

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

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



**Summary Report
February 24, 2016
Atlanta, Georgia**

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Final - February 18, 2016**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

February 24, 2016 (1-day meeting)

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Wednesday, February 24</u>		
8:00 Welcome & Introductions		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:15 Agency Updates CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	CDC and <i>ex officio</i> members
8:30 Human Papillomavirus (HPV) Vaccines Introduction Background: 2-dose schedules 9-valent HPV vaccine 2- vs 3-dose trial data Summary: 2-dose schedules, bivalent and quadrivalent HPV vaccines Work Group plans	Information & Discussion	Dr. Allison Kempe (ACIP, WG Chair) Dr. Lauri Markowitz (CDC/NCIRD) Dr. Alain Luxembourg (Merck) Dr. Lauri Markowitz (CDC/NCIRD) Dr. Elissa Meites (CDC/NCIRD)
9:50 Break		
10:20 Meningococcal Vaccines Introduction MenB-FHbp vaccine update Results of a mass immunization campaign with MenB-4C in Quebec, Canada Considerations for use of MenACWY vaccines in HIV-infected persons Meningococcal disease among men who have sex with men (MSM), United States, January 2012-June 2015 Considerations for use of MenACWY vaccines in MSM	Information & Discussion	Dr. Lorry Rubin (ACIP, WG Chair) Dr. Laura York (Pfizer) Dr. Gaston De Serres (Quebec, Canada) Ms. Jessica MacNeil (CDC/NCIRD) Dr. Temi Folaranmi (CDC/NCIRD) Ms. Jessica MacNeil (CDC/NCIRD)
12:10 Lunch		
1:20 Japanese Encephalitis (JE) Vaccine Introduction Duration of protection following primary series and booster dose in adults Duration of protection and need for booster dose in children JE Vaccine Work Group summary and plans	Information & Discussion	Dr. Lorry Rubin (ACIP, WG Chair) Dr. Katrin Dubischar (Valneva) Dr. Katrin Dubischar (Valneva) Dr. Susan Hills (CDC/NCEZID)
2:10 Influenza Introduction Influenza surveillance update Quadrivalent Recombinant Influenza Vaccine Influenza Vaccination and Egg Allergy Proposed Recommendations for 2016-17	Information, Discussion <u>Vote</u>	Dr. Ruth Karron (ACIP, WG Chair) Ms. Lynnette Brammer (CDC/NCIRD) Dr. Wayne Hachey (Protein Sciences) Dr. John Kelso (University of California, San Diego) Dr. Lisa Grohskopf (CDC/NCIRD)
3:10 Break		
3:30 Update on Zika Virus Update on CDC response to Zika Virus Public Health Emergency Medicinal Countermeasure Enterprise		Dr. Toby Merlin (CDC/NCEZID) Dr. Bruce Gellin (DHHS/NVPO)

Final - February 18, 2016

3:40	Cholera Vaccine		
	Introduction		
	Vaxchora™ clinical data	Information &	Dr. Art Reingold (ACIP, WG Chair)
	Cholera Vaccine GRADE evaluation and Work Group plans	Discussion	Dr. Lisa Danzig (PaxVax) Dr. Karen Wong (CDC/NCEZID)
4:50	Vaccine Supply		Dr. Jeanne Santoli (CDC/NCIRD)
4:55	Public Comment		
5:10	Adjourn		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
LAIV	Live Attenuated Influenza Vaccine
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
NVPO	National Vaccine Program Office
VFC	Vaccines for Children
WG	Work Group

Acronyms

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACAAI	American College of Allergy, Asthma, and Immunology
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACP	American College of Physicians
ACS	Advisory Committee Statement
AS04	Adjuvant System 04
AE	Adverse Events
AEFI	Adverse Events Following Immunization
AIN	Anal Intraepithelial Neoplasia
AMA	American Medical Association
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
BCH	Boston Children's Hospital
BLA	Biologics License Application
BMC	Boston Medical Center
CBRN	Chemical, Biological, Radiological, and Nuclear Threats
CDC	Centers for Disease Control and Prevention
CEO	Chief Executive Officer
CFU	Colony Forming Units
cLIA	Competitive Luminex Immunoassay
CICP	Countermeasures Injury Compensation Program
CIQ	Quebec Immunization Committee
CISA Project	Clinical Immunization Safety Assessment Project
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
CVD	Center for Vaccine Development
DEET	N,N-diethyl-meta-toluamide
DD	Deputy Director
DHS	Department of Homeland Security
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DPEI	Division of Preparedness and Emerging Infections
DSMB	Data Safety Monitoring Board
DSTDP	Division of STD Prevention
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
EAACI	European Academy of Allergy and Clinical Immunology
ED	Emergency Department
EHR	Electronic Health Record
EID	Emerging Infectious Diseases
EIS	Epidemic Intelligence Service
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPA	Environmental Protection Agency
EOC	Emergency Operation Center

Epi-X	Epidemic Information Exchange
FDA	Food and Drug Administration
fHbp	Factor H-Binding Protein
FLU VE	Influenza Vaccine Effectiveness Network
GAVI	Global Alliance for Vaccines and Immunization
GBS	Guillain-Barré Syndrome
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCP	Healthcare Personnel
HCW	Healthcare Workers
HD-IIV	High-Dose Inactivated Influenza Vaccine
HHS	(Department of) Health and Human Services
HI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
HOPS	HIV Outpatient Study
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICON	International Consensus
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IgA	Immunoglobulin A
IgG	Immunoglobulin G
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
ISD	Immunization Services Division
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
MCM	Medical Countermeasure
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MERS	Middle East Respiratory Syndrome
MFI	Median Fluorescence Intensity
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
MVPDB	Meningitis and Vaccine Preventable Diseases Branch
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NAIP	National Adult Immunization Plan
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
NFID	National Foundation for Infectious Diseases
NHBA	Neisserial Heparin-Binding Antigen
NHBS	National HIV Behavioral Surveillance
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health

NP	Nasopharyngeal
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NYC	New York City
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHEIC	Public Health Emergency of International Concern
PHEMCE	Public Health Emergency Medical Countermeasure Enterprise
PIDS	Pediatric Infectious Diseases Society
PMD	para-menthane-diol
PPB	Prime-Prime-Boost
RCT	Randomized Controlled Trial
RIV4	Quadrivalent Recombinant Influenza Vaccine
SAEs	Serious Adverse Events
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Experts
STI	Sexually Transmitted Infection
SVA	Serum Vibriocidal Antibody
TBE	Tick-Borne Encephalitis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
UK	United Kingdom
US	United States
USAID	United States Agency for International Development
USDA	US Department of Agriculture
VAERS	Vaccine Adverse Event Reporting System
<i>V. cholera</i>	<i>Vibrio cholerae</i>
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VIMM	VistA Immunization Enhancements
VLP	Virus-Like Particle
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VTEU	Vaccine and Treatment Evaluation Units
WAO	World Allergy Organization
WG	Work Group
WHO	World Health Organization
WOCBA	Women of Child Bearing Age
WRAIR	Walter Reed Army Institute of Research
YF	Yellow Fever

Welcome & Introductions

Welcome and Introductions

Nancy Bennett, MD, MS
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Bennett called the February 2016 Advisory Committee on Immunization Practices (ACIP) meeting to order and welcomed those present. She introduced Dr. Amanda Cohn, the New ACIP Executive Secretary. Dr. Cohn joins ACIP from the Immunization Services Division (ISD) where she was the Deputy Director. She obtained her medical degree from Emory University, completed her Residency in Pediatrics at Boston Children's Hospital (BCH) and Boston Medical Center (BMC). She came to the Centers for Disease Control and Prevention (CDC) in 2004 as an Epidemic Intelligence Service (EIS) Officer, and joined the Meningitis and Vaccine Preventable Diseases Branch (MVPDB) in 2006. She focused on meningococcal disease, and served as the CDC Lead for the ACIP Meningococcal Vaccines Work Group (WG) from 2007 through 2014. She is Board Certified in Pediatrics and is a Fellow of the American Academy of Pediatrics (AAP). She is also the mother of three daughters, as is Dr. Bennett, so they have more in common than just sitting in the front of the room.

Dr. Cohn thanked everyone for welcoming her to the role of ACIP Executive Secretary. She reported that her older daughters have received all doses of Human Papillomavirus (HPV) vaccine, and that her youngest daughter is not yet old enough. She welcomed everyone to the February 2016 ACIP meeting. She 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. She 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, Chris Caraway, and Dr. Jean Claire Smith. She expressed appreciation for all of the work these individuals perform every meeting. She reported that because Dr. Rima Khabbaz was unable to attend, Dr. Nancy Messonnier was joining them in her place. Dr. Messonnier is the Deputy Director of the National Center for Immunization and Respiratory Diseases (NCIRD).

Dr. Cohn 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 after being made visually accessible to all viewers, including the visually disabled. 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 be convened at CDC on Wednesday and Thursday, June 22-23, 2016. Registration for all meeting attendees is required. The registration deadline for Non-US citizens is May 18, 2016 and for US citizens registration closes June 6, 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 are 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. Cohn then introduced and welcomed the following new *Ex Officio* members and Liaison Representatives:

Ex Officio Members

- Dr. Narayan Nair replaces Dr. Melissa Houston for the Health Resources and Services Administration (HRSA)
- Dr. Jane Kim replaces Dr. Linda Kinsinger for the Department of Veterans Affairs (DVA)
- Dr. Sergienko, Department of Defense (DoD), was unable to attend and was represented by Col. Margaret Yacovone who joined the meeting via teleconference

Liaison Representatives

- Dr. Sean O’Leary, Associate Professor of Pediatric Infectious Diseases and General Academic pediatrics at Children’s Hospital Colorado at the University of Colorado School of Medicine, replaces Dr. Mark Sawyer for the Pediatric Infectious Diseases Society (PIDS), who served as a voting member of ACIP from July 2008 through June 2013, following which he joined ACIP as a Liaison Representative
- Dr. Kimberly Martin was in attendance representing the Association of State and Territorial Health Officials (ASTHO)

Regarding public comments, Dr. Cohn indicated that topics presented during ACIP meetings include open discussion with time reserved for public comment. She 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 a vote. During this meeting, there was one public comment opportunity scheduled for 4:55 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.

