali et al. BMJ 2013].

Although there are substantial international data, Dr. Markowitz focused on US data during this session. Impact monitoring in the US is being conducted evaluating HPV prevalence, genital warts, cervical pre-cancers, and cancers in a variety of settings. In terms of prevalence, vaccine types in self-collected vaginal swabs in National Health and Nutrition Examination Survey (NHANES), data ACIP has seen before, show a decline in prevalence of types targeted by the quadrivalent HPV vaccine. As noted, there was a 56% decline in 6,11,16,18 prevalence among all 14 through 19 year olds in the first four years of the vaccination program, while no decline was observed in other age groups. Of note, there was no reported decline in sexual behavior or declines in other categories of HPV types between the two time periods. Data from further years of NHANES data will be available soon [Markowitz et al. JID 2013;208:385-93].

More recently, impact on prevalence among women in their 20s has been demonstrated. A study by Dunne et al evaluated HPV prevalence among women age 20 through 29 years of age who were undergoing cervical screening in an integrated health care system in the Northwest. Residual cervical specimens were tested for HPV in 2007, 2012, and 2013. Of the subjects, 21% had received 3 doses and 32% had received at least one dose. Prevalence of 6,11,16,18 deceased between these two time periods from 10.6% to 6.2%, which is a 40% decline. In 2012-2013, vaccine type prevalence was 3.2% among those had received at least 1 dose and 7.6 among those who were unvaccinated. In multi-variable analyses controlling for race, age, and markers of sexual activity, having received 3 doses before 19 years of age was highly protective, with an adjusted prevalence ratio of 0.1 [Dunne et al. JID 2015].

Data for genital warts are available from MarketScan® commercial claims and encounters database for 2003 through 2010. The main finding is the decline in genital warts prevalence among females aged 15 through 19 from 2.9/1000 persons-years in 2006 to 1.8/1000 persons-years in 2010. In women aged 20 through 24 and 25 through 29, prevalence increased or remained level through 2009 and decreased in 2010. Among males, prevalence increased initially or was stable during most of this time period and there was no decrease in 15 through 19 year olds. [Flagg et al. AJPH 2013;103:1428–35]. Data from MarketScan® are being further evaluated now. The early decrease in 15 through 19 year old females is consistent with the decline in vaccine type HPV prevalence seen in NHANES during this time period

There are a variety of challenges in monitoring HPV vaccine impact on cervical lesions. First, these lesions are detected through cervical cancer screening and there have been changes in screening recommendations. In 2009, ACOG recommended to start screening at age 21 rather than within 3 years of onset of sexual activity, and less frequent screenings in older age groups. In 2012, multiple advisory groups made similar recommendations. Also, there are no national cervical cancer screening registries and there are incomplete linkages with vaccination registries.

In spite of these limitations, an ongoing CDC project is assessing cervical cancer precursor lesions and associated types in five catchment areas. This project, HPV IMPACT, capitalized on the infrastructure of the EIP. The project collects data on CIN2+, cervical intraepithelial neoplasia grade 2 or worse, and adenocarcinoma in situ in women 18 years and older. HPV types are determined in a subset of women 18 through 39 years of age, and there is a search for vaccine history. Each site also collects data to estimate population level cervical cancer screening annually in the catchment area.

In terms of incidence rates of CIN2+ by age group and by site in 2008 and 2012 and the percent change between these years, among 18 through 20 year olds the incidence dropped 82% to 94%. This cannot be attributed primarily to vaccine as screening dropped dramatically as well during this time period. In 21 through 29 year olds, there were significant declines in CIN2+ in Connecticut and New York, but not in California or Oregon. In the oldest group, 30 through 39 year olds, little difference is observed in any of the sites.

In three IMPACT sites (New York, Oregon, California), trends in CIN2+ incidence per 100,000 and percent screened by age and year were evaluated. In all sites there was clearly a decline in screening in the youngest age group and declines in CIN2+. This suggests that the declines in lesions in the youngest age group are primarily due to decreases in detection through screening. However, the declines in CIN2+ exceeded declines in screening by 5% in New York, 7% in California, and 15% in Oregon in this age group. Among women 21 through 29 years of age, screening rates also decreased, but to a smaller degree. CIN2+ decreased in New York, but not in Oregon or California. There were inconsistent changes in screening and CIN2+ rates in the oldest age group. These data illustrate the challenges in assessing vaccine impact at this time due to changes in screening practices. The reductions in lesions in 18 through 20 year olds and the more variable declines in 20 through 29 year olds are largely due to concurrent decreases in screening. Further work is ongoing to investigate the contribution of vaccination.

Although there are challenges in determining impact due to vaccination in terms of overall incidence of CIN lesions, evaluation of HPV type-specific CIN lesions provides some clearer evidence. Regarding HPV 16/18 associated CIN2+ among women eligible for vaccination, by year and vaccination status, there is a linear decline of the percent of lesions associated with vaccine type HPV among vaccinated women from 55% in 2008 to 29% in 2012. There was no change in the percent of lesions due to 16/18 among the unvaccinated or among those with unknown vaccine status.

In this same study, using the indirect cohort method, vaccine effectiveness was estimated by looking at HPV types in vaccinated and unvaccinated cases. This analysis evaluated the percentage of CIN2+ attributable to HPV 16/18 by timing of vaccination in relation to the abnormal cervical cancer screening test which led to the CIN diagnosis. Increasing time between vaccination and screening test increases the likelihood that vaccination occurred before infection with the type causing the pre-cancer lesion. Vaccine effectiveness would be expected to increase with increases in this interval. The percent of lesions in unvaccinated women due to 16/18 was 53.6%. In those vaccinated before the screening test, the percent attributed to 16/18 decreased from 50% to 13% with increasing interval. The adjusted prevalence ratio was significant for those vaccinated 25 months or more before the screening test. For those vaccinated 48 months or more before the abnormal test, the adjusted prevalence ratio was .28 for an estimated VE of 72%.

This same analysis was repeated limited to the highest grade lesions of CIN3 or worse, lesions which are more likely to progress to cancer. There are fewer cases of CIN3 than CIN2+. The prevalence of 16/18 was higher in these lesions, but the findings were very similar. Again, the percent attributable to HPV 16/18 decreased with increasing time between vaccination and the screening test from 80% to 40%, and the adjusted prevalence ratio was significant for those vaccinated 37 to 48 months before screening test [Hariri et al. Cancer 2015;121:2775-81].

A variety of other studies are ongoing, including an evaluation of prevalence among MSM, further analyses using administrative data, and vaccine effectiveness studies by number of doses.

In summary, available data from the US and other developed countries show early impact of HPV vaccine on HPV prevalence and other early HPV-associated outcomes. As expected, the first US impact observed was on HPV prevalence and genital warts among females 14 through 19 years of age and later among those in their 20s. There are challenges in evaluating vaccine impact on incidence of cervical pre-cancers in the US, but available data suggest early impact. Further data are forthcoming on vaccine impact and vaccine effectiveness. Achieving higher vaccine coverage will lead to greater impact of the vaccination program.

As a reminder, 9vHPV was licensed by the FDA in December 2014 and was recommended by ACIP in February 2015. An *MMWR Policy Note* was published in March 2015. The vaccine became available through the VFC program in April 2015. By September 2015, 94% of CDC's 64 awardees had placed orders for this vaccine. In September 2015, 36% ordered 9vHPV only. Over 85% of managed care plans decided to cover 9vHPV. As of September 2015, 5 million doses have been distributed in the US.

Future ACIP HPV Vaccines WG plans are to review data on reduced dose schedules, including a 9vHPV 2- vs 3-dose immunogenicity trial, other immunogenicity data, post-licensure effectiveness studies, and cost-effectiveness analyses. The WG plans to present reduced dose data to ACIP starting in February 2016, so the HPV Vaccine WG's work with ACIP over the next year is anticipated to be focused on this topic.

Discussion Points

Dr. Susan Lett (CSTE) requested clarification about the effectiveness data that are expected to be available comparing 2 versus 3 doses.

Dr. Markowitz replied that one problem with assessing the effectiveness of 2 versus 3 doses is that most people who have received only 2 doses did not receive the doses in a 0,6 month interval but rather started the 0,2,6 month schedule and did not receive the third dose. Therefore, the effectiveness data might not inform the 2-dose schedule being evaluated in the immunogenicity trials, in which there is a longer interval between the 2 doses.

Dr. Stephens asked whether there are any data or any plans to assess head and neck cancers associated with HPV and the impact of the vaccine.

Dr. Markowitz replied that this has been challenging because there is no precursor lesion for the oral pharyngeal cancers. This has been an impediment to conducting a trial to assess the efficacy of the vaccine on these cancers. This has been the topic of a lot of discussion. There are some data from a post hoc analysis from a trial in Costa Rica to evaluate the impact of the

vaccine on prevalence of oral infection. The entire topic of HPV-related oral pharyngeal cancers and head and neck cancers were reviewed with ACIP in the past in preparation of making an HPV recommendation. Impact on oral HPV prevalence could be evaluated in some studies.

Regarding reduction of HPV 16/18 associated CIN2+ among women whose vaccination status is unknown with vaccination defined as 1 or more doses, Dr. Strikas asked Dr. Markowitz to comment on what proportion of the women had fewer than 3 doses.

Dr. Markowitz did not have these data with her, but thought it was fairly comparable to US data in which approximately 70% of people who have initiated the series have received all 3 doses.

Dr. David Kimberlin (AAP) asked whether any comments could be made about efforts to monitor for juvenile onset of laryngeal papillomatosis.

Dr. Markowitz indicated that a system has been initiated to collect data on recurrent respiratory papillomatosis through a network of pediatric ear, nose, and throat (ENT) providers. That was just set up in 2015, and CDC hopes to have data from this prospectively and retrospectively.

It was unclear to Dr. Walt Orenstein (NVAC) whether the data presented for the indirect cohort was with the full 3 doses, or if it was 1 or more doses. The numbers seemed to be inconsistent with the pre-licensure trials for at least the 3-dose series, which seemed to have far higher estimates of effectiveness.

Dr. Markowitz replied that this was for at least 1 dose, and that CDC is in the process of performing this analysis to assess 2 versus 3 doses. She would say it is not that inconsistent with the pre-licensure trials, because many of these people would have been vaccinated after infection, even with the longer interval between vaccination and screening test that led to detection of the lesion. The very high efficacy found in the pre-licensure trials is from the per protocol population, comprised of those people who were sero- and PCR-negative at the time of vaccination.

Japanese Encephalitis Vaccine

Introduction

Lorry Rubin, MD
ACIP, Workgroup Chair

Dr. Rubin reminded everyone that inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (JE-VC; IXIARO®) is the only JE vaccine available in the US. JE-VC is manufactured by Valneva, formerly Intercell. Inactivated mouse brain–derived JE vaccine (JE-MB; JE-VAX®) is no longer available in the US.

In terms of how ACIP recommendations for the use of JE-VC have evolved, in 2009 the FDA licensed JE-VC for use in adults and ACIP approved recommendations for a primary series in adults. In 2010, the *MMWR* Recommendations and Reports from 1993 were updated. In 2011, ACIP approved recommendations for use of a booster dose in adults based on new information

and published a Policy Note in the *MMWR.* In 2013, ACIP approved recommendations for use of a primary series in children and published an additional Policy Note in the *MMWR*.

The JE Vaccine WG's current objectives are to: 1) review newly available safety and immunogenicity data for JE-VC; 2) review epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler risk data; and 4) update the *MMWR* Recommendations and Reports published in 2010.

Presentations during this session pertained to the change in the JE vaccine distributor, immunogenicity in adults ≥65 years of age, an accelerated dosing schedule, concomitant administration with rabies vaccine, and the JE Vaccine WG's summary and plans.

New Clinical Data for IXIARO®

Dr. Katrin Dubischar
Senior Scientist, Clinical Research
Valneva Austria GmbH

During this session, Dr. Dubischar discussed the change in the IXIARO® distributor for the US, immunogenicity of IXIARO® in older adults, and results of a clinical trial investigating an accelerated dosing schedule for IXIARO® and concomitant administration with rabies vaccine.

Novartis Vaccines was the US distributor of IXIARO® from FDA approval in 2009 to February 2015. In March 2015, GSK acquired US distribution rights to IXIARO® as part of a multi-product transaction with Novartis. In June 2015, Valneva announced termination of the marketing and distribution agreement for IXIARO® with GSK. Valneva plans to handle these commercial activities on its own and with already established vaccine distributors and wholesalers. The transition from GSK to Valneva is anticipated to be completed by year-end 2015. Both GSK and Valneva are fully committed to a smooth transition to ensure continuous supply of IXIARO® to patients and customers, and ongoing access to medical affairs and pharmacovigilance for IXIARO®.

Regarding immunogenicity of IXIARO® in adults aged ≥65 years, clinical trial IC51-315 was conducted as part of a post-marketing commitment with the US FDA to determine the safety and immunogenicity of the vaccine in an elderly population. Subjects with stable underlying conditions such as hypercholesterolemia, hypertension, cardiovascular disease (CVD), or non insulin-dependent diabetes mellitus (DM) were included. This was an open-label, single arm study in which IXIARO® was administered using the standard dose and schedule of 0.5 ml administered intramuscularly (IM) on Days 0 and 28. The study cohort size was 200 subjects. The study included two follow-up visits, one on Day 70 to determine safety and for serology assessments and one at Month 7 via telephone. The population was enrolled from five trial sites in Germany and Austria. The primary endpoints of the study were rate of serious adverse events (SAEs) and medically attended AEs until Day 70. The main secondary endpoints included the rate of subjects with SAEs and medically attended AEs until Month 7, unsolicited AEs until Day 70 and Month 7, solicited AEs 7 days after each dose, and immunogenicity at Day 70 as determined by GMTs and seroconversion rates (SCRs). SCR was defined as subjects who had a 50% plaque reduction neutralization test ($PRNT_{50}$) titer of $\geq$ 1:10. This neutralizing antibody titer is widely accepted as protective.

On day 70, 65% of the 197 adults aged ≥65 years had a $PRNT_{50}$ titer ≧1:10 and the GMT was 37. The results from this study were compared with a SCR of 96% and GMT of 240 in younger adults in the pivotal licensure trial. Stratified by age, the data were further assessed to understand whether an advanced age of 75 years and older would have an additional impact on immunogenicity. There was no significant difference in SCRs and GMTs in those aged 65 through 74 years and those aged ≥75 years.