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. During every meeting, an update is provided on the status of ACIP recommendations. There have been three ACIP publications since October 2015, which are reflected in the following table:

ACIP Recommendations Published Since October 2015		
Title	Publication Date	MMWR Reference
• Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults	October 23, 2015	64(41):1171-6
• Advisory Committee on Immunization Practices Recommended Immunization Schedules for Persons Aged 0 Through 18 Years — United States, 2016	February 5, 2016	65(4):86-87
• Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2016	February 5, 2016	65(4):88-90

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

Applications for ACIP membership are due no later than November 4, 2016 for the 4-year term beginning July 1, 2017. 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.

Dr. Bennett announced that two individuals with long histories with ACIP, Dr. Larry Pickering and Carol Baker, will be honored in the next several months:



The National Foundation for Infectious Diseases (NFID) will present Dr. Larry Pickering, past ACIP Executive Secretary, with the John P. Utz Leadership Award. The Award is presented to individuals who exemplify and support National Foundation for Infectious Diseases (NFID) leadership goals through service to NFID and/or the field of infectious diseases. The second award is to Dr. Larry Pickering and Dr. Carol Baker, former ACIP Chair, who will both be honored with the 12th Annual Stanley A. Plotkin Lectureship in Vaccinology during the 2016 Pediatric Academic Societies (PAS) meeting in May. This lectureship was established to honor Dr. Plotkin, PAS's Founding Father. Dr. Baker will be presenting *A Time to Save: The Vaccine Story* and Dr. Pickering will be presenting *Complexities of Vaccine Recommendations: Lessons Learned*. Dr. Bennett invited everyone to join her in congratulating these two important members.

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.
- The remainder of the ACIP members declared no conflicts.

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

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that it continues to be a very busy time at CDC. Apparently, the agency has set a new record because there are four simultaneous activations in the Emergency Operations Center (EOC) with Ebola, polio, the Michigan situation, and now Zika.

Regarding Ebola, the Sierra Leone vaccine trial has completed vaccination. Over 8,000 HCP and other frontline workers were vaccinated in 5 districts in Sierra Leone. Current ongoing work includes adverse event (AE) monitoring of participants, blood draws at 6 through 12 months post-vaccination, and follow-up of pregnancies. Trial results are expected by Fall 2016.

In terms of polio containment, a major part of the polio eradication effort is containment of laboratory samples. There is an extensive survey underway of laboratories throughout the country to determine whether anyone has polio-containing materials, and to ensure that those are handled appropriately.

Regarding upcoming meetings, the theme of the 2016 National Adult and Influenza Immunization Summit scheduled for May 10-12, 2016 in Atlanta is "Making Vaccination Happen in a Changing Environment." The Division of Viral Diseases (DVD) is hosting a small meeting in May 2016 titled "RSV Disease in the United States: Identifying Gaps in Epidemiology Prior to the Advent of Vaccines."

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance announced that CMS conducted a survey of state Medicaid agencies to try to determine exactly what preventive services they are covering for adults, including immunizations. The survey also focused on cost sharing. CMS will soon release the report on this survey, which will be released through the website: www.Medicaid.gov

Department of Defense (DoD)

No report.

Department of Veterans Affairs (DVA)

Dr. Jane Kim reported that the Veterans Information Systems and Technology Architecture (VistA), DVA's nationwide immunization system, has a project known as VistA Immunization Enhancements (VIMM) that will be initiating data sharing to state and city immunization registries. Pilot testing will begin later in 2016. VA is also developing clinical reminder support tools for the electronic medical record (EMR) to prompt clinicians to offer tetanus; tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap), and herpes zoster immunizations to patients who meet criteria. These tools will be disseminated nationwide throughout the VA system in March 2016.

Food and Drug Administration (FDA)

Dr. Sun reported that since the last ACIP meeting, FDA approved the first adjuvanted seasonal influenza vaccine, FLUAD™, for individuals 65 years of age and older. GARDASIL® 9 received supplemental approval for boys 9 through 16 years of age for the prevention of anal cancer, genital warts, and anal intraepithelial neoplasia (AIN). A supplement was also approved for the anthrax vaccine, BioThrax®, for post-exposure prophylaxis (PEP). This is noteworthy because it is the first animal rule approval for a vaccine indication. FDA convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on November 13, 2015 on the topic of maternal immunization. Topics discussed included:

- Use of serologic endpoints as markers for protection
- Safety assessment of infants after maternal immunization
- Duration of follow-up
- Potential immunologic interference of maternal immunization with infant immunization
- Use of observational studies for vaccines recommended by ACIP, such as Tdap and influenza, to evaluate the effectiveness of maternal immunization

Health Resources and Services Administration (HRSA)

Dr. Nair reported that the national Vaccine Immunization Compensation Program (VICP) has had a busy year processing claims. As of January 2016, over 375 claims have been filed for the current fiscal year. Thus far in this fiscal year, 127 claims have been adjudicated. Of those, 125 were compensable and 2 were dismissed. Approximately \$75 million in awards have been paid to petitioners, and \$6 million have been paid to attorneys for fees and costs for compensated and dismissed claims. More data about the program can be obtained on the HRSA website. HRSA has completed development of proposed regulations to make changes to the Vaccine Injury Table. The Notice for Proposed Rulemaking was posted for public comments in July 2015, and was available for 180 days. A hearing to obtain comments from the public on the proposed changes took place on January 14, 2016. Comments received from the public are still being reviewed. To date in this fiscal year, the Countermeasures Injury Compensation Program (CICP) has compensated 2 claims totaling \$125,000. Both programs are involved in outreach programs to inform providers and make the public aware of this safety net program.

Indian Health Services (IHS)

Ms. Groom announced that this year, IHS rolled out a mandatory influenza vaccination policy for its healthcare personnel (HCP). Because bargaining had not been completed with unions, IHS was able to implement the policy only partially. However, a 10% increase was observed among IHS's HCP even with partial implementation. Bargaining was recently completed with the largest union, so hopefully there will be more complete implementation of the policy next year. In addition, IHS is rolling out two performance measures for the agency that pertain to immunizations. The first is a composite adult immunization measure that will assess the proportion of adults 19 years of age and older who have received all age-appropriate vaccinations with Tdap, herpes zoster, and pneumococcal vaccines. The second is a developmental measure to assess Tdap and influenza vaccination among pregnant women.

National Institutes of Health (NIH)

Dr. Gorman reported that Dr. Carole Heilman would retire as the Division Director of the Division of Microbiology and Infectious Diseases (DMID) on February 12, 2016 following an illustrious 38-year career at NIH. Since her 1999 appointment as DMID director, Dr. Heilman has managed a highly complex global research program in infectious diseases, providing scientific direction and oversight for an extensive extramural research portfolio. Under her leadership, DMID has built a robust research infrastructure encompassing national and regional biocontainment laboratories, Centers of Excellence, and Vaccine and Treatment Evaluation Units (VTEU).

Known for fostering a collaborative work environment and encouraging open scientific discourse, Dr. Heilman has received numerous awards for scientific management and leadership. Her honors include three Department of Health and Human Services (HHS) Secretary's Awards for Distinguished Service, recognizing her contributions to developing pertussis, biodefense, and AIDS vaccines. [Dr. Irene Glowinski](#) will serve as Acting Director of DMID while NIH conducts a national search for Dr. Heilman's replacement. Dr. Gorman said that when he wonders whether one person can make a difference in a group as large as the federal government, he thinks of Dr. Heilman and realizes that it can be done.

In terms of research and publications, Dr. Gorman indicated that Dr. Gellin would provide a detailed presentation during the Zika Virus session. NIH is in the process of collecting serum, now on an impromptu and soon on a systematic basis, so that reagents and determinants of immune correlates of protection can be studied. NIH is also considering vaccine development and hopes to pivot rapidly from the experience with dengue and Chikungunya to the new virus that is vector-borne. The National Institute of Allergy and Infectious Diseases (NIAID) has initiated work on several fronts to address Zika virus including the development of animal models to better understand the impact of the virus on the body; *in vitro* assays to test therapeutics for activity against the virus; and improved diagnostics to rapidly identify the virus and distinguish it from its close relatives (e.g., dengue). Several NIAID-supported Zika vaccine efforts already are under way, including the use of the following vaccine approaches: Deoxyribonucleic acid (DNA) vaccines, live attenuated vaccines, and VSV-vectored vaccines [Fauci AS1, Morens DM. Zika Virus in the Americas - Yet Another Arbovirus Threat. *N Engl J Med*. 2016 Jan 13. [Epub ahead of print] <http://www.nejm.org/doi/full/10.1056/NEJMp1600297>]. NIAID recently issued a notice to highlight the NIH's interest in supporting research and product development to combat Zika virus. Areas of high priority include: diagnostics, therapeutics, vaccines, and basic research to better understand infection; pathogenesis; biology of mosquito vectors, host-virus interaction and identification of relevant biomarkers [NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-AI-16-026.htm>]

NIAID is organizing a workshop to be convened March 28-29, 2016 to bring together researchers from around the world with HHS entities (CDC, FDA, ASPR/BARDA, and NIH) and industry partners. The discussion will include a review of the latest information on the virology, pathogenesis, and epidemiology (including the potential link to microcephaly) of Zika virus, as well as efforts toward the development of diagnostics, therapeutics, vaccines, and novel vector control strategies.

There has been a recent publication of NIH's safety and immunogenicity study of sequential rotavirus vaccine schedules. NIAID-supported researchers studied the two rotavirus vaccines licensed for infants in the United States (US), RotaTeq[®] and Rotarix[®], to determine whether switching from one vaccine product to another works as well as using the same vaccine for all of the doses. According to current recommendations and depending upon which vaccine is used, infants receive a series of two or three doses. In many cases, infants receive the same vaccine for all of their doses. However, in some situations HCPs may switch from one product to the other to complete the vaccine series. In this study, researchers determined that mixed rotavirus vaccine schedules are safe and non-inferior in immunogenicity when compared with each licensed rotavirus vaccine when administered alone [Libster R, McNeal M, Walter EB, Shane AL, Winokur P, Cress G, Berry AA, Kotloff KL, Sarpong K, Turley CB, Harrison CJ, Pahud BA, Marbin J, Dunn J, El-Khorazaty J, Barrett J, Edwards KM; [Safety and Immunogenicity of Sequential Rotavirus Vaccine Schedules](#). VTEU Rotavirus Vaccine Study Work Group.

Pediatrics. 2016 Jan 28. pii: peds.2015-2603. [Epub ahead of print; <https://www.clinicaltrials.gov/ct2/show/NCT01266850>].

NIH has a new dengue vaccine entering a Phase 3 trial in Brazil. This is a large-scale clinical trial to evaluate whether a candidate vaccine can prevent the mosquito-borne illness dengue fever. The vaccine, TV003, was developed by scientists in the laboratory of Stephen Whitehead, PhD, at NIAID. The Butantan Institute, a non-profit producer of immunobiologic products for Brazil, licensed the NIAID dengue vaccine technology and is sponsoring the placebo-controlled, multi-center Phase 3 trial using test vaccine produced in Sao Paulo. The new trial plans to enroll almost 17,000 healthy people 2 through 59 years of age in 13 cities, beginning in Sao Paulo [<https://clinicaltrials.gov/ct2/show/NCT02406729>].

An experimental vaccine to protect against the mosquito-borne illness Chikungunya is being tested in a Phase 2 trial sponsored by NIH. Results from an initial trial of the vaccine, which was developed by scientists at NIAID, were reported in 2014. [In that study, all 25 vaccine recipients developed robust immune responses and no safety concerns were noted](https://www.clinicaltrials.gov/ct2/show/NCT02562482?term=NCT02562482&rank=1). The new trial is designed to enroll 400 healthy adult volunteers 18 through 60 years of age at six sites in the Caribbean. It will continue to collect data on the candidate vaccine's safety and ability to elicit immune responses, including antibodies [<https://www.clinicaltrials.gov/ct2/show/NCT02562482?term=NCT02562482&rank=1>].

There was a special issue of *Vaccine: Advancing Maternal Immunization Programs through Research in Low and Medium Income Countries*. This builds upon a long and storied history from ACIP in promoting maternal immunizations, and brings together a lot of the research in a single area. This work is ongoing [Volume 33, Issue 47, 25 November 2015, ISSN 0264-410X; Guest editors M. Neshin (NIH), J. Read (NIH), M. Koso-Thomas (NIH), M. Brewinski Isaacs (NIH) and A. Sobanjo-ter Meulen (B&M Gates Foundation)].

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that NVAC last met on February 2-3, 2016. A topic of significant focus has been drivers of vaccine innovation, potential ways to incentivize innovation, and possible barriers. They look forward to the June 2016 meeting when an initial landscape analysis will be done of what those barriers can be. They have heard from domestic and global groups, including Dr. Seth Berkley, who is the Chief Executive Officer (CEO) of the Global Alliance for Vaccines and Immunization (GAVI), and who is talking about creation of a vaccine development fund. During the June 2016 NVAC meeting, there will be a report of selected recommendations from NVAC's Maternal Immunization WG, which is assessing overcoming barriers to developing vaccines and vaccine recommendations for existing vaccines for pregnant women. Another major focus is the National Vaccine Plan (NVP) 2010-2020, for which NVAC will be intimately involved with a midcourse review. NVAC is following adult immunization implementation issues, and has heard information about efforts pertaining to containment of polioviruses. Type 2 poliovirus is now formally eradicated, so there is an extensive area to prevent reintroduction from laboratories.

National Vaccine Program Office (NVPO)

Dr. Gellin noted that many had participated in the NVP midcourse review, the purpose of which is to determine whether the direction set in 2010 is the same direction that should be continued. The National Adult Immunization Plan (NAIP) has been launched. The NAIP has the following four broad goals:

Goal 1: Strengthen the adult immunization infrastructure

Goal 2: Improve access to adult vaccines

Goal 3: Increase community demand for adult immunizations

Goal 4: Foster innovation in adult vaccine development and vaccination-related technologies

In related work with CDC and the Immunization Action Coalition (IAC), NVPO is co-sponsoring the National Adult and Influenza Immunization Summit, which will be in Atlanta May 10-12, 2016.

NVAC issued a vaccine confidence report last summer, which is now the “playbook” for moving forward. NVPO is sponsoring a funding opportunity of up to \$250,000 to assess the outlines of the recommendations from NVAC. The announcement can be found on www.grants.gov

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Kempe reminded everyone that in February 2015, ACIP voted on the 9-valent HPV (9vHPV) vaccine recommendations. In June 2015, the WG reviewed the status of the 9vHPV vaccine introduction, reviewed a variety of data, and discussed the issue of potential additional 9vHPV vaccination for those who received a different HPV vaccine. In October 2015, the WG reviewed the HPV vaccination program in terms of coverage and implementation, safety, and impact.

To frame the discussion for this session, Dr. Kempe reminded everyone of some historical recent dates pertaining to 9vHPV vaccine. The vaccine was licensed by the FDA in December 2014 and was recommended by ACIP in February 2015, with a *Morbidity and Mortality Weekly Report (MMWR) Policy Note* published in March 2015. 9vHPV vaccine was recommended as 1 of 3 HPV vaccines that can be used for females and 1 of 2 for males in the currently recommended age groups.

Regarding the male age indications at the time of the first application to FDA, 9vHPV immunogenicity trials in males 16 through 26 years of age were not completed. In December 2014, the vaccine was licensed for females 9 through 26 years of age and males 9 through 15 years of age. On December 14, 2015, FDA extended the age indication to include males 16 through 26 years of age. Regarding manufacturer plans, Merck previously reported that they intended to maintain 4vHPV in the US market until 9vHPV was approved by the FDA for use in males 16 through 26 years of age. This has now occurred, so Merck plans to retire 4vHPV by the end of 2016 in the US.

Since the last ACIP meeting, the WG has been reviewing data on 2-dose schedules, including 9-valent HPV vaccine 2- versus 3- dose immunogenicity data and 2-dose trials for other HPV vaccines, as well as modeling and cost-effectiveness data. The WG also has been discussing policy considerations related to 2-dose schedules, including what additional data may be needed for policy plans, the timeline, and decisions that would go along with those considerations.

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

- Data on 2-dose HPV vaccination schedules
- Information and background needed for discussion and decisions about HPV vaccine policy options that ACIP will address over the next few meetings
- WG's future plans

Background: 2-Dose Schedules

Lauri Markowitz, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Markowitz began with some brief background information for the HPV session, including general background and previous ACIP considerations of 2-dose schedules.

There are three licensed HPV vaccines. They are all virus-like particle (VLP) vaccines that are made from the L1 protein of the virus, which is the major capsid protein of the virus. They differ by the types targeted as listed here:

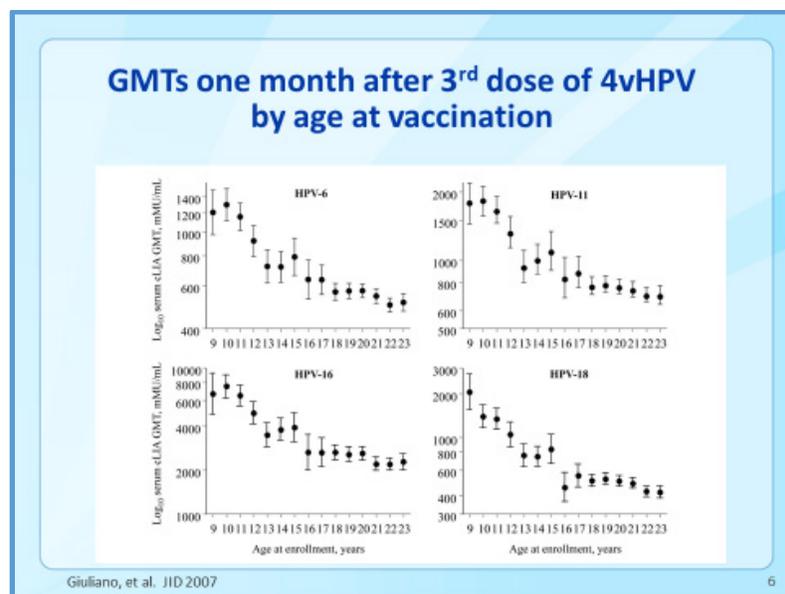
	Bivalent 2vHPV (Cervarix)	Quadrivalent 4vHPV (Gardasil)	9-valent 9vHPV (Gardasil 9)
VLP types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	AS04 500 µg aluminum hydroxide 50 µg 3-O-desacyl-4'- monophosphoryl lipid A	AAHS 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS 500 µg amorphous aluminum hydroxyphosphate sulfate
FDA Licensed	2009	2006	2014
Sex/age groups	Females 9-25	Females and males 9-26	Females and males 9-26
Schedule	3 doses (0,1,6 months)	3 doses (0,2,6 months)	3 doses (0,2,6 months)

VLP, virus like particle 4vHPV licensed in 2006 for females and 2009 for males 3

The bivalent vaccine has a different adjuvant, AS04, which has been shown to produce higher antibody titers than the adjuvant in the 4vHPV vaccines. The 4vHPV vaccine and the 9vHPV vaccine have the same adjuvant, but there is more adjuvant content in the 9vHPV vaccine. There is a higher antigen content for HPV 6, 16, 18 in the 9vHPV compared with 4vHPV. The dates of FDA licensure are shown, as well as the licensed age groups. All vaccines are licensed as a 3-dose schedule as either a 0, 1, 6 month or 0, 2, 6 month schedule. Although there were three licensed vaccines through 2014, almost all vaccine used in the US was 4vHPV.

For licensure of the HPV vaccines, efficacy and immunogenicity data were obtained. These included efficacy data from trials in 15 through 26 year olds with trial endpoints of cervical pre-cancer lesions as well as some other pre-cancers and genital warts, and data from bridging immunogenicity trials in 9 through 15 year olds. Licensure in this age group, and age in which efficacy trials are not feasible, was based on non-inferior antibody response compared with young adult women in the efficacy trials. This is important as it is obviously relevant for how the trials were conducted for the 2- versus 3-dose schedules.