In conclusion, similar to other vaccines, IXIARO® shows lower SCRs and GMTs in elderly compared to younger adults. Advanced age of ≥75 years (range 75 through 83) has no further impact on GMTs and SCRs. No long-term data were gathered in this population. Duration of protection is thus uncertain, especially as immune response to the primary series is low. Elderly individuals may benefit from a booster before further exposure to JE virus.

Regarding an accelerated dosing schedule for IXIARO® and concomitant administration with rabies vaccine, Dr. Dubischar first provided some background from a study published by CDC authors on use of JE vaccine among US travelers. This study was conducted at Global TravEpiNet sites. Global TravEpiNet is a CDC-sponsored consortium of US clinical practices that provide pre-travel care. The study period was from September 2009 to August 2012, in a period after the licensure of IXIARO®. The travelers in the study were classified based on their itineraries as either high-risk or lower-risk travelers, and one factor that was addressed was to determine days to departure at which travelers visited the travel clinic. Only 50% of travelers at higher risk for JE presented in time for the FDA-approved, two-dose (Days 0 and 28) schedule of IXIARO®.

Novartis Vaccines, which was the distribution partner of IXIARO® at the time, sponsored and conducted the clinical study to test an accelerated schedule. However, the serological testing for the study was done by Valneva so the study has the same immunogenicity assessments as studies conducted through the trial program for this vaccine. The study was an observer-blinded, randomized, Phase III study in adults 18 through 65 years of age. There were four study groups. The first group consisted of 167 subjects who received the JE and rabies vaccines according to conventional administration schedules. Specifically, IXIARO® was administered on Days 0 and 28, and the rabies vaccine Rabipur® (identical to the US-licensed Rabavert®) was administered on Days 0, 7, and 28. Placebo administrations were given to obscure the treatment groups. The second group of 217 subjects received the accelerated schedules for both of the vaccines, with IXIARO® administered on Days 0 and 7, and Rabipur® administered on Days 0, 3, and 7. The third group of 221 subjects received Rabipur® alone administered according to its conventional schedule on Days 0, 7, and 28. The fourth group of 56 subjects received IXIARO® alone administered according to the conventional schedule on Days 0 and 28. Study follow-up was performed on Days 7 and 28 post-dose 2 of JE-VC for all study groups, and at 6 and 12 months after initiation of the series. In addition, the group who received the accelerated schedule had further visits to determine immune kinetics.

One of the study objectives was to assess non-inferiority of the accelerated schedule compared to the standard schedule as measured by SCR 28 days after the last active immunization. The groups that were compared were those who received an accelerated schedule of JE vaccine administered concomitantly with rabies vaccine versus those who received JE vaccine alone in a conventional schedule. The margin to accept non-inferiority was set to 10%, meaning that the accelerated schedule was considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% CI of the difference in the percentages of subjects with $PRNT_{50}$ titer ≥1:10 measured 28 days after last active vaccine administration was greater than

-10%. A second study objective was to determine if the concomitant administration of JE plus rabies vaccines has an impact on the immunogenicity of the JE vaccine. Here the test was for non-inferiority of the GMTs 28 days after the last active immunization comparing the group who received a conventional schedule of both vaccines versus the group who received the conventional schedule of the JE vaccine alone. The margin was a GMT ratio of 0.5. Pertaining to demographic data for the study population, the mean age was in the high 30s for all three groups who received the JE vaccine and the gender ratio was fairly well-balanced.

With respect to the results for the primary non-inferiority tests, on Day 0 the seropositive rate was about 6% for the groups receiving the accelerated JE and rabies schedules and about 9% in the group who received JE vaccine alone. At 28 days after the second dose of JE-VC, the accelerated schedule resulted in 99% seroconversion and the conventional schedule resulted in 100% seroconversion. Thus, non-inferiority was clearly demonstrated. In terms of the kinetics of the SCR, the onset of the immune response was rapid for subjects administered JE vaccine in an accelerated schedule with a SCR of 99% on Day 14, 7 days after the last active dose, The SCR remained at high levels throughout the 12-month study observation period.

Also, the accelerated JE vaccine schedule resulted in higher GMTs, with about a 3-fold higher maximum GMT compared to the conventional schedule. The titers peaked at a level of 1,255 on Day 21, which is 14 days after the second immunization. Furthermore the GMTs with the accelerated schedule remained higher than the titers observed with the standard schedule.

The group receiving concomitant JE vaccine and rabies vaccine had a GMT of 291 at 28 days after the last active dose compared to a GMT of 331 in the group receiving just the conventional schedule of the JE vaccine alone, resulting in a GMT ratio of 0.88 indicating non-inferiority. In terms of kinetics in the two groups, for all time points for which immunogenicity of JE vaccine was assessed, the titers were fairly comparable.

Safety data are shown in the following table, with the rates being fairly comparable for all of these measures between the three study groups described here:

	R/JE-Conv N=166 n (%)	R/JE-Acc N=217 n (%)	JE-Conv N=56 n (%)
Any AE (Solicited and Unsolicited)	140 (84)	191 (88)	49 (88)
Solicited AEs	137 (83)	185 (85)	44 (79)
Unsolicited AEs	69 (42)	108 (50)	29 (52)
Severe Related Unsolicited AEs	2 (1)	4 (2)	1 (2)
Related SAEs	0 (0)	0 (0)	1 (2)

One AE was thought to be possibly related to vaccination. This was a case of moderate eyelid edema that affected both eyes and a generalized pruritus that occurred on the day of vaccination. The subject had a complete recovery without medical treatment. The doctor who reported the event thought it was a medically important condition and did not further vaccinate the subject. Because there was no hospitalization and the event was not life-threatening, it did not fulfill the more stringent SAE criteria.

In terms of the solicited AEs within 7 days after any dose, the vaccine safety profile was generally similar across the groups. Local solicited reactions were reported by 63% to 75% of subjects across groups, and systemic solicited reactions were observed in 54% to 66%. As a reminder, solicited local AEs included erythema, induration, and pain. The predominant symptom was pain. Again, the rates are fairly comparable between the group receiving accelerated schedules of IXIARO® and Rabipur® and the group receiving the conventional vaccine schedules. They appear somewhat lower for the group who received just the JE vaccine. It is important to note that the two groups receiving IXIARO® and Rabipur® had vaccine administered during at least 3 of 4 study visits, while the group receiving IXIARO® alone had active immunizations administered during only two visits and the rest were placebo injections. Solicited systemic AEs included loss of appetite, nausea, fatigue, myalgia, arthralgia, and headache. The most common reactions were myalgia, headache, and fatigue.

In conclusion, the licensed immunization schedule for IXIARO® consists of two doses, 4 weeks apart. A high number of international travelers present too close to departure to complete this primary immunization schedule[1]. JE vaccine, administered according to an accelerated dosing schedule with a one-week interval between the 2 doses, induced short-term immune responses which were non-inferior to those obtained following the licensed immunization schedule[2]. This accelerated dosing schedule is not approved in the US. The accelerated dosing schedule resulted in titers that were consistently higher than with the conventional schedule both mid-term (6 months) and long-term (1 year)[3]. Both immunogenicity and safety results supported concomitant administration of JE and rabies vaccines, according to both the accelerated and conventional schedules [[1]Deshpande et al. Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. Am J Trop Med Hyg 2014;91:694; [2]Jelinek T et al. J Travel Med 2015;22:225; [3]Cramer et al. Abstract LB-3134, presented at 63rd Annual Meeting ASTMH, New Orleans, USA, November 2014].

Regarding regulatory review and updates to IXIARO® labelling, a use in elderly update to the European labelling was approved in April 2015. The recommendation contained there is as follows:

> *"As with many vaccines, the immune response in older persons (≥65 years of age) to IXIARO is lower than in younger adults. Duration of protection is uncertain in older persons, therefore a booster dose (third dose) should be considered before any further exposure to JE virus."*

An accelerated dosing schedule was approved in Europe in April 2015. The recommendation reads as follows:

> *"Persons aged 18-65 years can be vaccinated in a rapid schedule as follows: First dose at Day 0. Second dose: 7 days after first dose."*

- The European recommendation to administer a booster dose of IXIARO after 12 months if risk for JE exposure persists, remains unchanged.

With respect to the US, Valneva currently is exploring possible approaches to update the IXIARO® Prescribing Information with these and other new clinical data, and continues to work with FDA on respective plans. However, any FDA approved updates to the Prescribing Information for IXIARO would be unlikely to occur before 2017.

Discussion Points

Dr. Belongia requested that Dr. Dubischar elaborate on the approval by the European Medicines Agency (EMA) in Europe, plans with the FDA, and whether the regulatory requirements/expectations differ for EMA versus FDA in terms of the timing of one versus the other.

Dr. Dubischar explained that the scrutiny of the EU is comparable, but the efforts and number of documents that need to be provided and compiled for filing in the US are different from the filings in Europe. European variation of that type is a relatively short few-month process, and the European regulators require a study report. In contrast, filing with the FDA is a more complicated endeavor and is associated with significantly higher costs. In addition to study reports, it is expected that a study database and all programs to analyze that database are submitted to the FDA. The study was sponsored by Novartis, and Valneva is working with Novartis, now GSK, to obtain these additional files.

Regarding rates of AEs that occurred with the vaccines, Dr. Romero inquired as to whether there were any differences in the severity of the reactions.

Dr. Dubischar responded that there were not. In general, the majority of the reactions were mild and there was no difference in the rates for moderate or severe reactions between the study groups.

Dr. Karron wondered if anything was known about the number of travelers in the US over the age of 65 who are getting a primary series, how long they would stay in an area, and how many would be returning such that they might need a booster dose. In addition, she asked whether anyone could comment about protective levels of neutralizing antibody against JE.

Regarding the estimated rates of US travelers and their travel patterns, Dr. Dubischar deferred to Dr. Hills. In terms of the neutralizing antibody levels that would be considered a protective titer, the definition used for seroconversion in the Valneva trials was a neutralizing antibody titer of ≥1:10. It is not clear if a titer below that would also be protective but ≥1:10 is the measure that is accepted by WHO and is the licensure criterion used with FDA.

Dr. Hills replied that for US travelers, CDC has information on doses distributed but does not have information on doses administered nor a breakdown by age group.

JE Vaccine WG Summary and Plans

Dr. Susan Hills
Medical Epidemiologist
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Hills presented on behalf of the JE Vaccine WG a summary of the new safety, immunogenicity, and other data presented during this session. She also discussed plans and the timeline for presentation and discussion of additional data and topics.

As a reminder, when the JE Vaccine WG was reformed in March 2015, its objectives were to: 1) review newly available safety and immunogenicity data for JE-VC; 2) review updated data on the epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler risk data; and 4) prepare a revised *MMWR* Recommendations and Reports to update the document that was published in 2010.

The data on JE-VC immunogenicity in adults ≥65 years of age were presented earlier by Dr. Dubischar. In summary, there has been one observational study in adults aged ≥65 years. At 42 days after the second dose, 65% (128/197) of older adults were seroprotected and the neutralizing antibody GMT was 37. In comparison, in the previous pivotal licensure study in younger adults, at 28 days after the second dose 96% (352/365) of subjects were seroprotected and the neutralizing antibody GMT was 243.

The WG reviewed and discussed these data, and its assessment and summary of JE-VC immunogenicity in adults aged ≥65 years was that: 1) there are lower seroprotection rates and GMTs following the 2-dose primary series in adults aged ≥65 years compared to younger adults; 2) there are no data on safety, immunogenicity, or optimal timing of a possible third primary series or early booster dose; and 3) the data have been submitted to FDA, but no change is expected in the recommended dosing schedule for adults aged ≥65 years due to the lack of data on the safety, immunogenicity, or optimal timing of a possible third primary series or early booster dose.

Following this review, two options were considered by the WG. The first was an off-label recommendation for a third primary series dose or early booster dose for adults 65 years of age and older before further exposure to JE virus. The second was no off-label recommendation, but incorporation of the data into the updated *MMWR* Recommendations & Reports document to make the information available for vaccine providers. The WG concluded that the data were not sufficient to support an off-label recommendation. The plan is to incorporate the data into the updated *MMWR* Recommendations & Reports document. The issue will be reevaluated if new data become available.

The second topic presented by Dr. Dubischar was the use of JE-VC in an accelerated primary series of 2 doses administered 7 days apart in adults aged 18 through 65 years. In summary, the study showed that the accelerated primary series was not inferior to the conventional dosing schedule of 2 doses administered 28 days apart. In the accelerated schedule group, 99% (203/206) of subjects were seroprotected after 2 doses administered 7 days apart. In the comparison standard primary series group, 100% (49/49) of subjects were seroprotected after 2 doses administered 28 days apart.

The WG reviewed and discussed these data. Their assessment and summary of the topic of an accelerated primary series of JE-VC was that: 1) there are limited safety and immunogenicity data in approximately 200 adults with a 2-dose primary series administered 7 days apart; 2) there are no data in children aged <18 years or in adults aged >65 years; and 3) the data have not been submitted to FDA and it is not known if or when this will occur.

Again, two options were considered by the WG. The first was an off-label recommendation for an accelerated primary series of 2 JE-VC doses administered 7 days apart in adults aged 18 through 65 years. The second was no off-label recommendation, but incorporation of the data into the updated *MMWR* Recommendations & Reports document. The WG concluded that the data are promising for use of an accelerated 2-dose primary series, but should be submitted for FDA review. No off-label recommendation is requested by the WG. The WG plans to incorporate the data into the updated *MMWR* Recommendations & Reports document.

In addition to the data presented during this session, additional new JE-VC safety and immunogenicity data are available. The WG plans to present these new data during the ACIP meeting in February 2016. These include data on the duration of protection following the primary series and a booster dose in adults, duration of protection and booster doses in children, and updated post-licensure safety data. The remaining three ACIP JE Vaccine WG objectives will be addressed during the ACIP meeting in June 2016. These include a review of the epidemiology and risk of JE in travelers; a review of the ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler data; and a presentation of a draft of the updated *MMWR* Recommendations & Reports document.