In terms of some brief background about what is known about the immunogenicity of HPV vaccines, there is high seroconversion after vaccination at greater than 98%. In addition, vaccination induces higher antibody titers than natural infection. The main basis of protection is neutralizing antibody; however, the minimal protective antibody threshold is not known. Clinical trials used different serologic assays, and the results are difficult to compare across studies or HPV types. For the 4vHPV vaccine, Merck used a competitive Luminex immunoassay (cLIA) that measures neutralizing antibody to 1 epitope. The GlaxoSmithKline (GSK) trials for 2vHPV vaccine used an enzyme-linked immunosorbent assay (ELISA), which measures neutralizing and non-neutralizing antibody. Of note in the pre-clinical trials, some 4vHPV vaccinees lost detectable HPV 18 antibody as measured by the cLIA, but no loss of protection was detected. Vaccination at younger ages results in higher antibody titers. This last point is illustrated in this graphic, which shows the geometric mean titers (GMTs) one month after the 3rd dose of 4vHPV vaccine by age at vaccination, with age shown on the x axis:



As shown, the GMTs decreased with increasing age at vaccination for all 4 types. [Giuliano, et al. JID 2007]. The same decrease in GMTs with increasing age at vaccination was seen in the 2vHPV and 9vHPV trials

There has been global interest in simplified schedules for HPV vaccine. Such schedules could facilitate implementation, reduce logistical challenges, and decrease resource needs. They also might increase acceptability for providers, parents, and vaccinees. Interest in evaluating 2-dose schedules in young adolescents was stimulated by data from clinical trials with 3 doses showing high efficacy, high serologic response to vaccination, and higher antibody titers in the younger age groups.

The 3-dose schedules for which vaccines were originally tested and licensed (0 months, 1 to 2 months, and 6 months) can be considered a “prime-prime-boost” (PPB), with the first 2 doses being the priming doses and the third being the boost. The 2-dose schedule that has been studied is a 0, 6 month schedule. This schedule can be considered a prime and boost with the second prime eliminated. Memory B cells require at least 4 to 6 months to mature and differentiate into high-affinity B cells. The approximate 6-month interval between the first and last dose allows the last dose to reactivate memory B cells efficiently [Siegrist. Chapter 2. Vaccine Immunology. In Vaccines 2013; Stanley et al. Expert Reviews 2014].

Based on some of the data that Dr. Markowitz reviewed later during this session, regulatory approvals have been obtained for 2-dose vaccination schedules for the 2vHPV and 4vHPV vaccines in other countries. Approval for 2-dose schedules has been based primarily on the immunobridging data, which showed non-inferior antibody response with 2 doses (0, 6 months) in adolescents compared with a 3-dose schedule in young adult women. In 2014, the European Medicines Agency (EMA) granted marketing authorization for a 2-dose schedule for those 9 through 14 years of age for 2vHPV and 9 through 13 years of age for 4vHPV. Following regulatory approval by the EMA, in 2014 the World Health Organization (WHO) changed its recommendation from a 3-dose to a 2-dose schedule for those starting the vaccination series before age 15 [Weekly Epidemiologic Record 2014; 89: 221-236]. Many countries changed from a 3- to 2-dose schedule for this age group, including European and Latin American countries and some provinces in Canada.

During the June 2014 ACIP meeting, data on 2-dose schedules for 2vHPV and 4vHPV were reviewed by ACIP. At that time, there was no FDA indication for a 2-dose schedule for any HPV vaccine, and there were no plans by either manufacturer for submission of 2-dose data to FDA for 2vHPV or 4vHPV. Also at that time, data for the 9vHPV was being considered by ACIP and there were no data on 2-dose schedules in the initial Biologics License Application (BLA) under review by FDA at that time. However, a 2- versus 3-doses trial had been initiated by the manufacturer for the 9vHPV vaccine. In 2014, ACIP decided to continue to review 9vHPV as a 3-dose schedule, and to consider 2-dose schedules after the data from the 2- versus 3-dose trial of 9vHPV vaccine and other data become available.

Later that year, 9vHPV vaccine was licensed as a 3-dose schedule and was recommended by ACIP in February 2015 as one of the HPV vaccines that could be used for the routine immunization schedule. The 9vHPV vaccine became available through the Vaccines For Children (VFC) Program in April 2015. Approximately 7 million doses were distributed in the US through December 2015. At this point, the 9vHPV 2- versus 3-dose trial data became available and were to be reviewed by ACIP along with other data on 2-dose schedules.

Comparison of Immunogenicity of 2-Dose and 3-Dose Regimens of 9vHPV Vaccine

Alain Luxembourg, MD, PhD
Director, Clinical Research
Merck Research Laboratories

Dr. Luxembourg presented the latest data for Merck's 2- versus 3-dose trial for 9vHPV vaccine. The 3-dose regimen of 9vHPV vaccine was licensed in December 2014 in the US; in 2015 in Canada, the European Union (EU), Australia, Chile, and Hong-Kong; and in 2016 in Ecuador, Korea, and New Zealand under the name GARDASIL[®] 9 to prevent the following:

- Cervical, vulvar, vaginal, and anal cancers caused by HPV 16/18/31/33/45/52/58
- Cervical, vulvar, vaginal, and anal dysplasia caused by HPV 6/11/16/18/31/33/45/52/58
- Genital warts caused by HPV 6/11

In February 2015, ACIP recommended GARDASIL[®] 9 for routine vaccination. Licensure of 9vHPV vaccine is under review in other countries.

Initial licensure of 9vHPV vaccine was for 3 doses for all age ranges. WHO changed its recommendation for HPV vaccines in terms of dose schedules in October 2014 to 2 doses for girls 9 through 14 years of age with the following caveats:

- If dose 2 is administered <5 months after dose 1, a third dose should be given >6 months after the first dose*
- No maximum recommended interval (≤12-15 months suggested to complete schedule promptly and prior to becoming sexually active)*
- 3 doses in individuals ≥15 years of age and those known to be immunocompromised and/or HIV-infected*

At this time, there is no current licensure or recommendation of a 2-dose regimen in the US. The 2-dose data for 4vHPV vaccine became available around the time when efficacy data became available for 9vHPV vaccine. Considering the imminent submission of the 9vHPV vaccine data to FDA, the results of the 2-dose immunogenicity study of GARDASIL[®] were not submitted to FDA. 9vHPV was developed as a 3-dose vaccine because the development began in 2007, a year after 4vHPV vaccine was approved. At that time, the standard regimen was 3 doses and 2-dose regimens were not discussed very much. For that reason, all of the trials were conducted with a 3-dose regimen.

Protocol 10 was begun in 2013 to assess a 2-dose regimen of 9vHPV vaccine. The results of the primary immunogenicity analyses (4 weeks post-last dose) are expected to be reviewed by the FDA in 2016. The study will continue for 2 more years for assessment of antibody persistence and immune memory, and these results will be presented as soon as they become available. Merck is also planning a separate larger study known as Protocol 025 to assess long-term immunogenicity and effectiveness. Protocol 025 is still in the planning stage. Merck will update the WG as planning progresses.

Protocol 10 is an open-label study with males and females in which all subjects received 9vHPV vaccine. Cohort 1 is comprised of females 9 through 14 years of age who received 2 doses administered with a 6-month interval. Cohort 2 is comprised of males 9 through 14 years of age who received 2 doses administered with a 6-month interval. Cohort 3 is comprised of females and males 9 through 14 years of age who received 2 doses with a 12-month interval. Cohort 4 is a control group comprised of young women 16 through 26 years of age who received 3 doses at 0, 2, and 6 months. Cohort 4 serves as the control because it uses the population and dose regimen that were used to establish vaccine efficacy. Since there is no immune correlate of protection threshold of protective antibody determined for HPV vaccines, the only immunogenicity comparison that has clinical significance is a comparison to a group where efficacy was established.

Cohort 5 is an exploratory cohort comprised of females 9 through 14 years of age who received 3 doses to assess the dose effect in the same age range and same gender. It is exploratory because it is scientifically important and interesting, but is not necessarily a comparison for which a conclusion can be drawn regarding clinical significance. There was a 4-week window for all of the vaccination dates. The study will continue for two more years for assessment of immunogenicity, including assessment of immune memory at Month 36, with a challenge dose administered.

The duration of Protocol 10 is 37 months. The primary objectives are to:

- Demonstrate non-inferiority of GMTs at 1 month after the last dose in girls and boys who received a 2-dose regimen versus young women who received a 3-dose regimen
 - *Same approach as that previously accepted for licensure of 3-dose regimen of GARDASIL[®]*
 - *Non-inferiority criterion: exclude 1.5-fold decrease (2- versus 3-dose)*
- Perform 3 non-inferiority tests:
 - *Girls (0, 6) vs. Women (0, 2, 6)*
 - *Boys (0, 6) vs. Women (0, 2, 6)*
 - *Girls/Boys (0, 12) vs. Women (0, 2, 6)*

The objectives for the exploratory analyses are to:

- Compare GMTs 1 month after the last dose in:
 - *Girls (0, 6) vs. Girls (0, 2, 6)*
 - *Girls (0, 12) vs. Girls (0, 2, 6)*
- Assess antibody persistence at months 24 and 36
- Assess evidence of immune memory (*additional dose at month 36*)
 - *No hypothesis testing for the exploratory analyses*

In terms of the results for the primary objectives, at 1 month post-last dose in 2-dose (0, 6) girls versus 3-dose (0, 2, 6) women, the point estimates were higher for 2 doses for all HPV types.

The non-inferiority criterion was met for all 9 HPV types. The fold difference for girls/women was over 2 for most types. Types 45 and 52 were somewhat lower, but still, the non-inferiority criterion was met for all HPV types, with the lower bound of the 95% confidence interval greater than 0.67 (thereby excluding a 1.5-fold decrease). For boys receiving 2-doses (0, 6) versus women receiving 3-dose (0, 2, 6), substantially higher immunogenicity was achieved among boys receiving 2 doses versus women receiving three doses. The non-inferiority criterion was met for all 9 HPV types. Types 45 and 52 were in the lower range, while types 16 and 33 were among the highest. For 2-doses (0, 12) for girls and boys versus 3-doses (0, 2, 6) for women, the non-inferiority criterion was met for all 9 HPV types.

As part of the objectives, seroconversion rates were also assessed. It is very clear from the following table showing the 5 cohorts and 9 HPV types that all seroconversion rates for any type were greater than 97%, which very much aligns with what has been observed in 3-dose HPV trials:

**9vHPV 2-dose Study:
Seroconversion Rates at 4 Weeks Post-Last Dose**

Assay	Girls (0, 6) (N=301)	Boys (0, 6) (N=301)	Girls/Boys (0, 12) (N=300)	Girls (0, 2, 6) (N=300)	Women (0, 2, 6) (N=314)
HPV 6	99.6%	100%	100%	99.2%	99.6%
HPV 11	100%	100%	100%	99.6%	99.6%
HPV 16	100%	100%	100%	100%	99.6%
HPV 18	100%	100%	100%	99.6%	98.5%
HPV 31	99.6%	100%	100%	100%	99.6%
HPV 33	99.6%	100%	100%	100%	99.6%
HPV 45	99.3%	99.3%	100%	99.3%	97.9%
HPV 52	99.6%	100%	100%	99.6%	99.6%
HPV 58	100%	100%	100%	99.6%	99.6%

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For the exploratory analyses of 2 doses (0, 6) in girls 9 through 14 years of age versus 3 doses (0, 2, 6) in girls 9 through 14 years of age, at first glance GMTs look very similar for all 9 HPV types. But looking at the fold difference, the point estimate of the GMT ratio is greater than 1 for Types 6, 11, 16, 33, and 58 and lower than 1 for Types 18, 31, 45, and 52. A fold difference of greater than 1 means that the GMT is higher with the 2-dose than the 3-dose regimen, while a fold difference of less than 1 means that the GMT is higher with the 3-dose than the 2-dose regimen. For Types 31, 45, and 52 the 95% confidence interval of the GMT ratio does not include 1, which indicates a significantly lower GMT for 2-dose than 3-dose.

The same comparison was conducted between girls receiving a 2-dose regimen at 12 months (0, 12) versus girls receiving a 3-dose regimen (0, 2, 6). The GMTs were generally higher with the 0, 12 regimen. The fold difference was greater than 1 for Types 6, 11, 16, 18, 31, 33, 52, and 58. The fold difference was less than 1 for Type 45, and the 95% confidence interval of the GMT ratio did not include 1. Thus, there was a significantly lower GMT for Type 45 and a similar or higher GMT for all other types.

Given that GARDASIL[®] 9 is now a licensed product, a vaccination report card was not used and injection site and systemic adverse events (AE) were not systematically assessed. However, serious AE (SAE) and discontinuations due to an AE were assessed. During the study, a few SAEs were evenly distributed among the groups. Among these, there were no vaccine-related SAEs and no deaths. One (1) discontinuation due to urticaria was reported at 1 day post-dose 1 in Cohort 3 that resolved.

In summary, the primary study hypotheses were met. Non-inferiority was met for HPV 6/11/16/18/31/33/45/52/58 GMTs at 1 month after last vaccination in girls and boys 9 through 14 years of age who received 2 doses of 9vHPV vaccine versus women 16 through 26 years of age who received 3 doses. That supports extending the efficacy findings in women who received 3 doses to girls and boys who received 2 doses, using the same process that was used for 3 doses in boys and girls. The exploratory analyses showed that for some HPV types, GMTs were lower in girls who received 2 doses versus girls who received 3 doses. The clinical significance of this observation is unknown but may deserve further investigation, especially based on longer follow-up. With respect to safety, 9vHPV vaccine was generally well-tolerated in all vaccination groups. There were no vaccine-related SAEs, no deaths, and only 1 discontinuation due to an AE. There were no new safety findings compared with previous clinical studies of the 9vHPV vaccine.

There are a number of key points and potential limitations to be considered with these results. Regarding the time interval between dose 1 and dose 2, per WHO and EMA, if for any reason, the interval between doses 1 and 2 is less than 5 months, a third dose should be given 6 months after dose 1. There is a single post-marketing effectiveness study of GARDASIL[®] using genital warts as an end point that indicates lower effectiveness if the time interval between doses 1 and 2 is less than 5 months [Blomberg et al Clin Infect Dis 2015; 61:676-682]. This suggests that there may be less flexibility with a 2-dose regimen than with a 3-dose regimen. Though little is known about a single dose, there are post-marketing effectiveness studies of 4vHPV vaccine that indicate lower effectiveness of a single dose. Thus, ensuring series completion is essential. Duration of protection provided by 2 doses of 9vHPV vaccine has not been assessed, there is no efficacy assessment, and there are no long-term follow-up data. Data are forthcoming from the longer term follow-up study that is planned, but they are not available at this time. Immunogenicity assessment will continue through Month 37 in this study and a separate, larger, long-term immunogenicity and effectiveness study is planned given the absence of an immune threshold of protection.

In conclusion, administration of a 2-dose series of 9vHPV vaccine in girls and boys 9 through 14 years of age, with the second dose given at 6 or 12 months following the first dose (\pm 4 week window) generates non-inferior GMTs for all 9 HPV types compared with the 3-dose regimen in young women 16 through 26 years of age. The efficacy of the 2-dose regimen, durability of responses, and long-term effectiveness remain to be evaluated in long-term follow-up clinical studies and post-licensure epidemiological studies.

Discussion Points

Ms. Pellegrini requested clarification regarding whether Merck would be submitting these data to FDA, and whether an indication for a 2-dose schedule would be sought based on the data.

Dr. Luxembourg replied that Merck does not plan to submit the 2-dose data of GARDASIL[®] to FDA. GARDASIL[®] will likely exit the market in the United States at the end of the year.

Dr. Bennett requested clarification of Ms. Pellegrini's question regarding 9vHPV vaccine.

Dr. Luxembourg clarified that his first reply regarded the 4vHPV vaccine. FDA is currently reviewing the results of the 2-dose study for the 9vHPV vaccine.

Dr. Karron asked how GARDASIL[®] 9 is being used in the other countries where it has been approved.

Dr. Luxembourg responded that at this point, GARDASIL[®] 9 is commercially available in the US, Canada, and a few European countries only as a 3-dose schedule.

Dr. Belongia asked Dr. Luxembourg to comment further on the observation that the GMT ratio was higher for the 2-dose schedule at 0, 12 months versus the 2-dose schedule at 0, 6 months, and whether Merck would propose to utilize the longer interval in its application for a 2-dose schedule licensure.

Dr. Luxembourg explained that the study was designed to conduct a comparison with young women who received a 3-dose schedule. Both of those regimens testing 0, 6 and 0, 12 met the non-inferiority criterion, which means that both regimens are equivalent in that regard. There may be differences in GMT levels, but the differences in GMT levels in the HPV vaccine field do not have identifiable clinical significance aside from the comparison to an efficacy population. Merck's intent with respect to assessing a 0, 6 regimen and a 0, 12 regimen was not only scientific, but also was for practical reasons. Merck recognizes that depending upon how the vaccine is administered (school program, office setting, et cetera), it is important to provide the public health community with more flexibility in terms of time interval between the 2 doses.

Dr. Reingold requested further information regarding when results are anticipated from the planned long-term effectiveness and post-licensure epidemiological studies.

Dr. Luxembourg replied that Protocol 10 is ongoing, with two more years of follow-up planned. The analyses of antibody persistence and immune memory are anticipated to be completed by the end of 2017. The long-term effectiveness study is still in the planning stages and has not yet begun, given continued discussions with regulators. Merck anticipates that the study will begin in 2017 and will include at least 10 years of follow-up, and perhaps longer.

Dr. Kelly Moore asked whether there is a biological plausible mechanism by which starting at a higher or equivalent GMT with a 2-dose series could result in a more rapid degradation than in a 3-dose series.

Dr. Luxembourg responded that this will be assessed with the antibody persistence analyses. Studies have been conducted with other HPV vaccines, but this does not seem to present a concern as there does not seem to be a dramatic decrease over time in GMT ratios between girls who received 2 doses versus women who received 3 doses. Certainly, this is one point that needs to be monitored thoroughly in antibody persistence analyses.

Summary: 2-Dose Schedules, Bivalent and Quadrivalent HPV Vaccines

Lauri Markowitz, MD

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

In this presentation, Dr. Markowitz provided an overview of data on 2-dose vaccination schedules for 2vHPV and 4vHPV vaccines. Data on 2-dose schedules for these vaccines are useful to review as ACIP considers data on 2 doses for 9vHPV vaccine for two reasons. Although there are some differences between the vaccines, trials of 2vHPV and 4vHPV vaccines can provide contributory data to consider related to the 9vHPV decision. Importantly, the 2- versus 3-dose trials of these vaccines have longer follow-up to date than the 9vHPV trial. Also, recommendations for 2-dose schedules might be considered for 2vHPV and 4vHPV vaccines, and there certainly would be questions regarding persons who received less than 3 doses of 2vHPV or 4vHPV if 2 doses of the 9vHPV are recommended.

Data on 2-dose schedules of 2vHPV or 4vHPV vaccines include immunogenicity, efficacy, and post-licensure effectiveness data. Dr. Markowitz focused primarily on immunogenicity data in this presentation as a complement to the data presented by Dr. Luxembourg on 9vHPV vaccine, but briefly mentioned the efficacy and post-licensure effectiveness data.