The key components to be updated in the *MMWR* Recommendations & Reports document include the following:

- ❑ Removing the mouse brain-derived JE vaccine information and recommendations as this vaccine is no longer available in the US
- ❑ Incorporating recommendations for the JE-VC pediatric primary series and for a booster dose in adults, previously published as *MMWR* Policy Notes
- ❑ Updating the epidemiology and risk of JE in travelers
- ❑ Including new information on the JE-VC distributor and the new safety, immunogenicity, co-administration, and dosing schedule data

Discussion Points

Dr. Sun (FDA) commented on the issue of labeling changes in Europe versus the US. The issue is fairly complex because of the different approaches to the review of data by the FDA compared to other national regulatory agencies. Based on that, companies develop their strategy for submission. In terms of approvals, the FDA does not accept data from trials on face value. Instead, the agency also requests raw data and tries to reproduce the conclusions and findings through its own analyses, which is a fairly long and more rigorous process. In addition, the FDA performs pre-approval inspections of clinical trial sites and manufacturing facilities, especially if there are any concerns. All of this taken together makes this a rigorous but long and arduous process.

It occurred to Dr. Strikas that the data from the study of the Global TravEpiNet sites conducted by CDC in which an estimate was made of people at lower- and higher-risk of JE could be combined with airline data and/or National Health Interview Survey (NHIS) data, which used to ask people where they were traveling and if they had traveled to certain parts of the world in the past, to develop some semblance of a denominator of people at some degree of risk of JE. He asked if this had been done or contemplated.

Dr. Fischer responded that a previous study was published of an airport survey that assessed the proportion of travelers taking direct flights from the US to Asia that were at higher risk based on ACIP criteria. Those data were not broken down by age group, because there was no concern at that point regarding older age. The proportion of those people who had received JE vaccine was then determined. That study was conducted prior to licensure of IXIARO®, so the proportions are not directly relevant. The TravEpiNet study was conducted among all travel medicine clinics. The proportion of travelers who attend travel medicine clinics to get JE vaccine is not known. It is different from yellow fever vaccine which requires a certificate for travel, so the representativeness of those travelers is unknown. There likely would be data available by age group in that study, but he did not have those results.

Combination Vaccines

Introduction

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Combination Vaccine Work Group

Dr. Reingold reminded everyone that the ACIP Combination Vaccines WG was formed in February 2015 to review published and unpublished data related to the safety and immunogenicity of two new combination vaccines: 1) Quadracel® DTaP-IPV vaccine for children 4 through 6 years of age; and 2) an investigational hexavalent (HV) pediatric vaccine (DTaP5-IPV-Hib-HepB), which is a 3-dose series for children at 2, 4, and 6 months of age.

The WG's Terms of Reference for Quadracel® Vaccine have been satisfied with the presentation of safety and immunogenicity data to the ACIP in June 2015, followed by the publication of the Policy Note in the *MMWR* on September 4, 2015. During the July Combination Vaccines WG conference call, safety and immunogenicity data were presented by Sanofi Pasteur and Merck for the investigational HV pediatric vaccine. This is an interesting vaccine in that it is a joint venture of two different vaccine manufacturers, Sanofi Pasteur and Merck, who have come together to combine their respective products into a single vaccine.

The investigational pediatric HV vaccine includes antigens for diphtheria, tetanus, pertussis, and polio from Sanofi Pasteur and antigens for Hib and hepatitis B from Merck. There are licensed vaccines containing the same antigens. Although PedvaxHIB® contains 7.5 µg of polyribosylribitol phosphate polysaccharide linked to outer membrane protein complex (PRP-OMPC), the HV vaccine contains 3 µg. Recombivax HB® contains 5 µg of hepatitis B surface antigen (HBsAG), but the HV vaccine contains 10 µg.

The BLA was accepted by FDA for review in October 2014. The proposed indication is for a 3-dose series in children from 6 weeks through 4 years of age administered at 2, 4, and 6 months of age. Based on the materials reviewed, no safety or immunogenicity concerns were identified by the WG. This session focused on the safety and immunogenicity of the investigational pediatric HV vaccine.

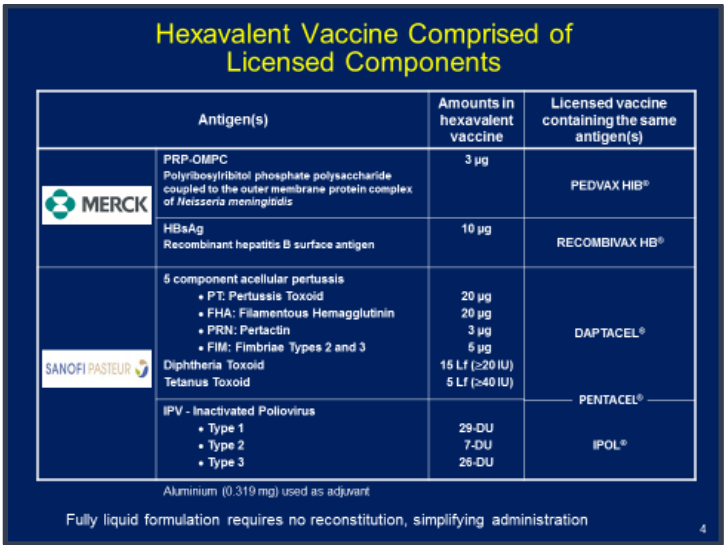
Immunogenicity and Safety of DTaP5-IPV-Hib-HepB: A Pediatric Hexavalent Combination Vaccine

Andrew W. Lee, MD
Director, Vaccines Clinical Research
Merck Research Laboratories

Dr. Lee thanked the WG for their helpful discussions to date and ACIP for the opportunity to speak during this session. On behalf of Sanofi Pasteur and Merck, he presented an overview of MCM Vaccine Co. (a partnership between Merck & Co., Inc. and Sanofi Pasteur Inc.), as well as the pediatric HV vaccine composition; Study 005 design and immunogenicity results; Study 006 design and immunogenicity results; and integrated safety results for DTaP5-IPV-Hib-HepB. Because the safety design was very similar across Study 005 and 006, it was possible to integrate the safety results across the two studies.

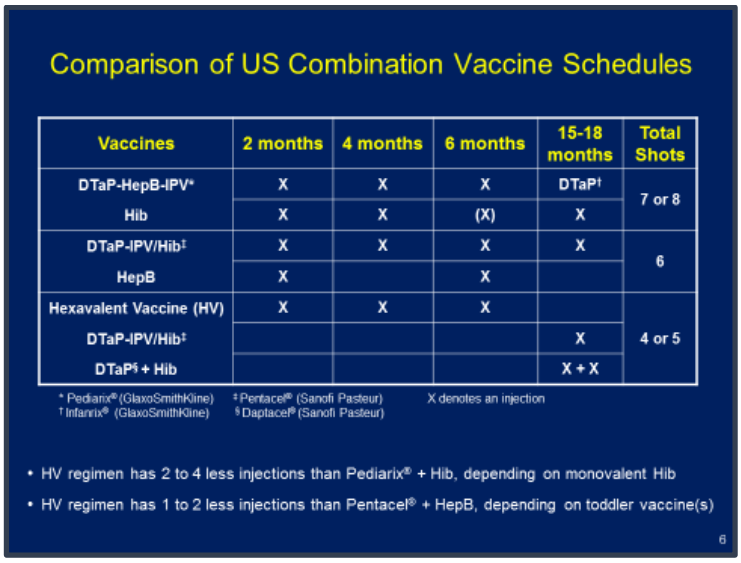
Merck and Sanofi Pasteur formed a partnership called the MCM Vaccine Co. in 1991 to develop this combination vaccine. The work related to the development and manufacturing of the vaccine was divided as equally as possible. Merck contributes the HepB and Hib components and Sanofi Pasteur contributes DTaP5 and IPV, and they are also responsible for the formulation and release of the product. In terms of development, Merck is the clinical lead and Sanofi Pasteur is the regulatory lead. Both companies will co-promote the product once it is approved. Merck is the lead for pharmacovigilance and holds the global safety database.

In terms of the composition of the HV vaccine, the components come from the licensed vaccines as depicted in the following table:



With the combination vaccine schedule being 3 doses at 2, 4, and 6 months, there is an additional dose as compared to the two infant dose schedules for the PEDVAX HIB® product. This permitted the exploration of lower amounts of the Hib antigen as compared to the amount contained in PEDVAX HIB®. Based on the results of a Phase II study that assessed several formulations of the HV vaccine and the level associated with long-term protection of ≥1.0 µg/mL from Hib disease and geometric mean concentrations (GMCs), the PRP-OMPC-containing formulations of the HV had acceptable Hib responses; whereas, the PRP-T formulation did not. While both the HV PRP-OMPC 3 µg and 6 µg formulations had similarly high Hib responses, the 6 µg formulation was associated with slightly higher rates of injection-site and systemic AEs. On balance, HV PRP-OMPC 3 µg was chosen for further development [Diaz-Mitoma et al. Vaccine 29 (2011) 1324–1331]. Diaz-Mitoma et al. Vaccine 29 (2011) 1324–1331].

The following is a table of the US combination vaccine schedules, which indicates how many shots are associated with each regimen:



For the HV vaccine, there are two options for completing the HV regimen at the toddler time point of 15 to 18 months of age. Either 1 injection of Pentacel® or Daptacel® plus the monovalent Hib, resulting in a total of 4 or 5 injections for the HV regimen. There is also variation in the number of injections associated with the Pediarix® regimen. Depending upon which Hib vaccine is used, there are either 2 or 3 infant doses, which results in either 7 or 8 total injections for that regimen. Overall, the HV regimen has 2 to 4 less injections than the Pediarix® + Hib regimen, depending upon the monovalent Hib used. The HV regimen has 1 to 2 less injections than Pentacel® + HepB, depending upon which vaccines are used for the toddler dose.

Regarding Study 005, the pivotal non-inferiority US study, HV immunogenicity was compared to the licensed component control. Most of the immunogenicity endpoints were after the third dose at 7 months. There also were some primary pertussis endpoints after the toddler dose due to the need for 4 doses for the pertussis vaccination series. After the third dose, immunogenicity was also evaluated for concomitantly administered RotaTeq® vaccine [Marshall et al. Pediatrics 136 (2015) e323-332].

The primary endpoints for Study 005, most of which pertained to the non-inferiority measures, included the following:

- Non-inferiority of antibody response rates to all HV antigens at one month Post-Dose 3 in HV versus control vaccine recipients
- Non-inferiority of pertussis antibody GMCs at one month Post-Dose 3 and at one month Post-Toddler Dose in recipients of HV versus control vaccine infant doses
- Acceptably high polio antibody titers at one month Post-Dose 3 in HV recipients

The secondary endpoints for Study 005, which related to different ways of measuring the Hib and concomitant responses, included the following:

- Non-inferiority of proportion of HV versus control vaccine recipients with PRP concentrations ≥0.15 µg/mL at one month Post-Dose 3
- Non-inferiority of PRP GMCs at one month Post-Dose 3 in HV versus control vaccine recipients
- Non-inferiority of anti-rotavirus immunoglobulin A (IgA) GMCs at one month Post-Dose 3 in HV versus control vaccine recipients

In general, the antibody response rates after the third dose were overlapping with the exception of the Hib responses at the two different thresholds when the responses appear to be higher for the HV regimen as compared to the control. This is consistent with the monovalent Hib literature that shows that the PRP-OMPC type of Hib vaccine has more rapid development of immune responses as compared to the PRP conjugated to tetanus toxoid (PRP-T)-based Hib vaccines. Otherwise, most of the antigens appear to be quite similar. Post-Dose 3 non-inferiority criteria were met for all pertussis antibody endpoints except filamentous hemagglutinin (FHA) GMC. However, for the same antigen, the response rate criteria were met for FHA. The confidence intervals were largely overlapping for the Post-Toddler dose, and all of the non-inferiority criteria were met for all pertussis antibody endpoints. Following Dose 3, rotavirus immunogenicity was non-inferior when given concomitantly with hexavalent or control vaccines. Again, the confidence intervals were overlapping. Thus, non-inferiority criteria were met whether measured by the percent of 3-fold increase or GMCs.

With respect to Study 006, the lot consistency study, was designed using three consecutive lots of the HV vaccine to account for the larger number of subjects who actually received HV. There is a control arm of a smaller size as well. Given that consistent immune responses to all antigens were demonstrated across all three lots, it was possible to combine the immunogenicity results for the three lots. Immunogenicity was also evaluated for concomitant administration of Prevnar 13® after the third dose in this study.

The results for Study 006 were very similar to those for Study 005 after the third dose in that all non-inferiority criteria were met except for the GMC measure of FHA. There was one difference in Study 006 versus Study 005 in the Post-Toddler dose in that the criteria for the GMC measure of the PRN pertussis antigen were narrowly missed. The non-inferiority criteria required that the lower bound exceed 0.67, which was missed. Regarding the anti-pneumococcal (PN) responses one month Post-Dose 3, the non-inferiority criteria were met for 12 of the 13 serotypes contained in the vaccine. For serotype 6B, the non-inferiority response was missed for the study endpoint but would have satisfied the Prevnar 13® non-inferiority criterion used for licensure, which required that the lower bound of the GMC ratio exceed 0.5.

As noted previously, safety measurements for US studies 005 and 006 were integrated across studies. Daily temperature measurements were taken for 5 days after each vaccination. The day of vaccination counted as Day 1. The ratings for mild, moderate, and severe are standard and are shown as follows in Centigrade and Fahrenheit:

38.0 ≤ Mild ≤ 38.4°C	100.4 ≤ Mild ≤ 101.1°F
38.5 ≤ Moderate ≤ 39.4°C	101.3 ≤ Moderate ≤ 102.9°F
Severe ≥ 39.5°C	Severe ≥ 103.1°F

For 5 days after each vaccination, systemic AEs were solicited for fever, vomiting, crying abnormally, drowsiness, appetite loss, and irritability. Solicited injection-site AEs included redness, swelling, and pain/tenderness. Unsolicited AEs were monitored for 15 days after each vaccination. SAEs were collected for 6 months after the infant vaccination series and for 15 days after the toddler vaccinations (which was not the HV vaccine). Deaths and vaccine-related SAEs at any time during the study were also collected. In terms of the percent of participants with any solicited injection-site AEs on Day 1 through Day 5 following any infant vaccination, the incidences appear to be quite similar. In general, solicited systemic AEs during the first 5 days following any infant dose also were quite similar across the different categories. However, there was an increased incidence of pyrexia for the total HV as compared to the control.

Further assessment of temperature data for the first 5 days following any infant dose showed that there was about a 13% higher incidence of subjects with any fever ≥ 38.0°C among HV recipients versus controls. The confidence intervals do not cross zero for mild and moderate; however, they do cross zero for severe temperature. Thus, there is no significant difference in severe temperature elevations, though there was for mild and moderate temperature elevations. Data not shown during this session but collected during the study showed that the vast majority of temperature elevations were 2 days or less in duration, as would be expected for an inactivated or subunit vaccine. Regarding participants with fever ≥ 38°C by dose for Days 1 through 5, there is less of a separation between HV and control fever rates after the first dose and more of a separation after the second and third doses. There also appears to be a plateau between Doses 2 and 3 in fever rates for the HV vaccine.

With the increase in fever rates, care was taken to monitor for fever-related medical events. There was a low and similar incidence of pyrexia SAEs in the HV group as compared to the control group. In addition, there were no febrile seizures or seizures within 15 days of any vaccination. When the safety monitoring period was extended to 180 days following the infant doses, some cases of febrile seizures and seizures were identified in both vaccination groups. However, these cases were quite distant from vaccination, and none of the cases were considered related to vaccination.

There was a low incidence of vaccine-related SAEs and study discontinuations due to AEs in both vaccination groups. The statistical analysis showed that there was no statistical difference between the HV group compared to the control group. None of the deaths that occurred during the study were considered to be vaccine-related. It is important to keep in mind that the ratio of HV to control subjects is approximately 4:1.

In summary, the pediatric HV vaccine is an investigational product that is under review by the FDA. A decision is anticipated from the FDA before the end of 2015. The data shown during this session demonstrated robust immunogenicity and an acceptable safety profile in rigorous Phase III studies with a total of over 4,250 infants. The infant series immune responses were

non-inferior to control, except for the GMC of FHA. However, FHA response rates were non-inferior. An increase was observed in self-limited, mild-to-moderate fever, but this was not associated with significant increases in clinical consequences. The concomitant rotavirus and pneumococcal conjugate vaccine immunogenicity was similar when given with HV or control. Combination vaccines improve vaccination compliance and timeliness. Overall, this DTaP5-IPV-Hib-HepB pediatric vaccine will provide a new option for meeting the recommended US vaccination schedule with fewer injections.

Discussion Points

In terms of there being no difference in the clinical consequence of fever between the two groups, Dr. Rubin wondered whether there was a difference in the necessity to go to the doctor or ED for evaluation or for admission to the hospital due to fever even if patients ultimately did well.

Dr. Lee replied that this is covered under the incidence of SAEs, and there was a small difference. There were three cases of SAEs of fever that required either hospitalization or ED visits. Given the ratio of HV to control subjects, this incidence does not represent a significant difference.

Dr. Bolongia asked whether there is any information about the expected cost of the vaccine once it is approved relative to the current vaccines.

Dr. Lee responded that he was unable to comment on the price of the vaccine at this time. The price of the vaccine will be announced once licensure is obtained.

Ms. Finley (AIM) noticed that the HepB amount is a higher dose, yet an increased percentage of children are receiving the birth dose. She requested an explanation for why a higher dose of HepB would be included.

Dr. Lee explained that the dose as compared to the monovalent pediatric dose of HepB was based on the potential for immune interference between the HepB responses and the other components of the vaccine. Similar to what was shown for Hib, various doses of HepB were evaluated in the Phase II studies. The 10 µg was optimal for immunogenicity and safety overall.

Dr. Sawyer (PIDS) asked whether this vaccine is the same as the one currently used in Canada, or if it has a different composition. If it is the same, he wondered how many doses have been given.

Dr. Lee replied that the Canadian formulation is different. The HV used in Europe is Infanrix® Hexa. There are differences primarily in the Hib component. DTaP5-IPV-Hib-HepB has a PRP-OMPC Hib component, while Infanrix® Hexa contains a PRP-T. The other difference is that DTaP5-IPV-Hib-HepB contains 5 antigens in the pertussis component of the vaccine, while Infanrix® Hexa has 3 antigens.

Dr. Walter asked whether there was an increase in antipyretic use among the subjects who had fever.

Dr. Lee responded that the study protocol included an instruction not to give antipyretics prior to the appearance of fever, given the paper from *The Lancet* showing that there could be blunting of immune response. However, antipyretic use was permitted in response to fever. There was a slightly higher rate of antipyretic use of 61% in the HV group compared to 57% in the control group. This was thought to be consistent with the slightly higher rates of fever observed.

From a consumer perspective, Ms. Pellegrini expressed gratitude on behalf of small children everywhere. Combination vaccines reduce the burden on families. This is not only about fewer needlesticks, but also is about improving compliance.

Cholera Vaccine

Introduction

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Cholera Vaccine Work Group

Dr. Reingold indicated that the ACIP Cholera Vaccine WG is a new WG, which is anticipated to have a relatively short lifespan. No cholera vaccine is currently licensed in the US. CVD 103-HgR is an oral cholera vaccine that is anticipated to be licensed in the US in 2016. The ACIP Cholera Vaccine WG was created to review the evidence for use of CVD 103-HgR in US adult travelers. The WG's specific Terms of Reference are to:

- ❑ Review data on safety, immunogenicity, and efficacy for CVD 103-HgR vaccine (PXVX0200)
- ❑ Propose ACIP recommendations for use of CVD 103-HgR in US adult travelers and publish approved recommendations in *MMWR Recommendations and Reports*

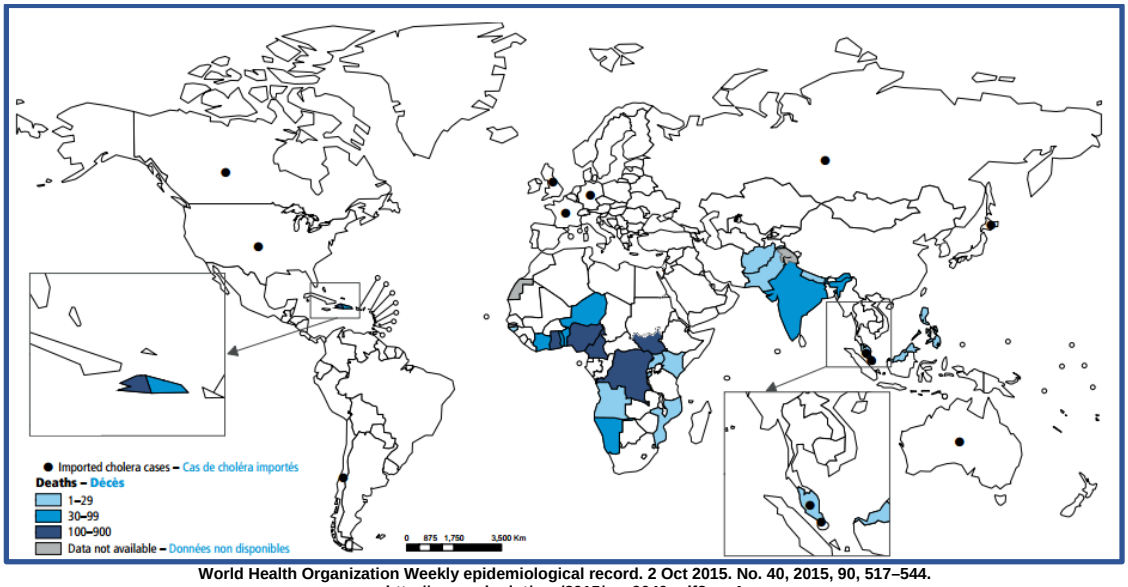
Regarding the timeline, PaxVax filed a BLA with the FDA with a request for priority review. The FDA review is anticipated to be completed by June 2016. The plan is to call for an ACIP vote on recommendations for use of CVD 103-HgR as soon as possible after the vaccine is licensed.

Cholera in US Travelers

Karen K. Wong, MD, MPH
Medical Officer
Division of Foodborne, Waterborne, and Environmental Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Wong presented an overview of cholera in the US. Cholera is caused by gram-negative, rod-shaped, toxigenic Vibrio cholera (*V. cholera*) O1, which accounts for over 99% of global cases, or O139. Cholera causes a watery diarrhea that may be severe and rapidly fatal without proper treatment. Cholera is endemic in over 50 countries, and it may also cause epidemics. It is estimated to cause 3 to 5 million cases of illness and 100,000 to 130,000 deaths annually.

Countries reporting cholera deaths and imported cases to the WHO in 2014 are depicted in the following map, followed by a specific list:



World Health Organization Weekly epidemiological record. 2 Oct 2015. No. 40, 2015, 90, 517–544.
http://www.who.int/wer/2015/wer9040.pdf?ua=1

The shaded blue countries located in Africa, Asia, and the Island of Hispaniola in the Caribbean are areas where cholera deaths have been reported. The black dots mark the countries that have reported imported cholera cases.

Deaths were reported by 24 countries in:

- Africa (1,882)
- Asia (42)
- Caribbean [Hispaniola] (307)

Imported cases were reported by 11 countries:

- Australia (2)
- Canada (2)
- Chile (1)
- France (1)
- Germany (1)
- Japan (5)
- Malaysia (33)
- Russia (1)
- Singapore (2)
- United Kingdom (14)
- United States (7)

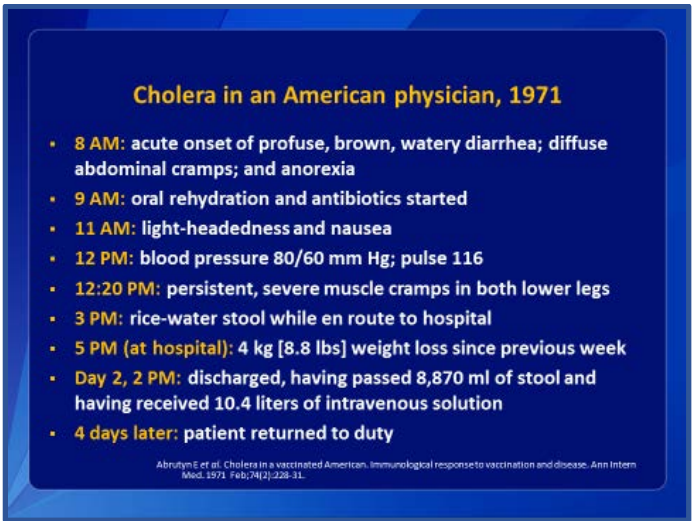
V. cholerae is classified by its O-antigen structure. More than 200 O serogroups have been identified. The WHO defines cholera as illness caused by toxigenic O1 and O139 because they have caused cholera epidemics. O1 can have two biotypes (El Tor and classical), as well as two serotypes (Inaba and Ogawa). *V. cholerae* colonizes the small intestine and produces cholera toxin. Cholera toxin is comprised of an A subunit that causes secretory diarrhea, as

well as five identical B subunits that surround the A subunit and bind the toxin to cell membrane receptors.

Cholera is easily transmitted by water and food contaminated by human feces or environmental reservoirs. It grows rapidly in warm, moist, non-acidic foods. It is a fragile organism that does not tolerate drying, acidity, or sunlight. Cholera attaches to copepods or zooplankton, which can be consumed with contaminated water or food. The incubation period of cholera ranges from hours to about five days, and the duration of illness ranges from one to a few days. Secondary cases are rare if sanitation is adequate.

The clinical presentation of cholera ranges from no apparent symptoms to severe hypovolemic shock, also known as cholera gravis. The risk factors for cholera gravis include high-dose exposure; low gastric acidity such as occurs with gastrectomy or antacid therapy; blood group O, the prevalence of which is approximately 45% in the US; and other strain and population factors [Harris JB *et al*. Blood group, immunity, and risk of infection with *Vibrio cholerae* in an area of endemicity. Infect Immun. 2005 Nov;73(11):7422-7; http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics].

Cholera gravis causes a profuse watery diarrhea, which can be one or more liters per hour. It typically causes something called “rice-water stools” named for its appearance of being flecked with mucus and epithelial cells. Vomiting and leg cramps may also be part of the clinical presentation. Cholera can cause severe dehydration characterized by loss of skin turgor, hypotension, weak pulse, and altered mental status. It can be rapidly fatal if untreated. A descriptive account of cholera in an American physician was published in 1971. The timeline and symptoms described here are typical of severe cholera:

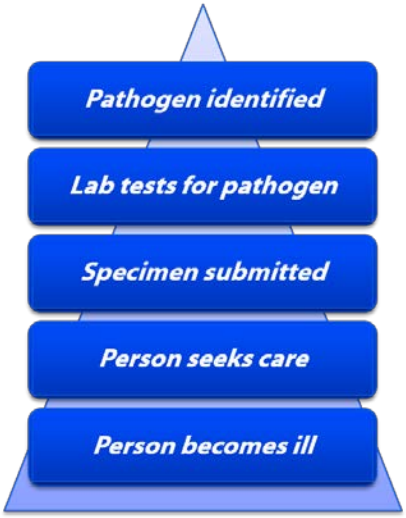


Diagnosis of cholera is made by bacterial culture of a rectal swab or stool specimen. However, under-diagnosis is common because special transport media and culture media are needed to isolate the organism. Serologic diagnosis may also be made using acute and convalescent vibriocidal titers. These antibodies typically increase two weeks after exposure and decrease two months after the illness.

The mainstay of clinical management is supportive care. Oral and intravenous rehydration can reduce the fatality rate to less than 1%. Antimicrobial therapy may also be used in conjunction with hydration. It is recommended for severely ill patients and all hospitalized patients, and it reduces fluid loss, duration of illness, and duration of fecal carriage. Zinc supplementation in children reduces the duration of illness and the volume of diarrhea.

Vibriocidal antibodies are the best marker for protection against *V. cholerae* infections. Lipopolysaccharide (LPS)-specific memory B cells may play a role in mediating long-term protection. Protection against cholera is serogroup-specific; that is, it protects against O1 *or* O139, but it protects across the biotypes El Tor *and* Classical and the serotypes Inaba *and* Ogawa.