For the bivalent vaccine, Dr. Markowitz reviewed three trials designed to evaluate 2-dose schedules. The following table shows where each trial was conducted; age groups; number of doses; the schedule, with interval in months between doses; and the longest follow-up available to date:

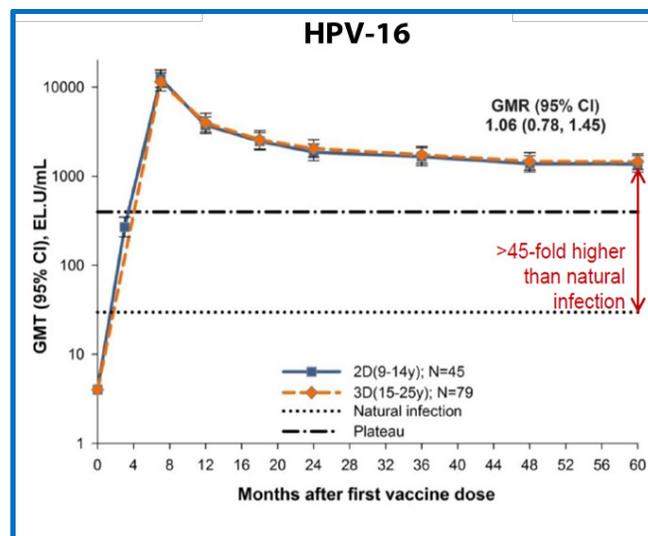
Study	Country	Age (yrs) and doses	Schedule (months)	Longest follow-up
Romanowski Hum Vaccin 2011* Hum Vaccin 2014 Hum Vaccin 2016	Canada,	9–14 2 doses	0, 6	24 months*
	Germany	9–14 3 doses	0, 1, 6	60 months**
		15–25 2 doses	0, 6	
		15–25 3 doses	0, 1, 6	
Unpublished NCT01381575	Canada,	9–14 2 doses	0, 6	36 months
	Germany,	9–14 2 doses	0, 12	
	Italy, Taiwan, Thailand	15–25 3 doses	0, 1, 6	
Lazcano-Ponce Vaccine 2014	Mexico	9–10 2 doses	0, 6	21 months
		9–10 3 doses	0, 1, 6	
		18–24 3 doses	0, 1, 6	

*dose ranging study, included other groups as well **followup study of licensed formulations

The first two are industry-sponsored studies used to obtain regulatory approval and the third is independent. As noted, all three trials provide a comparison of 2 doses in the younger age group with 3 doses in the young adult women, which was the primary comparison. The first and last studies also provided a direct comparison of 2 and 3 doses in the younger age group. The second trial compared two different 2-dose schedules in the younger age group: 0, 6 and 0, 12 months schedules—similar to the 9vHPV vaccine trial just presented.

The first study by Romanowski was considered a proof of concept study. It also included a dose ranging component and other groups as well, but Dr. Markowitz showed only the groups of interest for ACIP's discussion during this session. A follow-up extension study evaluated groups that received the licensed formulation through 60 months. From this proof of concept study, there were many findings but the main ones of interest for this discussion were that the 2-dose schedule in girls 9 through 14 years of age was immunologically non-inferior to the 3-dose schedule in the young adult women. Within the same age group, GMTs were lower with 2-dose schedule given at 0 and 6 months compared with the 3-dose schedule. This was observed for both girls 9 through 14 years of age and women 15 through 25 years of age.

In terms of the longer follow-up of two groups of interest, those 9 through 14 years of age who received 2 doses and those 15 through 25 years of age who received 3 doses, all subjects remained seropositive for HPV 16 and 18 through month 60 after vaccination. The GMTs over time for HPV 16 are shown in the following figure:



The antibody kinetics are similar to those seen in all of the HPV vaccine trials, with a peak antibody titer after the first dose, a decline, and then a plateau reached at about 24 months. GMTs were non-inferior in the 2-dose group compared with 3-dose group through month 60. The lines are almost identical, so they are difficult to see. GMTs were substantially higher than after natural infection shown by the lower dotted line through Month 60 of follow-up.

The unpublished trial of the bivalent vaccine was a larger trial that was designed to confirm the findings in the proof of concept trial. Though the results are unpublished, data have been presented at meetings and are available online [Clinical Study Report HPV-070 (114700) at <http://www.gsk-clinicalstudyregister.com> Clinicaltrials.gov NCT01381575]. There were two 2-dose groups of subjects 9 through 14 years of age (0,6 and 0,12 month schedules) and a single 3-dose group 5 through 25 years of age (0, 1, 6 months—the standard schedule). Results for this study are presented here as GMT ratios:

**Bivalent HPV vaccine
2 vs 3 dose immunogenicity trial
(1 month after last dose)**

HPV Type	2 dose 9–14 yrs (0,6 mos)/ 3 dose 15–25 yrs		2 dose 9–14 yrs (0,12 mos)/ 3 dose 15–25 yrs	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 16	0.92	(0.82, 1.03)	1.12	(0.99, 1.27)
HPV 18	1.18	(1.05, 1.32)	1.33	(1.18, 1.49)

- >99% seroconversion in all groups
- One month after last dose, GMTs with 0,6 and 0,12 schedules in 9-14 yr olds were non-inferior to the 3 dose (0,1,6) schedule in 15-25 yr olds

Note: GMTs presented as 3 doses/2 doses in abstract
Antibody measured by ELISA; non-inferiority criterion = lower 95% CI of GMT ratio >.5

Tang R-B. Asia-Pacific Conference on Medical Virology, 2015, and GSK Study Register HPV-070 (ID #114700)
ClinicalTrials.gov NCT01381575

For the above and subsequent slides, Dr. Markowitz showed the GMT ratios as 2 doses over 3 doses for consistency though they were presented differently in some of the publications. Non-inferiority was defined as the lower 95% CI for the GMT ratio being >.5 in all studies. On the left, the 2-dose 0, 6 month schedule in 9 through 14 year olds is compared with the 3-dose schedule in young adult women. The non-inferiority criterion was met. On the right is the comparison of the 2-dose at 0, 12 month schedule in 9 through 14 olds with the 3-dose schedule in young adult women. GMT ratios are greater than 1 and again, the non-inferiority criterion was met. There was over 99% seroconversion in all groups. In summary, one month after the last dose, GMTs with both 0, 6 and 0,12 schedules in subjects 9 through 14 years of age were non-inferior to the 3-dose 0,1,6 schedule in subjects 15 through 15 years of age. Recently posted on the GSK website are the results for 36 months, which are very similar to these results.

The third bivalent vaccine trial by Lazcano-Ponce was an independent study conducted in Mexico. There were two groups 9 through 10 years of age (0, 6 months and 0, 1, 6—the standard schedule) and a group 18 through 24 years of age who received 3 doses in the standard schedule. The group providing data on 2 doses was on a 0-, 6-, 60-month schedule with a planned interim analysis at Month 21. Shown in this table are the data from this trial:

HPV Type	2 dose 9–10 yrs/ 3 dose 18–24 yrs		2 dose 9–10 yrs/ 3 dose 9–10 yrs	
	GMT Ratio	(95% CI)	GMT Ratio	(95% CI)
HPV 16	1.4	(1.3, 1.4)	0.6	(0.6, 0.7)
HPV 18	1.4	(1.3, 1.7)	0.6	(0.5, 0.7)

All vaccinees were seropositive when tested at 7 and 21 months. For the comparison of 2 doses in subjects 9 through 10 years of age with 3 doses in subjects 18 through 24 years of age, the antibody response was generally higher after 2 doses in subjects 9 through 10 years of age as noted by GMTs greater than 1. The non-inferiority criterion was met. In the comparison of 2 doses and 3 doses in subjects 9 through 10 years of age, GMTs were lower in the 2-dose schedule. The GMT ratios were less than 1, but the lower limit of the CI was greater than 0.5. The non-inferiority criterion for this study was considered to be met.

Regarding the data available for 4vHPV vaccine, Dr. Markowitz reviewed the following three trials that were designed to evaluate the immunogenicity of 2 doses of 4vHPV vaccine:

Study	Country	Age (yrs) and doses	Schedule (months)	Longest follow-up
Dobson JAMA 2013	Canada	9–13 2 doses	0, 6	36 months
		9–13 3 doses	0, 2, 6	
		16–26 3 doses	0, 2, 6	
Hernandez-Avila Hum Vaccin & Immunother 2015	Mexico	9–10 2 doses	0, 6	21 months
		9–10 3 doses	0, 2, 6	
		18–24 3 doses	0, 2, 6	
Sankaranarayanan Lancet Oncol 2016	India	10–18 2 doses	0, 6	48 months
		10–18 3 doses	0, 2, 6	

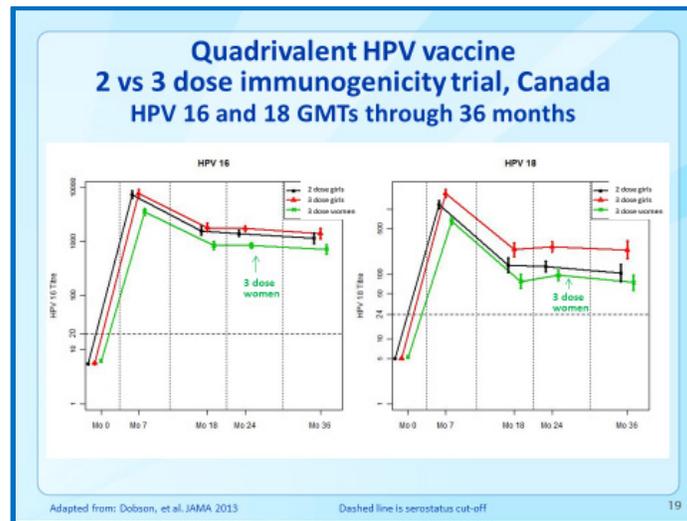
Data from the Hernandez-Avila and Sankaranarayanan trails were not available when ACIP reviewed the data in 2014. The first two studies included a comparison of 2 doses at 0, 6 months in the younger age group with 3 doses in young adult women, which was the main analysis for these studies. All studies allowed for a direct comparison of 2 and 3 doses within the same age group, although the age ranges differed slightly in these studies. Follow-up was through 36 months in Dobson, 21 months in Hernandez-Avila, and 48 months in Sankaranarayanan.