Cholera is very rare in the US and other countries with safe water and modern sanitation. There are few domestically acquired cases in the US, many of which are associated with Gulf Coast seafood consumption. Most US cases are associated with travel to cholera-endemic countries. Cholera is under-reported in the US, because testing for *V. cholerae* is not routine, and some cholera illnesses in travelers are not severe and may resemble other causes of traveler's diarrhea. The following diagram shows the surveillance pyramid:



Beginning at the bottom of the pyramid, of all of the people who become ill, only a fraction seek medical care. Of those, only some may have a diagnostic specimen submitted for testing. Only some of those specimens may be tested for cholera, which is not routine. Of those tested for cholera, not all will identify the pathogen. Thus, the cases that are confirmed and reported represent only the tip of the iceberg in terms of the true burden of illness.

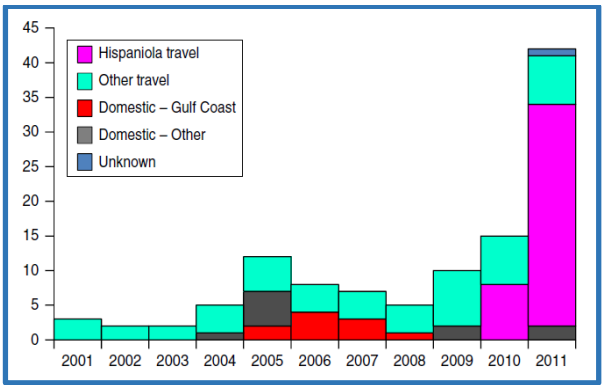
With that in mind, there are some estimates of laboratory-confirmed cholera incidence in returning travelers. Among European and North American travelers to South America during the 1991 cholera epidemic, the incidence was estimated to be 0.3/100,000 people. Among Japanese travelers to Indonesia, the estimated incidence was higher at 13/100,000 people. Among all travelers returning from travel to the developing world who sought care at certain surveillance clinics from 1996 through 2004, the incidence was estimated at 5.8/100,000 people. Note that the interpretation of these estimates should consider differences in the surveillance methods. Surveillance of the European and North American travelers relied on passive reporting; whereas, surveillance of the Japanese travelers was somewhat enhanced as

travelers were specifically tested for cholera infection [Wittlinger F *et al*. Risk of Cholera Among Western and Japanese Travelers. J Travel Med. 1995 Sep 1;2(3):154-158; Freedman DO *et al*. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med. 2006 Jan 12;354(2):119-30].

There are also some estimates of laboratory-confirmed cholera incidence among persons traveling or living in cholera-affected areas. Among US citizens living in Peru the incidence of cholera was estimated to be 44/100,000 people per month of exposure from 1991 through 1993. Among US citizens providing medical services in Haiti during the cholera epidemic from 2010 to 2011, the incidence was estimated at 321/100,000 people (1 of 311 study respondents reported receiving a diagnosis of cholera). Among travelers who sought care for diarrhea in multiple years between 1986 and 2011 during travel to Nepal, a cholera-affected country, zero cases of cholera were diagnosed. Cholera outbreaks have also been described among travelers. In Haiti in December 2010, a suspected cholera outbreak affected 10 of 14 French medical volunteers and 11 of 72 French military police engaged in response efforts and living in the same site [Taylor DN *et al*. Cholera among Americans living in Peru. Clin Infect Dis. 1996 Jun;22(6):1108-9; Schilling KA *et al*. Diarrheal illness among US residents providing medical services in Haiti during the cholera epidemic, 2010 to 2011. J Travel Med. 2014 Jan-Feb; 21(1):55-7; Murphy H, Pandey P. Pathogens for travelers' diarrhea in Nepal and resistance patterns. Curr Infect Dis Rep. 2012 Jun;14(3):238-45; Haus-Cheymol R *et al*. A cluster of acute diarrhea suspected to be cholera in French travelers in Haiti, December 2010. J Travel Med. 2012 May-Jun;19(3):189-91].

A cholera outbreak has also been described on a commercial airline flight. In 1992, a flight from Buenos Aires, Argentina stopped in Lima, Peru before landing in Los Angeles. A contaminated seafood salad was prepared in Lima and served to the flight passengers. Of the passengers, 100 of 194 tested had evidence of *V. cholerae* O1 infection. Of those, 75 had diarrhea that began a median 2 days after arrival, 10 patients were hospitalized, 1 patient died who was 70 years of age, and 19 of the cholera patients were US citizens [Eberhart-Phillips J *et al*. An outbreak of cholera from food served on an international aircraft. Epidemiol Infect. 1996, Feb;116(1):9-13].

A case series of surveillance data from 2001 through 2011 showed that 111 cholera cases were reported in US over an 11-year period. Of note, epidemic cholera began in Haiti in October 2010. Of the cases over the study period, 46% were reported after the Haiti epidemic began. No secondary cases were reported in this series. Of the cases, 20 (18%) were domestically acquired and most of them reported seafood consumption. Of the cases, 90 (81%) were associated with international travel. The most common reason for travel was visiting friends and relatives (62%). Other reasons for travel included medical missions or other relief work (9%), tourism (7%), business (7%), and immigration to the US (5%). Of 87 travel-associated *V. cholerae* O1 cases, 74 (85%) had an isolate with a multidrug resistant pattern. Of the 111 cases identified in this 11-year period, 108 were diagnosed by stool culture. Of those, 99% (n=107) were *V. cholerae* O1. Of the 107 *V. cholerae* O1, 22 (21%) were El Tor Inaba and 85 (79%) were El Tor Ogawa. This graph shows the number of cholera cases by year and source from 2001 through 2011:



Cases increased after 2010 due to travel to Hispaniola during a cholera outbreak, and these cases are shown in purple. Travel to other areas, shown in green, remains an important source of cholera cases. Domestically acquired cases along the Gulf Coast are shown in red [Loharikar A *et al*. Cholera in the United States, 2001-2011: a reflection of patterns of global epidemiology and travel. *Epidemiol Infect*. 2015 Mar;143(4):695-703].

More recently in 2012 to 2013, 30/32 (94%) patients with cholera reported in the US had traveled to a cholera-endemic area, including 18 from Haiti and 4 from the Dominican Republic. Unusually, there was 1 case in a healthcare worker with no travel exposure who cared for a cholera patient in the hospital. There was also 1 case in a person who reported exposure in a laboratory. The age of these patients ranged from 1 through 87 years. [http://www.cdc.gov/ncezid/dfwed/ pdfs/covis-annual-report-2012-508c.pdf. Accessed October 8, 2015; http://www.cdc.gov/ncezid/dfwed/pdfs/covis-annual-report-2013-508c.pdf . Accessed October 8, 2015].

To summarize some of the key cholera features, severe cholera (cholera gravis) can be rapidly fatal if untreated. Cholera is often under-reported. Few cases are reported in the US, although incidence increased after the outbreak in Haiti began. Most cases in the US occur in persons who have recently traveled to cholera-affected areas. A few cases have been identified in healthcare workers and laboratory personnel providing medical services to cholera patients.

Current CDC prevention recommendations for US travelers to cholera-affected areas center on safe food and water precautions and frequent handwashing. Chemoprophylaxis with antibiotics is not indicated. There is no vaccine recommendation, and no cholera vaccine is currently licensed in the US. WHO prequalified vaccines, Dukoral® and Shanchol™, are mentioned as being available outside of the US [http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/cholera. Accessed October 8, 2015].

The current WHO recommendations for travelers to cholera-endemic areas state that:

> *The risk for most travelers is very low, even in countries where cholera epidemics occur, provided that simple precautions are taken. However, humanitarian relief workers in disaster areas and refugee camps may be at risk.*
>
> *Consider for travelers at high risk:*
>
> - *Killed oral O1 with whole-cell with B-subunit (Dukoral®)*
> - *Killed oral O1 and O139 (Shanchol™)*

On October 2, 2015, there was an announcement that a Strategic Advisory Group of Experts (SAGE) Working Group is forming to revise the WHO recommendations on oral cholera vaccines.

As mentioned earlier, there is no cholera vaccine currently licensed in the US. However, there are two oral cholera vaccines available in other countries. Shanchol™ is licensed in India and requires 2 oral doses spaced 2 to 6 weeks apart. Dukoral® is licensed in more than 60 countries, primarily as a vaccine for travelers to cholera-endemic areas. In Sweden and Canada, it is also approved for traveler's diarrhea prevention. It provides some short-term protection against enterotoxigenic *E. coli* (ETEC). It also requires 2 oral doses spaced 7 or more days apart, and requires a buffer solution. No country currently requires vaccination against cholera as a condition for entry.

The vaccine the ACIP Cholera Vaccine WG is focused on is a different oral cholera vaccine known as CVD 103-HgR. Unlike the other two vaccines, CVD 103-HgR is a single dose, live attenuated oral cholera vaccine. CVD 103-HgR is soon to be under consideration for US travelers. It uses a recombinant *V. cholerae* O1, classical biotype, serotype Inaba. It confers protection against multiple biotypes and serotypes. Of the enzymatically active A subunit of toxin gene, 94% is deleted. The gene for the antigenic, non-toxic B subunit of the toxin is intact. The vaccine does not express enzymatically active cholera toxin, and it contains a marker to differentiate the vaccine strain from wild-type *V. cholerae* O1. This vaccine was previously licensed as Orochol® or Mutacol® and was used in non-US countries, including Switzerland, Canada, and Australia. Manufacture ceased for business reasons in 2004. In 2009, PaxVax acquired the licensure rights to redevelop CVD 103-HgR, or Vaxchora™, for commercial use. They recently filed a BLA for use in adults travelers.

The ACIP Cholera Vaccine WG will review evidence for use of CVD 103-HgR and evaluate that evidence according to the GRADE framework. The WG hopes to inform recommendations for use of CVD 103-HgR in adult travelers in anticipation of the US licensure. In February 2016, the WG anticipates a presentation of the GRADE evaluation, as well as a presentation by the vaccine manufacturer. In June 2016, a presentation is anticipated of WG recommendations regarding the use of this vaccine in adult travelers.

Ebola Vaccine Trial Update

Susan Goldstein, MD
National Center for Immunizations and Respiratory Diseases
On behalf of the STRIVE Team

Dr. Goldstein described the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE), first recognizing the over 200 CDC staff who have participated in this trial within Sierra Leone and in Atlanta. In response to the West Africa Ebola outbreak that was unprecedented in size and complexity, WHO convened a consultation on potential Ebola therapies and vaccines in September 2014. One of the recommendations from the meeting was to "Accelerate [vaccine] development and safe use in countries with outbreaks." With this recommendation noted and a large CDC presence in West Africa, CDC decided to expand the West Africa response to include a vaccine trial.

The overarching goal of STRIVE is to accelerate introduction and use of an Ebola prevention vaccine among at-risk people in Sierra Leone with concurrent evaluation of the efficacy and safety of the vaccine. The three primary objectives are to: 1) Estimate the efficacy of a single dose of vaccine in preventing laboratory-confirmed Ebola virus disease (EVD); 2) Assess SAEs following administration of the vaccine; and 3) Collect and store serum for baseline seroprevalence and immunogenicity evaluations. STRIVE principal study partners include the College of Medicine and Allied Health Sciences (COMAHS) and the Ministry of Health and Sanitation (MOHS) in Sierra Leone; and CDC, the Biomedical Advanced Research and Development Authority (BARDA), and Merck/New Link Genetics in the US.

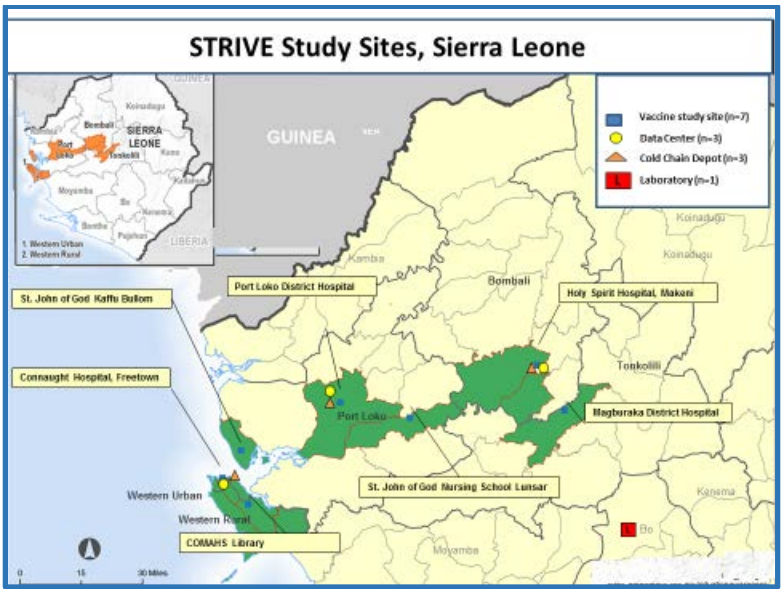
The vaccine, rVSV-ZEBOV, is a live-attenuated recombinant vesicular stomatitis virus (rVSV) vaccine that expresses the glycoprotein of the Kikwit strain of the Zaire Ebola virus (ZEBOV). The vaccine was developed by the Public Health Agency of Canada (PHAC), and Merck currently holds the license. rVSV-ZEBOV is administered as a single dose at a concentration of 2×10^7 pfu/mL, and it is stored at -80°C.

STRIVE is an unblinded, randomized trial with phased enrollment over a period of 4 months. Participants are individually randomized to either the immediate group and are vaccinated at or within 7 days of enrollment, or the deferred group and are vaccinated 18 to 24 weeks after enrollment. There is no placebo. All participants will be vaccinated by the end of the study. Vaccine efficacy is measured by comparing EVD incidence in the vaccinated and deferred groups. AEs are assessed by following participants post-vaccination for 6 months. The study population is comprised of adults 18 years of age and older who are healthcare workers (HCW) in either an Ebola or non-Ebola facility. Being a healthcare worker is defined by working in a healthcare facility setting rather than by the specific job:

Physicians	Laboratorians	Cleaners
Nurses	Pharmacists	Administrators
Health aids	“Dressers”	Security Guards

The study population also includes selected Ebola frontline workers: Surveillance Officers, Ambulance Drivers, Swabbers, and Burial Workers.