The study conducted in Canada by Dobson has been reviewed with the ACIP previously. The 9 through 13 year olds were randomized to receive 2 or 3 doses. A third group of women 16 through 26 years of age received 3 doses. There were 36 months of follow-up. Although an independent study, data from this trial were submitted to regulatory authorities in other countries to obtain approval for a 2-dose schedule of 4vHPV vaccine. The following table shows the 36 month results:

HPV Type	2 dose 9–13 yrs/ 3 dose 16–26 yrs		2 dose 9–13 yrs/ 3 dose 9–13 yrs	
	GMT Ratio	(95% CI)	GMT Ratio	(95% CI)
HPV 6	1.36	(0.97, 1.90)	0.64	(0.46*, 0.90)
HPV 11	1.43	(1.03, 1.99)	0.73	(0.52, 1.02)
HPV 16	1.70	(1.16, 2.49)	0.81	(0.55, 1.20)
HPV 18	1.46	(0.88, 2.41)	0.43	(0.26*, 0.73)

The main analysis on the left was comparing the 2-dose girls with the 3-dose young adult women. Non-inferiority criteria were met for all types, and the titers were generally higher in the 9 through 13 year olds shown by the GMT ratios being greater than 1. In the comparison of the 2- and 3-dose schedules within subjects 9 through 13 years of age on the right, GMTs were generally lower in the 2-dose group and non-inferiority was lost for HPV 6 and 18. At earlier time points in this study not shown on this table, GMTs were lower in the 2-dose group, but the non-inferiority criterion was still met for these comparisons. Non-inferiority was lost by 24 months for HPV 18, and by 36 months for HPV 6.

The following graphic shows more detail of the antibody kinetics through 36 months for the three groups:



The dashed line at the bottom of the above graphic is the serostatus cut off value of the assay. Of note, the antibody kinetics were similar in all groups, with the peak antibody titer 1 month after the last dose and then declined and a plateau at about 18 to 24 months. For HPV 18, GMTs for the 3-dose, 9 through 13 year old group were higher than the 2-dose girls. At later time points, the lines diverge and this is where GMTs lost non-inferiority. However, as shown here, the GMTs in this 2-dose group were not inferior to the GMTs in the 16 through 26 year olds who received 3 doses.

The Hernandez-Avila 4vHPV vaccine was conducted in Mexico. There were also three groups in this trial: 2 groups at age 9 through 10 (a 2-dose and a 3-dose group), and a 3-dose group of subjects 18 through 24 years of age. In this trial, over 98% in all groups were seropositive for HPV 16. For HPV 18, seropositivity was lower in all groups compared with Month 7. HPV 18 seropositivity was 56.6% in women 18 through 24 years of age who received 3 doses, 86% among the girls who received 3 doses, and 70% among girls who received 2 doses. The 56% seropositivity in women 18 through 24 years of age is consistent with findings in pre-licensure efficacy trials of 4vHPV; whereas, HPV 18 seropositivity measured by the cLIA declined over time but no loss of protection was detected in these trials. The following table shows GMTs at Month 21 after vaccination:

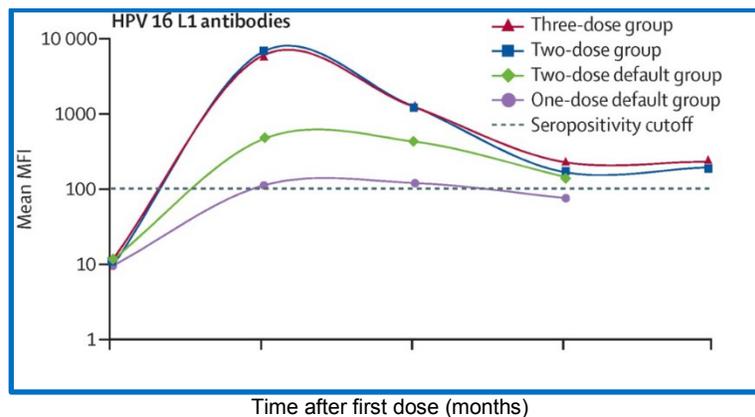
HPV Type	2 dose 9–10 yrs/ 3 dose 18–24 yrs		2 dose 9–10 yrs/ 3 dose 9–10 yrs	
	GMT Ratio	(95% CI)	GMT Ratio	(95% CI)
HPV 6	1.29	(1.02 – 1.62)	1.21	(0.96 – 1.52)
HPV 11	1.52	(1.21 – 1.91)	0.87	(0.69 – 1.10)
HPV 16	1.49	(1.12 – 1.98)	1.16	(0.88 – 1.55)
HPV 18	1.27	(0.96 – 1.67)	0.74	(0.57– 0.98)

In the analysis comparing the 2-dose schedule among girls 9 through 10 years of age with the 3-dose schedule among women at 18 through 24 years of age, the non-inferiority criterion was met for all types. The antibody response was generally higher in girls 9 through 10 years of age who received 2 doses, with GMTs ratios greater than 1. In the comparison of the 2- and 3-dose schedules within girls 9 through 10 years of age, the GMT ratios were less than 1 for a few of the types, but again, the study's non-inferiority criteria were still met.

The Sankaranarayanan trial was designed as an immunogenicity and efficacy trial of 2 versus 3 doses of 4vHPV vaccine in India. Girls 10 through 18 years of age were enrolled. The design was a cluster randomized trial of 2 doses at 0, 6 months versus 3 doses in the standard 3-dose schedule. This was designed to be an efficacy trial assessing pre-cancer outcomes. However, recruitment and vaccination were suspended for reasons unrelated to this study. Because of this, vaccination did not occur as scheduled and the randomized design was lost. The study was analyzed as an observational cohort. Over 17,000 girls were enrolled and randomized to the two groups. However, vaccination occurred according to 4 different schedules:

- 1-Dose Group: Women who were randomized to the 2 dose or the 3 dose group, but only received one dose
- 2-Dose Group (0, 2 Months): Women who were randomized to the 3-dose arm, but did not receive the third dose
- 2-Dose Group (0, 6 Months)
- 3-Dose Group (0, 2, 6 Months)

The following figure shows median fluorescence intensity (MFI) for HPV 16 antibodies, expressed as mean MFI:



The number of girls with specimens tested was far less than the number who received vaccine in each group, ranging from about 300 to 500. The dashed line is the seropositivity threshold established by the investigators for this assay. For HPV16, the antibody kinetics of the 2-dose 0, 6 month schedule was similar to antibody response of the 3-dose group. The mean MFI of the 2-dose group was non-inferior to the 3-dose group at all time points through 48 months. The antibody response after 2 doses administered at 0 and 2 months reached lower peak titer and was inferior to the 3-dose group at 18 months and 36 months. For the 1-dose group, GMTs

were inferior to 3-dose group at 18 and 36 months. There were some differences, but a similar pattern was observed for HPV 18, 6, and 11.

In summary for the immunogenicity of 2-dose schedules of 2vHPV and 4vHPV vaccine, for the comparison of 2 doses (0,6 months or 0,12 months) in girls versus 3 doses in young adult women, antibody response was non-inferior in the 2-dose group and was generally higher for both vaccines. Antibody kinetics were similar, and these findings were consistent in all trials that evaluated the 2 doses (0, 6 months) versus 3 doses in girls the same age. In the comparison of 2 doses (0, 6 months) versus 3 doses (standard schedule) in girls of the same age for the 2vHPV vaccine, GMTs were generally lower in the 2-dose group, although formal hypothesis testing was not done in some of the studies. For 4vHPV vaccine, GMTs were lower for some types in 2 of the 3 studies.

There are some data on efficacy with 2-dose schedules. For the bivalent vaccine, there are data from a post-hoc analysis of efficacy against incident HPV 16/18 infection. This is an analysis of combined data from two randomized controlled efficacy trials in women 15 through 25 years of age. In these 2 trials, participants were randomized to receive a 3-dose vaccine schedule or control. Most, but not all, women completed the 3-dose schedule and there was a post-hoc analysis of efficacy against incident infection by number of doses received. There was high efficacy in all groups and no significant difference by number of doses. There are limitations to these data including that in this post-hoc evaluation. Women who were randomized to receive 3 doses but received fewer doses could have been different from those who completed the series. However, these data suggest efficacy with less than 3 doses. It is important to note that the 2-dose schedule in these studies was not a 0, 6 months schedule, but instead was a 0, 1 month schedule because the study was designed to evaluate vaccine at 0, 1, 6 months [Kreimer, et al. Lancet Oncol 2015].

While the same type of data are not available for 4vHPV vaccine, there are some relevant data from the recently published trial in India in which girls 10 through 18 years of age were randomized to receive 2 or 3 doses of HPV vaccine. As mentioned earlier, this trial was suspended and lost its randomized design and was analyzed as an observational cohort study. Girls were followed up for the immunogenicity evaluation just presented, and with cervical samples. The median time between first vaccination and cervical sample was 3.9 years. The incidence of infection was 0.6% in the 3-dose group and 1% in the 2-dose 0, 6 month group; 2% in the 2-dose 0, 2 month group; and 1.6% in the one dose group. While point estimates varied, there was no statistically significant difference between these groups and all groups were lower than what was expected from historical data. Further analyses are needed for this study, which hopefully will be forthcoming. Unvaccinated age and residence matched women are being enrolled into a cohort and will be followed to provide incidence data for comparison. Follow-up of women in this study is planned for 20 years [Sankaranarayanan, et al. Lancet Oncol 2016].

While Dr. Markowitz did not review post-licensure studies of vaccine effectiveness for 2 doses, but briefly mentioned the scope of these studies and noted that these data will be reviewed during a future ACIP meeting. There are at least 6 studies that have evaluated post-licensure effectiveness after introduction of HPV vaccination programs by number of doses (5 of 4vHPV and 1 of 2vHPV):

Vaccine	Country	Design / Study Population	Outcome
4vHPV	Australia ¹	Retrospective cohort study using linked registry data	Cytological and histological cervical abnormalities
	Australia ²	Case-control study using linked registry data	Histological cervical lesions
	Sweden ³	Open cohort using nationwide health registers	Condyloma
	Denmark ⁴	Cohort using nationwide health registries	Condyloma
	Belgium ⁵	Retrospective cohort using reimbursement database	Condyloma
2vHPV	Scotland ⁶	Women screened for cervical cancer	HPV prevalence

¹Gertig BMC Med 2013, ²Crowe BMJ 2014, ³Herwijer JAMA 2014, ⁴Blomberg CID 2015, ⁵Dominiak-Felden PloS One 2015, ⁶Kavanagh BJC 2014

These studies have mainly been conducted in countries with good national health registries. Outcomes evaluated included cervical cytological or histological abnormalities, condyloma, or HPV prevalence. There are a variety of challenges and limitations pertaining to these types of studies. For example, there could have been differences between 2- and 3-dose recipients. Most 2-dose recipients did not receive a 0, 6 month 2-dose schedule as these analyses were conducted when a 3-dose schedule was recommended and the 2-dose recipients were those who did not complete the recommended 3-dose schedule. Moreover, there are a variety of methodologic challenges for these post-licensure studies. Most of these studies did show lower efficacy for those who received less than a 3-dose schedule. As noted, these data will be reviewed in more detail during a future ACIP meeting.