The study sites selected reflect the epidemiology of Ebola early in the course of the outbreak and the need for an appropriate sample size, which is a minimum of 6000 participants. Sites were also selected based on the logistical considerations of the existing infrastructure and the ability to enhance the infrastructure for buildings, cold chain, roads, and transportation. The ability to monitor for and ensure standard of care for AEs and EVD was also important. Work is performed in five districts, including Freetown, the country capital and urban center. There are 7 vaccination sites, 3 data centers, 3 cold chain depots, and 1 laboratory. The main data hub and main vaccine depot are in Freetown. The following map shows the locations of the study sites, data centers, cold chain depots, and laboratory in Sierra Leone:



Participants are monitored for AEs, SAEs, EVD, and pregnancy for 6 months post-vaccination. The deferred group is monitored from enrollment until vaccination and then for 6 months thereafter. Follow-up is done through monthly phone calls to each participant. If a participant cannot be contacted, there is a home visit. All SAEs are evaluated by one of the study physicians. Surveillance is also conducted to identify any participant who is admitted to an Ebola holding center, treatment center, or hospital isolation unit with suspect EVD.

Within the larger STRIVE study, there are two sub-studies for safety and immunogenicity. The safety sub-study is an intensive evaluation of safety and reactogenicity among over 400 initial participants, comprised of approximately 200 from the immediate group and 200 from the deferred group. These subjects filled out daily health cards for Day 1 through 28 for the immediate group after vaccination and the deferred group after enrollment. Follow-up was done by phone on Days 1, 3, 7, 14, and 28. The immunogenicity sub-study is being conducted in collaboration with Merck. The objective is to assess the baseline seroprevalence of Ebola and long-term immunogenicity after vaccination. Specimens are drawn at Time 0 (pre-vaccination) and at 1, 6, and 12 months post-vaccination. The specimens will be sent to the US and will be tested by Merck/Focus Diagnostics.

Enrollment is complete, with 8680 participants enrolled between April 9, 2015 and August 21, 2015. As of October 18th, 5550 participants have been vaccinated. Of these, 4173 are in the immediate vaccination group and 1350 are in the deferred vaccination group. Deferred vaccination is ongoing. Deferred vaccination is planned to be finished by mid-December 2015. The safety profile to date is consistent with other published studies. There have been no safety signals in sub-study and no vaccine-related SAEs. Of the 8 deaths reported to date among study participants, none was vaccine-related. In terms of surveillance, 43 participants have been evaluated for suspected EVD. All were EVD negative, 19 were found to be malaria positive by laboratory testing (RDT, ICT, smear), and 6 additional participants had clinically-diagnosed malaria. Enrollment in the immunogenicity sub-study is complete with a total of 506 subjects and 92% follow-up on eligible 1-month blood draws. The 6-month blood draws will commence in December 2015.

The interim results from the WHO Guinea Ring Vaccination Trial were published in *The Lancet* on July 29, 2015. This trial utilizes a cluster-randomized ring vaccination with rVSV-ZEBOV around contacts and contacts of contacts of an index case. The vaccine is the Merck vaccine, which is the same vaccine used in the STRIVE trial. The rings are randomized to either immediate vaccination or delayed vaccination, which is 21 days after randomization. The primary outcome of this study is laboratory-confirmed EVD 10 or more days after randomization. The interim analysis included 90 rings (48 immediate, 42 delayed). The authors concluded that VSV-ZEBOV "might be highly efficacious" and is "most likely effective at the population level when delivered during an EVD outbreak via a ring vaccination strategy." Everyone is anxiously awaiting publication of the final results, which will have additional rings and probably more decisive conclusions [Henao-Restrepo AM. Lancet. 2015; 386: 857–866; Henao-Restrepo AM. BMJ. 2015:351].

Based on the interim results from Guinea, the WHO Ring Trial was expanded into Sierra Leone. There was no longer randomization, meaning that all rings are immediately vaccinated. To date, two rings have been vaccinated in Sierra Leone. The STRIVE protocol was amended to allow for early vaccination of deferred participants who have not yet been vaccinated if they are considered to be at higher risk of exposure to EVD. In early September 2015, an Ebola case was identified in a STRIVE study district. The case was treated in a peripheral health unit and an Ebola treatment unit where STRIVE participants worked and lived in a community where enrolled STRIVE participants lived. The amendment was activated and approximately 100 deferred participants were vaccinated early.

Given the changing epidemiology of Ebola, with fewer and fewer reported Ebola cases in Sierra Leone, assessment of vaccine efficacy became unlikely. The low incidence of EVD meant that there was little likelihood of exposure among the study participants. Only 145 cases were reported in Sierra Leone since the study commenced, and few of these reported cases were among HCW. The expansion of the WHO Ring Trial into Sierra Leone further decreased the likelihood of exposure. However, STRIVE continues with the collection of important safety and immunogenicity data that will be used for licensure.

The following table summarizes the Phase I, II, and III Ebola trials currently ongoing in the three affected countries:

Ebola Vaccines in Phase II/III Clinical Trials in West Africa

rVSV-ZEBOV (Merck/NewLink)	STRIVE (CDC) - Sierra Leone	Phase II; HCW, FLW
	PREVAIL (NIH) - Liberia	Phase II; Comparison ChAd3 and placebo
	Ca Sufit (WHO) - Guinea +SL	Phase III; Ring vax
	FLW (MSF) - Guinea	Phase II; HCW, FLW
ChAd3-ZEBOV (NIAID/GSK/PHAC)	PREVAIL (NIH) - Liberia	Phase II; Comparison rVSV and placebo
Ad26-EBOV/MVA-EBOV (J&J/BN)	Sierra Leone (J+J)	Phase I/II Adults, adol, children Includes CMI
Ad5-EBOV vaccine (China)	Sierra Leone	Phase II Adults

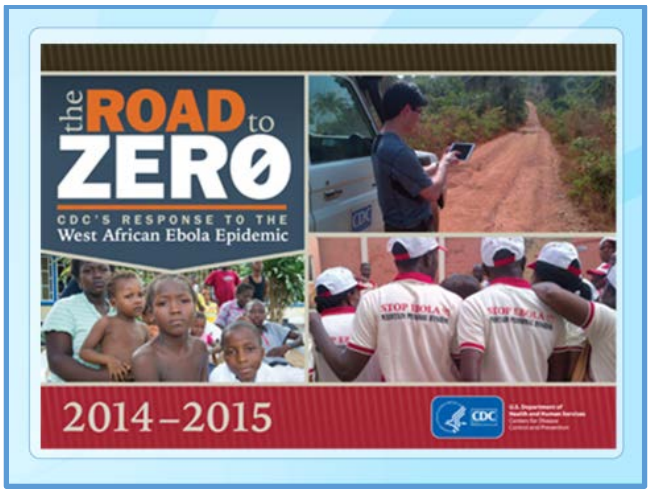
The Merck and GSK vaccines are being used in most of the trials. Two trials were recently commenced in Sierra Leone, one with a Johnson & Johnson prime-boost vaccine and one with a Chinese manufactured vaccine.

In terms of some of the potential strategies for use of Ebola vaccines, for outbreak control there are likely to be recommendations for ring vaccination around cases. However, there may be other strategies such as vaccination of groups of people in defined geographic areas based on the outbreak epidemiology. There are also likely to be recommendations for groups at increased risk for Ebola (e.g., HCW, Ebola frontline workers, laboratory workers, and others). Consideration also must be given to whether there is a role for vaccination around survivors as a way to remain at zero, and whether there is a role for vaccination of the general community.

In thinking about how to use Ebola vaccines, there are scientific and regulatory considerations that must be addressed. First, the duration of long-term protection from vaccination must be determined. This is particularly relevant for vaccinating HCW, frontline workers, and laboratory staff. This applies to those in affected countries, as well as international responders. A determination must also be made regarding whether vaccines can be use in special populations (e.g., children, pregnant women, HIV-infected persons, and others). Consideration also must be given to whether the vaccine can be used for post-exposure prophylaxis (PEP). The vaccines are currently available only under an Investigational New Drug (IND) program. Emergency licensure through an FDA Emergency Use Authorization (EUA) or a WHO Emergency Use Assessment and Listing (EUAL) would increase flexibility and ease of use. Full licensure would provide the most flexibility.

There are currently two Ebola vaccine advisory groups. The first is the Global Ebola Vaccine Implementation Team (GEVIT), which is a consortium that includes WHO (lead), CDC, United Nations International Children's Emergency Fund (UNICEF), Global Alliance for Vaccines and Immunization (GAVI), and the Bill & Melinda Gates Foundation. GEVIT's mandate is collaborative planning for the future introduction of Ebola vaccines. At WHO, a SAGE Working Group on Ebola Vaccines and Vaccination was formed in November 2014. Over the past year, this working group has developed a framework for the use of Ebola vaccines. This framework was presented to SAGE on October 20, 2015. The preliminary report from that meeting is that SAGE will not make any formal recommendations for vaccine use until it is licensed for either emergency use or full licensure. Dr. Goldstein said she also wondered whether ACIP would form an Ebola Vaccine WG in the future.

Despite some challenges, STRIVE has been immensely successful. It is providing an opportunity to vaccinate over 8500 HCW and frontline workers, with over 5550 vaccinated to date. Over 400 Sierra Leonean staff have been trained who are on-the-ground conducting the study. Safety and immunogenicity data are being accumulated for vaccine licensure, increasing research and response capacity in country, and developing a platform for future vaccine and infectious disease research in Sierra Leone. While there is more work to be done, Dr. Goldstein believes that Sierra Leone and West Africa are on the road to zero. The hope is that STRIVE will contribute to the use of an Ebola vaccine that will prevent what occurred this past year in West Africa.



Discussion Points

Regarding safety in the context of what was found earlier in Guinea and regarding the observation in this presentation that no safety signals have been detected in the STRIVE sub-study, Dr. Karron said she did not know of a vaccine that does not cause some reaction.

Dr. Goldstein explained that she was not at liberty to present any specific results, so she could only be very general at this point. Nothing in the safety sub-study appeared to be any different from the safety data that had already been published, and nothing to raise concern among the investigators, the DSMB, or the Scientific Steering Committee.

Dr. Romero asked whether children who were exposed during the ring vaccination were offered vaccine.

Dr. Goldstein replied that only adults 18 years of age and older were included in the WHO Ring Vaccination Trial. When the trial was expanded into Sierra Leone, the age range remained at 18 years and older. In Guinea, the age range was expanded downward to 15 years of age and older. Consideration is being given to lowering the age even further.

Dr. Riley asked whether the STRIVE study excludes pregnant women, and whether a pregnant woman in the ring study who had been exposed would not be given the vaccine.

Dr. Goldstein emphasized that the STRIVE trial is different from the WHO Ring Vaccination Trial. The STRIVE study excludes pregnant women, and all women between 15 and 49 years of age have a urine pregnancy test. Any woman who has a positive pregnancy may not participate in the study. Once a participant is enrolled and vaccinated, there are going to be some pregnancies and those will be followed. The WHO Ring Vaccination Trial offers women a pregnancy test, but the women do not have to have a confirmed negative pregnancy test to enroll.

Dr. Ezeanolue wondered why, if children have the greatest lethality, they will not be vaccinated if an adult close to them is enrolled in the study who has been exposed and may have developed disease.

Dr. Goldstein clarified that STRIVE is not doing ring vaccination, and that she could not speak for the WHO trial other than to say that she knew they were working to decrease the age for enrollment into the WHO Ring Trial. STRIVE is pre-exposure prophylaxis of high risk groups (HCW, frontline workers, laboratory workers).

Dr. Bennett emphasized that the STRIVE trial is not a ring trial. The WHO trial is ring vaccination around a case.

Dr. Riley said she thought Dr. Goldstein said that after the WHO trial was published, if there were people in the STRIVE trial who were in the deferred group, they were vaccinated if they were a contact.

Dr. Goldstein replied that they were not quite that prescriptive. An enrolled participant in the deferred group who has not yet been vaccinated but is at increased risk of exposure, such as living in a community where a case has been identified, they are eligible to be vaccinated in STRIVE only. That is separate from the ring vaccination. That participant may or may not have been included in the ring trial definition of a ring.

Given the concerns about sexual transmission of Ebola, Dr. Reingold wondered whether consideration had been given to vaccinating the sexual partners of survivors.

Dr. Goldstein responded that there have been some initial discussions about vaccination of sexual contacts of survivors. She thinks that much more must be learned about sexual transmission of the disease in terms of how frequently it is sexually transmitted and whether all other modes of transmission have been excluded. In the context of the discussions, consideration has been given to how easy it is to identify a sexual contact. Who is your sexual contact today? How do we know who your sexual contact will be a month from now or six months from now? This has raised a discussion of possible geographic vaccination around a survivor in the hope of reaching current and possible future sexual contacts who may not be identified.

Dr. Reingold quipped that many people know who their current sexual partners are now, but no one is certain of who they will be in the future.

Dr. Goldstein noted that HIV and STD experts say that often the formal sexual contact is known, but the informal sexual contacts are often not public. If the sexual contact of a sexual contact of a survivor today is vaccinated and person X or persons X and Y a month from now, there would need to be some mechanism to identify and vaccinate the new sexual contacts. The logistics are quite difficult, but this has been discussed. She told Dr. Reingold that he would probably be a good person to have on the working group.

Dr. Ezeanolue asked whether there was an express reason that the STRIVE trial did not use the ring design that WHO used.

Dr. Goldstein responded that there was a lot of discussion initially as WHO, CDC, and other groups were thinking about how to conduct a clinical trial. Nobody knew which study design was going to work. There are many ways of conducting trials and reasons for doing so. WHO conducted the ring trial, while CDC took responsibility for vaccination of the high risk group of HCW, frontline workers, and laboratory workers.

Dr. Belongia commended everyone at CDC and everyone in Sierra Leone who worked on-the-ground on this study, given the difficulty there must have been in implementing a study such as this within the circumstances and timeline under which it was done.

Dr. Bennett added that there are many investigators in the US who cannot enroll 100 people for an RCT, so this is really amazing.

Dr. Goldstein emphasized that from the beginning, Dr. Schuchat has been a cheerleader for STRIVE who ensured them that it would happen, and it did.

Dr. Moore said she was intrigued by the vaccine storage and handling issues, particularly given that the vaccine must be stored at -80°C. She asked Dr. Goldstein to speak more about the transport, storage, and handling issues in terms of getting the vaccine out to the patients.

Dr. Goldstein confirmed that the vaccine does have to be stored at -80°C. There are three vaccine depots, with the main depot being in Freetown. The three main depots have freezers that store at -80°C. Constant power sources are needed, which is not easy there. Back-up generators were also needed. There must be staff available 24 hours a day. Transport from site-to-site was done in an Arktek cooler which kept the vaccine at -80°C. This cooler was developed as part of a Gates challenge. Once the vaccine was diluted and put into syringes at the vaccine depot, it was transported to sites in CryoQ cooler, which kept the vaccine at 2 °C to 8 °C. The vaccine has to be administered within 8 hours of dilution. Though quite a feat, it works quite well.

Arktek Cooler

CryoQ Cooler

Dr. Moore emphasized how impressive this was, and said she did not know whether this could be done in a clinic in the US.

Dr. Neuzil noted that she chaired the Scientific Steering Committee for this trial. She congratulated CDC, the many partners, and the hundreds of people on-the-ground in Sierra Leone who worked through a very difficult situation. To help people understand, the WHO trial in Guinea was a ring vaccination trial, which is an outbreak response strategy. Where there were breakthrough cases, those ocurred in the first 7 days. That makes sense because that is before the vaccine could have a biologic effect, or when the patient was in an incubation period. However, the Sierra Leone trial was a preventive strategy for first responders and people who were likely to be exposed. A couple of West African countries, Mali and Nigeria, had an incredible response to contain this virus. Because Mali is another West African country that has tested two

Ebola vaccines, she asked Dr. Mike Levin whether she could coax him to the microphone to discuss these for completeness.

Dr. Mike Levine (CVD, UM SOM) explained how the WHO Guinea Ring Vaccination trial came to exist and how it was designed. With the huge outbreak in three countries (Liberia, Sierra Leone, and Guinea), the US government went into Liberia with extraordinary resources and had an impact fairly quickly. Sierra Leone is split in a competition between who to test and what to test with between the UK and the US. Guinea was an orphan. Nobody was showing up to work in Guinea. Guinea asked WHO for help, and WHO responded by quickly assembling partners, including the Norwegian Institute of Public Health (NIPH). This was key because NIPH quickly provided resources to conduct a trial. WHO involved some very senior individuals to help with the Ebola outbreak who were French and were able to establish special dialogue and communications. WHO convened a couple of planning committees. When this was going on, one of the other factors that had not been mentioned was the scarcity of doses of vaccine for at least one of the two major vaccines. Even the vaccine that was used in Guinea and Sierra Leone was only possible with Big Pharma getting involved with NewLink so that many more doses became available. A design had to be created that would minimize the number of doses needed, and recognizing that the vaccine had to be kept at -80^{o}C. The Arktek was a game-changer breakthrough. The cold chain worked well in Guinea and was quite amazing. This could not have been done five years ago. The beauty of the ring design is that instead of enrolling a large number of individuals and letting Mother Nature or human nature determine where the cases of Ebola would be, investigators went to where the cases were just as was done in the smallpox eradication days. One of the members of the committee ran a smallpox program for the WHO, and a couple of other smallpox veterans were on the committee as well, including Dr. Lavine. This design uses a very small amount of vaccine. The Norwegians felt that everyone had to receive vaccine for ethical reasons, and that was a widely held view in Europe. The elegance of the Guinea design, pressured by all of the constraints, was that everybody got vaccine but some people got it 21 days later. That is what would occur in a huge outbreak with surveillance and containment—not everyone would be receiving vaccine at once. Guinea was a “Wild West Show” in terms of having to start from scratch and train people very quickly to conduct a trial where there was no infrastructure. The other leading candidate vaccine, the chimp adenovirus type 3 (ChAd3), was tested in Mali. Particularly for the ChAd3 vaccine, information on how long the vaccine works comes from non-human primate studies. This is also true of vesicular stomatitis virus (VSV)-based vaccine. Those data show that there is 100% protection for several months, but then it falls off at 10 months to about 50%. Using the ring design to vaccinate the the high risk contacts around cases maximizes what is known about how vaccine works. The Mali site was the only one amongst the WHO consortium that involved folks in Bethesda and Oxford, and Mali was the only West African site that was able to test the vaccine. The highest dose that was used in Mali turned out to be the dose selected for large-scale manufacture. Mali had two importations and chains of transmission. The second one was a relatively big one. In a sense, it was lucky that it took place in Bamako. It was classic shoe leather epidemiology that contained it. Every single

contact was identified, put in house quarantine and kept there throughout the observation period. In a relatively short period of time, transmission was interrupted. There is pretty much an open border between Mali and Guinea and people go back and forth. The two importations came from Guinea. Because the individual who brought the disease into Bamako was a dignitary, he went to a private hospital instead of going to a government health facility. The hospital was thought to be the best care, but it is a mystery how they missed his diagnosis. They called it malaria with renal failure, and the individual died as did his physician, nurse, and fiancé of the nurse. It was an explosion and everyone was very worried. However, with the good leadership of Dr. Samba Sow, the Director of the Center for Vaccine Development (CVD-Mali), and a good friend of the Ebola Czar of Guinea, every resource went into this effort. Combined with shoe leather epidemiology, transmission was interrupted and that is a very special legacy.

An unidentified participant commented on the ongoing Guinea trial in an area he recently left. Before he left there, the clinical trial expanded the enrollment down to participants 7 years of age and older. This information is not shared by the clinical trial team, so they asked questions of the contacts to find out who has been vaccinated.

Public Comment

Mara Berger
Parent

It is not unreasonable for all ages of people to be protected with a safe and effective vaccine and to be aware that vaccines are available for meningococcal disease for healthy adults 21 to 55 and healthcare personnel. I'm here today to ask the ACIP to consider recommending the conjugate vaccine for routine usage more broadly. My son, Adam Berger, was a 44-year old healthy adult enrolled in private teaching hospital in nursing school in Chicago, a very prestigious hospital. In 2014, he passed away from the vaccine-preventable meningococcal bacterial infectious disease *Neisseria meningitides* C and sepsis within 16 hours of going to the hospital. After Adam passed away, I learned that the nursing registrar never gave him the conjugate vaccine to prevent meningococcal disease, nor gave him literature about the disease or vaccine because the ACIP and CDC don't recommend the vaccine for routine usage for healthcare personnel with the exception of epidemiologists and adults at increased risk with particular medical problems. Therefore, I was devastated to find out that Adam died before his time needlessly from a vaccine-preventable infectious disease that we weren't aware of because it was not promoted or talked about. Had Adam and I known about the conjugate vaccine to prevent meningococcal disease, he would have gotten the shot. Hospitals are occupational risks. Knowledge is power and healthy adults and healthcare personnel have the right to choose their healthcare based factual medical and vaccine information, even though the vaccine isn't recommended. People cannot be left in the dark about dangerous and deadly infectious diseases. The conjugate vaccine is effective, safe, and immunogenic. If the FDA approves and licenses a vaccine, doctors can give the shot or send their patients to Walgreen's to receive it. Physicians take an oath to "Do No Harm" and must protect their patients and make

a concerted effort to raise awareness about meningococcal disease and the vaccine to prevent it so that adult immunization rates increase.

I believe adults would get the vaccine if their physicians recommended it. Most US adults never heard of meningococcal disease or the conjugate vaccine. Medical facilities must also give their healthcare workers handouts about the disease and vaccines so that they can make an informed decision to reduce their risk from the disease. Adam didn't have that choice. Many insurance companies already pay for the shot as preventive care. In 2015, the FDA licensed meningococcal vaccine and it was approved. ACIP recommended it for adolescents 11 to 13. In the last decade, thousands of people have contracted the disease and suffered. Ninety-eight percent of cases are sporadic all over the United States, many in healthy adults, and two percent occur in outbreaks. Perhaps if the vaccine was recommended, adults would get vaccinated. Anyone at any time in any place can contract meningococcal disease. Healthy adults are just as at increased risk as adults with medical conditions. It's a fallacy that healthy people of any age are immune. Vaccination is the only way to prevent and eradicate meningococcal disease. As a matter of fact, the hospital that Adam taught at—I mean that he was getting his nursing degree at, I believe he caught the disease when he was doing his clinicals. I don't know if he was wearing a mask, but he was probably taking someone's heart monitoring, got in their face, they spat, coughed, sneezed—I don't know. But, he got it. We don't know. It was an unknown carrier. A broader recommendation for the vaccine would be a wonderful legacy for all of us who lost someone they love. Now the hospital wrote me an email that they are giving mandatory meningococcal vaccine shots to all incoming nursing students in 2016. This is a big deal. So, if you have questions, feel free to contact me at maraberger@hotmail.com. Thank you.

Dr. Bennett: Thank you very much, Mrs. Berger, and we are very sad for your loss.

Laurel Wood
Immunization Action Coalition

Thank you. I can't imagine a much more difficult speaker to follow. So if you'll forgive me for something that may seem a little bit lighter, but in fact, directly relates to the importance of giving adult immunizations. In keeping with the ACIP discussions about low adult rates and the 2000 recommendation for the use of standing orders, the Immunization Action Coalition, in conjunction and with support from Pfizer, has developed a program that is occurring all over the United States now called "Take a Stand" about the use of standing orders to vaccinate adults because we, like you, know that many adult providers have widespread misunderstandings about the benefits of using standing orders, as well as many perceived burdens of implementation. We have developed this project to offer free workshops on using standing orders to raise clinics' adult immunization rates and streamline their practices. These workshops are targeted for clinicians, nurses, and clinical managers in medical practices that serve adults. Speakers that are recognized, many of whom have been in this room today, are LJ Tan, Bill Atkinson, and Alexandra Stewart of George Washington University. We wanted to let you know about this opportunity that may perhaps be coming to a city near you. We have 22 workshops that have been scheduled. Some have already begun and then we will be continuing this through early 2016. So, please take a look at standingorders.org and see if it is something that might be of benefit to providers in your area or that you can help us spread the word, because we're all about, as you are, trying to increase adult immunizations as well as child immunizations. Thank you very much.

Dr. Bennett: Thank you very much, and we really appreciate your efforts and knowing about them. I think with that we are finished. This is the end of the October 2015 meeting, and I thank you all for all of your participation. Safe travels home.

Certification

Upon reviewing the foregoing version of the October 21, 2015 ACIP meeting minutes, Dr. Nancy Bennett, 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.

ACIP Membership Roster

CHAIR

BENNETT, Nancy, MD, MS
Professor of Medicine and Public Health Sciences
Director, Center for Community Health
Co-director, Clinical and Translational Science Institute
University of Rochester School of Medicine and Dentistry
Rochester, NY
Term: 07/01/2015-06/30/2018

ACTING EXECUTIVE SECRETARY

STRIKAS, Raymond, MD, MPH
Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases
Atlanta, GA

MEMBERS

BELONGIA, Edward, MD
Director
Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation
Marshfield, WI
Term: 07/01/2014-06/30/2018

EZEANOLUE, Echezona, MD, MPH
Professor of Pediatrics and Public Health
Department of Epidemiology and Biostatistics
Director, Global Health and Implementation Research Initiatives
University of Nevada
Las Vegas, NV
Term: 07/01/2015-06/30/2019

HARRIMAN, Kathleen, PhD, MPH, RN
Chief, Vaccine Preventable Disease Epidemiology Section
Immunization Branch
California Department of Public Health
Richmond, CA
Term: 07/01/2012 – 06/30/2016

HARRISON, Lee H., MD
Professor of Medicine and Epidemiology
Infectious Diseases Epidemiology Research Unit
University of Pittsburgh
Pittsburgh, PA
Term: 07/01/2012 – 06/30/2016

KARRON, Ruth A., MD
Professor and Director
Center for Immunization Research
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Term: 07/01/2012 – 06/30/2016

KEMPE, Allison, MD, MPH
Professor of Pediatrics
Director of Primary Care Fellowship
University of Colorado School of Medicine
Director of Research
Division of General Academic Pediatrics
Director of Children's Outcomes Research Program
The Children's Hospital of Denver
Denver, CO
Term: 07/01/2013 - 06/30/2017

MOORE, Kelly, MD, MPH,
Director, Tennessee Immunization Program
Tennessee Department of Health
Assistant Clinical Professor, Department of Health Policy
Vanderbilt University School of Medicine
Nashville, TN
Term: 07/01/2015-06/30/2019

PELLEGRINI, Cynthia
Senior Vice President
Public Policy and Government Affairs
March of Dimes
Washington, DC
Term: 07/01/2013-06/30/2017

REINGOLD, Arthur L., MD
Professor of Epidemiology
Edward Penhoet Distinguished for Global Health and Infectious Disease
Associate Dean for Research
School of Public Health
University of California
Berkeley, CA
Term: 07/01/2013-06/30/2017

RILEY, Laura E., MD
Associate Professor, Obstetrics, Gynecology and Reproductive Medicine
Harvard Medical School
Maternal Fetal Medicine
Massachusetts General Hospital
Boston, MA
Term: 07/01/2014-06/30/2018

ROMERO, José R., MD, FAAP
Professor of Pediatrics
Horace C. Cabe Endowed Chair in Infectious Diseases
Director, Pediatric Infectious Diseases Section
University of Arkansas for Medical Sciences and Arkansas Children's Hospital
Director, Clinical Trials Research
Arkansas Children's Hospital Research Institute
Little Rock, AR
Term: 07/01/2014-06/30/2018

RUBIN, Lorry, MD
Director
Pediatric Infectious Diseases
Steven and Alexandra Cohen Children's Medical Center of New York
North Shore-Long Island Jewish Health System
New Hyde Park, NY
Professor of Pediatrics, Hofstra-North Shore LIJ School of Medicine
Hempstead, NY
Term: 07/01/2012 – 06/30/2016

STEPHENS, David, MD
Professor of Medicine, Division of Infectious Diseases
Chair, Department of Medicine
Emory University School of Medicine
Emory University
Atlanta, GA
Term: 07/01/2015-06/30/2019

WALTER, Emmanuel (Chip), Jr., MD, MPH
Professor of Pediatrics
Duke University School of Medicine
Durham, NC
Term: 07/01/2015-06/30/2019

***EX OFFICIO* MEMBERS**

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification
Centers for Medicare and Medicaid Services
Baltimore, MD

Department of Defense (DoD)
SERGIENKO, Eric, MD, MPH
CAPT, Medical Corps, United States Navy
Department of Defense Liaison
Centers for Disease Control and Prevention
Atlanta, GA

Department of Veterans Affairs (DVA)
KIM, Jane A., MD, MPH
Deputy 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, MD
Director, Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Food and Drug Administration
Rockville, MD

Health Resources and Services Administration (HRSA)
HOUSTON, A. Melissa, MD, MPH, FAAP
Chief Medical Officer
Division of Vaccine Injury Compensation
Health Resources and Services Administration
Rockville, MD

Indian Health Service (IHS)
GROOM, Amy, MPH
Immunization Program Manager
Indian Health Service
Albuquerque, NM

National Vaccine Program Office (NVPO)
GELLIN, Bruce, MD, MPH
Director
National Vaccine Program Office
Department of HHS, Public Health and Science
Washington, DC

National Institutes of Health (NIH)
GORMAN, Richard L., MD
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)
SAVOY, Margot, MD, MPH, FAAFP, FABC, CPE
Medical Director, Department of Family & Community Medicine
Christiana Care Health System
Wilmington, DE

American Academy of Pediatrics (AAP)
BYINGTON, Carrie L., MD
Chair, AAP Committee on Infectious Diseases
H.A. and Edna Benning Presidential Professor of Pediatrics
Associate Vice President for Faculty and Academic Affairs
University of Utah Health Sciences Center
Salt Lake City, UT

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C
Senior Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
EVEN, Susan, MD
Executive Director
Student Health Center
University of Missouri
Columbia, MO

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH
Atlanta Perinatal Associates
Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Pregnancy & Birth Center,
Middlesex Hospital,
Middletown, CT

American College of Obstetricians and Gynecologists (ACOG)
AULT, Kevin A., MD, FACOG
Professor and Division Director
Department of Obstetrics and Gynecology
University of Kansas Medical Center
Kansas City, KS

American College of Physicians (ACP)
FRYHOFER, Sandra Adamson., MD, MACP
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American College of Physicians (ACP) (alternate)
POLAND, Gregory A., MD
Mary Lowell Professor of Medicine and Infectious Diseases
Mayo Clinic
Rochester, MN

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
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., MD, MBA, FAAP
Market Medical Executive, CIGNA
Houston, TX

American Medical Association (AMA)
FRYHOFER, Sandra Adamson., MD, MACP
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN, FAAOHN
Assistant Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E., DO, FACOP
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
FOSTER, Stephan L., PharmD, FAPhA
Professor and Vice Chair, Department of Clinical Pharmacy
University of Tennessee Health Sciences Center, College of Pharmacy
Memphis, TN

Association of Immunization Managers (AIM)
FINLEY, Christine
Immunization Program Manager
Vermont Department of Health
Burlington, VT

Association for Prevention Teaching and Research (APTR)
McKINNEY, W. Paul, MD
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

Association of State and Territorial Health Officials (ASTHO)
DWELLE, Terry L, MD, MPHTM, FAAP, CPH
State Health Officer
North Dakota Department of Health
Bismarck, ND

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A., MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization
Idaho Department of Health and Welfare
Boise, ID

Canadian National Advisory Committee on Immunization (NACI)
GEMMILL, Ian MacDonald, MD, CCFP, FCFP, FRCP(C)
Medical Officer of Health
Kingston, Frontenac and Lennox & Addington Public Health
Kingston, Ontario, Canada

Infectious Diseases Society of America (IDSA)
NEUZIL, Kathleen M., MD, MPH, FIDSA
Vaccine Development Global Program (PATH)
Clinical Professor
Departments of Medicine and Global Health
University of Washington School of Medicine
Seattle, WA

Infectious Diseases Society of America (IDSA) (alternate)
BAKER, Carol J., MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and 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 and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A., RN, MS, CPNP
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Immunization Council and Child Health Program, Mexico
VILLASEÑOR RUIZ, Ignacio
Directora del Programa de Atencion da la Salud de la Infancia y la Adolescencia / Director General, Child and Adolescent Health
Centro Nacional Para la Salud de la Infancia Y La Adolescencia / National Center for Child and Adolescent Health
Ministry of Health / Secretaría de Salud
Mexico

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD
Professor and Chair
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

National Vaccine Advisory Committee (NVAC)
ORENSTEIN, Walter, MD
Chair, NVAC
Associate Director, Emory Vaccine Center
Emory University
Atlanta, GA

Pediatric Infectious Diseases Society (PIDS)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pediatric Infectious Diseases Society (PIDS) (alternate)
ENGLUND, Janet A., MD
Professor, Department of Pediatrics
Seattle Children's Hospital
University of Washington
Seattle, WA

Pharmaceutical Research and Manufacturers of America (PhRMA)
JOHNSON, David R, MD, MPH
Associate Vice President, Global Medical Affairs, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
WEBER, David, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology
University of North Carolina Schools of Medicine and Public Health
Medical Director, Hospital Epidemiology and Occupational Health, UNC Health Care
University of North Carolina
Chapel Hill, NC

Appendix A: Public Comment Letter

September 8, 2015

To: Sylvia Burwell, United States Secretary of Health & Human Services

cc: Dr. Thomas Frieden, Director of the CDC
cc: ACIP Committee

Dear Secretary Burwell,

I researched meningococcal disease and conjugate vaccines thoroughly and spoke during public comments at the June 2015 ACIP meeting in Atlanta. I told the ACIP committee to recommend the conjugate vaccines Menactra and Menveo which protect from meningococcal disease Neisseria meningitidis bacterial strains A, C, Y and W135, but it wasn't on their agenda. The "unprotected" must be protected, healthy adults (HA) 21-55 and healthcare personnel (HCP). Anyone at any time and any place can contract meningococcal disease! Meningococcal disease isn't just for children and it doesn't stop at the dorm. The average age to contract the disease is 45 and male and women contract it too. I implore you to treat meningococcal disease as though it were Ebola when protocols and policies were revised and put into place quickly with the first US Ebola case of a nurse in Houston. I'm urging you to insist that the ACIP add the conjugate vaccines Menactra and Menveo to their October 21, 2015 agenda and to recommend the vaccines for routine use for healthy adults 21-55 years old and to highly recommend routine vaccinations for all healthcare personnel who wish to reduce their risk from meningococcal disease. I have hundreds of medical reports and articles from independent infectious disease experts that conflict with those of the ACIP. Knowledge is power and being informed about a vaccine preventable infectious disease vaccine is the only way to prevent and eradicate potentially deadly meningococcal disease. Physicians must "do no harm." In my opinion, the current ACIP and their predecessors must take responsibility for their irrational decisions to not recommend an available vaccine to prevent meningococcal disease, which would have saved the lives of healthy adults and healthcare personnel for the past ten years. Health policies have to change. This is a very serious matter.

If you remember from my letter on May 14, 2015, my son Adam was a 44 year old healthy adult enrolled in a private teaching hospital/nursing school in Chicago. In 2014, Adam passed away within hours from the vaccine preventable infectious disease Neisseria meningitidis C/sepsis, needlessly! Adam received all the required vaccinations for nursing school. But, the nursing registrar never mentioned a Menactra vaccination for meningococcal disease because the ACIP and CDC have not recommended Menactra for routine use for healthy adults 21-55 years old and healthcare personnel with the exception of epidemiologists. Most healthy adults 21-55 don't even know what meningococcal disease is or that there's a vaccine to prevent it. Therefore, Adam wasn't informed about the disease and vaccine to protect himself and died before his time! My son's death was a senseless tragedy and our family's grief is beyond recovery or adjusting.

Primary care physicians should give their healthy adults and medical facilities should give their healthcare personnel meningococcal disease literature and vaccine information so that they can make an informed decision about wanting to receive the vaccine to reduce their risk from the disease even though the ACIP and CDC don't recommend the vaccine. The ACIP cannot keep the lid on meningococcal disease and the vaccine to prevent it anymore. The jig is up as they say. The FDA approved and licensed Menactra in January 2005 for routine use in 9 month-55 year olds. The fact is that once the FDA approves and licenses a vaccine for routine use for a particular age group, those individuals can get vaccinated even if the ACIP and CDC don't recommend the vaccine. It's not forbidden to get vaccinated as most adults believe. In fact, if the disease and vaccine literature were available, anyone can go to Walgreen's and get vaccinated if internists and primary care physicians don't want to store or supply the vaccine.

The ACIP must recommend the meningococcal vaccines to ensure that all insurance companies will be required to cover the cost. Currently, even without the ACIP's non- recommendation, most insurance companies do cover the cost of Menactra, which is approx. $140 and they consider it "preventative care." But, there are some insurance companies that don't cover the cost. Even The Affordable Care Act pays for the vaccinations for families including children and college students up to 26 years of age.

Patients rely on their primary care physician for accurate medical advice. Since Menactra isn't recommended, many doctors think it's prohibitive to vaccinate healthy adults or haven't kept up on meningococcal disease and don't discuss it with them. It's a "don't ask" "don't tell" situation. Most healthy adult patients 21-55 never heard of meningococcal disease, so they don't ask. Or, if they have heard of meningococcal disease, they may believe that they don't qualify to receive the vaccine because they don't have medical problems on "at increased risk" list, so they don't ask and forget about it. They may also have a false sense of security and believe that because they're healthy, they won't contract the disease! The CDC focuses on babies, children, adolescents and college students and the elderly over 64 years old. The CDC states on its meningitis pages that routine vaccination is not recommended for 21-55 year olds. The ACIP writes that the vaccine is not routinely recommended for healthcare personnel.

Healthcare personnel, paramedics and firemen have contracted meningococcal disease. Everyone knows that hospitals are occupational risks and endemic full of bacteria and sick patients. That's where Adam caught the disease. A perfectly healthy adult 21-55 or healthcare personnel can contract meningococcal disease from an unknown carrier who carries Neisseria bacteria in their nasal cavity or throat and then spews respiratory droplets such as a sneeze, cough or spit within three feet of a healthy adult or healthcare personnel. Carriers are approximately 20% of the general population in the United States and don't contract the disease or may not even know they're carriers. That is precisely why no one is immune to this insidious disease unless they get vaccinated.

Meningococcal disease – Neisseria meningitidis C is the leading infectious disease in the United States. It is serious and potentially deadly especially with sepsis the number one illness in the United States. Healthy adults who contract Neisseria meningitidis and sepsis can die within hours. Healthy adults are just as "at increased risk" as adults with medical conditions because natural antibodies wane as children grow into healthy adults. That's why there's a vaccine to boost immunity in adults, but it's not recommended! Therefore healthy adults 21-55 and healthcare personnel who were never vaccinated, under vaccinated or received the polysaccharide Menomune more than three years ago or conjugates Menactra or Menveo vaccines more than 5 years ago may be due for a booster vaccine now.

Neisseria meningitidis C has increased for four decades. The CDC wrote that meningococcal vaccination in adults is low and that the disease has not decreased in adults, which is correct. The propaganda that meningococcal disease is rare must be debunked! The CDC states that in the US approx. 98% of cases of meningococcal disease are sporadic all over the United States, which is correct. Other experts in the field say that currently the disease causes approximately 3,000 reported cases and that many cases go unreported. Outbreaks continue to occur. There were approximately 69 outbreaks identified in the US between 1994 and 2002, most of which were Neisseria meningitidis strain C. Between 2005 and 2015 approximately 20,000 people contracted meningococcal disease and the ACIP turned a blind eye.

Since 2002, there have been additional outbreaks of strain C as you've seen in the newspapers and TV. Controlling outbreaks is useless, which is like putting gas on a fire. Vaccinations must be given before an outbreak, which would increase herd immunity. It makes no sense to vaccinate after an outbreak in which it's an open invitation for individuals to contract the disease and become maimed or die. When is it going to end? Meningococcal disease is life-threatening and can cause sequelae or death in previously healthy adults and healthcare personnel. Between 2003 and 2007, the CDC wrote that 4,100 people contracted meningococcal disease annually. With that being said, weren't 4,100 cases in 2005 enough for the ACIP to recommend Menactra to healthy adults 21-55 year olds and healthcare personnel? Apparently not, because just before Menactra was about to become available in 2005, the ACIP wrote "that for unknown reasons, incidence has declined since the peak of disease in the late 1990s." Then they just cut off the vaccine from healthy adults altogether and instead only recommended Menactra to adolescents. The ACIP failed to state that incidence of Neisseria meningitidis C did not decline, which Menactra would have prevented!

In 2006, the Menactra vaccine supply decreased and the ACIP then prioritized again and recommended the vaccine to adults "at increased risk" with a caveat of medical conditions, which excluded healthy adults.

In 2007, when Menactra's supply increased, the ACIP still didn't recommend Menactra to healthy adults 21-55 and hasn't to date! Was the reason just bureaucratic indifference? The ACIP should never have been oppositional to recommending Menactra, which was proven to be safe, immunogenic and effective by the FDA. It's cost effective too!

I'm wondering why the CDC, AMA, IDSA and other medical professionals around the country haven't challenged the ACIP about excluding healthy adults 21-55 and healthcare personnel from Menactra vaccine based on lame excuses and certainly not for medical reasons.

I went to Adam's former nursing school and gave the nursing director and infectious disease doctor a lesson about meningococcal disease strain C. They recently wrote me that all incoming 2016 nursing students must have mandatory conjugate Menactra vaccinations.

In conclusion, I appreciate your attention in this matter. I'm going to honor my beautiful son Adam and in his memory create awareness through any means possible about meningococcal disease and the conjugate vaccines that prevents it. This endeavor is called "The Adam Berger Meningococcal Disease and Vaccination Information Initiative."

Please contact me if you so choose.

Thank you.

Mara Berger
5801 N. Sheridan Road, 5B
Chicago, IL 60660
Email: maraberger@hotmail.com