To summarize all of these data, the main analyses for immunogenicity and those used by regulatory agencies are comparisons of antibody response of 2 doses in young adolescents, with 3 doses in young adult women—the age during which efficacy has been demonstrated in clinical trials. This is because there is no established minimum antibody threshold for protection. Two doses (0, 6 months or 0, 12 months) in subjects 9 through 14 years of age were non-inferior compared with 3 doses in young adult women. Follow-up was through 36 months for 2vHPV and 4vHPV vaccines. In some trials, antibody titers were lower for some types after 2 doses (0, 6 months) compared with 3 doses in the same age group.

There are limited efficacy data. For 2vHPV vaccine, data are from a post-hoc analysis of 3-dose RCTs in subjects 15 through 25 years of age. For 4vHPV vaccine, data are from the interrupted RCT of 2- versus 3-dose in vaccination among subjects 10 through 18 years of age that was analyzed as an observational study. The studies suggest efficacy with less than 3 doses, but also raise a variety of interesting questions. For 2vHPV vaccine in particular, the study evaluated an older age group than those who have been the focus of the 2-dose immunobridging studies and provided data on a different dose interval, perhaps suggesting efficacy for a wider age range and for shorter intervals between doses. Also, while the criteria that have been used and will be used to evaluate reduced dose schedules are non-inferior antibody compared to a 3-dose schedule in the age groups in which efficacy was demonstrated in the clinical trials, some available data suggest that lower levels of antibody might be also be

protective. Post-licensure effectiveness, most of which found lower effectiveness with less than 3 doses, will be reviewed with ACIP during the next meeting.

In summary, data on 2-dose schedules for 2vHPV and 4vHPV vaccines can provide supplementary evidence for consideration of 2-dose schedules for 9vHPV vaccine; however, it is important to remember that there are some differences between vaccines. These data also could be used for consideration of 2-dose recommendations for 2vHPV and 4vHPV vaccines themselves. The HPV Vaccines WG will further review and evaluate these and other data using GRADE, and findings will be presented and discussed at a future ACIP meeting.

Work Group Plans

Elissa Meites, MD, MPH
Medical Epidemiologist
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Meites summarized that information presented during this session provided background for considering 2-dose schedules for HPV vaccines. New data were presented from the 2-dose immunogenicity trial of 9vHPV vaccine in girls and boys, and an overview of current data on 2-dose schedules for 2vHPV and 4vHPV vaccines. There are plans to present additional 2-dose data during a future ACIP meeting. There also will be a variety of issues for ACIP to consider:

- GRADE for 2-dose schedules
- Review of post-licensure effectiveness data
- Modeling data and cost-effectiveness
- Programmatic considerations
- Additional follow-up data from the 9vHPV vaccine trial

There are a number of issues for ACIP to consider. One issue pertains to whether a 2-dose schedule should be recommended. If so, the following would need to be addressed:

- The target age or age range for a potential 2-dose recommendation
- The recommended interval or range of intervals (there could be a minimum number of months-between-doses in a 2-dose schedule, or a specific interval, such as 0-6 or 0-12)
- Wording of a potential recommendation to clarify whether exactly 2 doses are recommended versus allowing for 2 or 3 doses
- Whether special populations should be included in a potential 2-dose recommendation, or if three doses would continue to be recommended for some groups, such as immunocompromised persons or others
- Which HPV vaccines would be included in a 2-dose recommendation

Another issue to be aware of is FDA approval. All HPV vaccines currently available in the US are FDA-approved as a 3-dose series. For 9-valent vaccine, data from the 2-dose trial in a Supplemental Biologics License Application (sBLA) will be reviewed by the FDA. A 2-dose schedule for this vaccine would be off-label unless the label is changed at some point. For

4vHPV vaccine, there are no plans for the manufacturer to submit 2-dose data to FDA, so a 2-dose schedule would be off-label. Similarly, there are no plans for the manufacturer to submit 2-dose data to FDA for 2vHPV vaccine, so a 2-dose schedule would be off-label.

A further issue to consider is incomplete series, since currently about 20% of teens starting a 3-dose series did not complete it. If a 2-dose recommendation is made, it could specify for each HPV vaccine whether and when a 2nd dose or a 3rd dose should be given. For 4vHPV vaccine, the manufacturer plans to retire this vaccine in the US at the end of 2016. However, if a 2-dose recommendation is made, it might still apply to people who began but did not complete a 3-dose series.

The workgroup plans to present the following data at the next ACIP meeting in June 2016:

- GRADE for 2-dose schedules, including immunogenicity, efficacy, and post-licensure effectiveness data
- Modeling data for cost-effectiveness of 2-dose schedules
- Programmatic considerations
- Initial discussion of potential recommendations

Additional topics that will be presented to ACIP in the future include:

- Further follow-up data from the 9-valent vaccine trial, when available
- Decisions from the FDA, if any, that might change the indicated number of doses of 9vHPV vaccine
- Proposed recommendations and vote on 2-dose schedules

Discussion Points

Dr. Reingold noted that according to a *New York Times* article a couple of days before this meeting [summarizing the 2016 research by Markowitz et al published in *Pediatrics*], current coverage seems to be having an even more impressive herd immunity effect than predicted. He wondered whether anything was known about the likely herd effect of a 2-dose schedule versus a 3-dose schedule, or whether the fact that the impressive herd effect might give ACIP even more impetus to make a 2-dose recommendation given the context of the epidemiologic situation. He also requested that Dr. Bennett comment on the implications of ACIP making an off-label recommendation.

Dr. Markowitz replied that in terms of impact, the data suggest that there is either some efficacy from less than a complete 3-dose schedule or herd immunity. It is not possible to say which it is. Certainly, the fact that greater impact is being observed than expected if a complete 3-dose schedule is needed for high efficacy suggests that one or both of those is operating. In terms of whether a similar herd immunity effect would be observed with a 2-dose schedule, if there is high efficacy from a 2-dose schedule, the same herd effect would be anticipated from a 2-dose as for a 3-dose schedule. It is known from other countries that there is a profound herd effect from vaccination programs. The most compelling data come from Australia where they have been able to demonstrate a very large impact on genital warts among males, even though they were targeting only females in the vaccination program. Australia had very high coverage. Therefore, it is known that herd protection can be achieved through high coverage.

Regarding the implications of off-label recommendations, Dr. Bennett replied that it is clear that ACIP has and will continue to make off-label recommendations. With respect to how those are implemented, particularly in the environment of the new data, she did not believe the implications would be negative if ACIP chose to make an off-label recommendation.

Dr. Messonnier added that ACIP has made off-label recommendations in the past, but the context of those was quite different from this. There have been off-label recommendations for small subgroups or that have been seen as bridges to something that is not recommended. The programmatic complexities of an off-label recommendation in this setting would be much greater in terms of how to communicate that, how providers would implement that given the different messages they would be getting from different sources, et cetera. One of the reasons the workgroup outlined further discussion in June 2016 is to allow time to consider some of the programmatic considerations. From the CDC perspective, the hope is that FDA and Merck can do an efficient consideration of the BLA and that there will be a rapid response.

Dr. Sun (FDA) responded that the FDA is reviewing the submission pertaining to 2 doses, and a regulatory decision will be made in short order. Given that the review process is ongoing, he was not at liberty to say more than that at this point.

Dr. Karron expressed her hope that ACIP could take into consideration any deliberations and decisions that occur earlier than June 2016 in terms of timelines for bringing draft recommendations forward to ACIP for a vote. They may not want to wait until the October 2016 meeting to be making decisions about 2 and 3 doses.

Carol Hayes (ACNM) reminded everyone that every vote ACIP has made regarding immunization and pregnancy has been off-label.

Meningococcal Vaccines

Introduction

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

Dr. Rubin explained that this session would include two parts. The first part of the session would focus on an update pertaining to serogroup B meningococcal vaccines, including newly available data. No discussion of changes to current recommendations was planned. The second part of the session would focus on a discussion of meningococcal disease in HIV-infected persons and men who have sex with men (MSM). No vote was anticipated during this session.

Additional data for MenB vaccines reviewed by the WG since June 2015 has included safety and immunogenicity data from two Phase 3 studies for MenB-FHbp, including immunogenicity data on 10 secondary strains and 10 outbreak strains and the results of a mass immunization campaign with MenB-4C in Quebec, Canada. In addition, the WG reviewed reports to the Vaccine Adverse Events Reporting System (VAERS) to monitor MenB safety. No safety signals have been reported to date.

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) 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 June 2016 ACIP meeting. Harmonized outbreak guidelines will be published on CDC's website.

Dr. Rubin indicated that the presentation topics for this session would include the following:

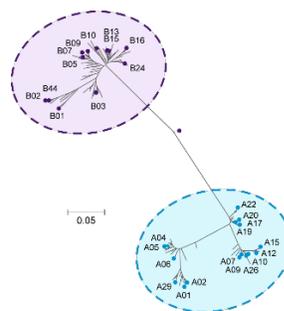
- MenB-FHbp vaccine update
- Results of a mass immunization campaign with MenB-4C in Quebec Canada
- Considerations for use of MenACWY vaccines in HIV-infected persons
- Meningococcal disease among MSM, United States, January 2012-June 2015
- Summary of Work Group Discussions on Meningococcal Disease in MSM

MenB-FHbp Vaccine Update

Dr. Laura York
Medical Development
Scientific and Clinical Affairs
Pfizer

Trumenba[®], Pfizer's MenB-FHbp vaccine, is based on a surface-exposed factor H binding protein (FHbp) expressed in over 97% of invasive meningococcal B (MenB) strains. The fHbp sequences segregate into two genetically and immunologically distinct subfamilies, A and B, as shown in the following phylogenetic tree:

Subfamily B: 71%



Subfamily A: 29%

Pictorially, it is easy to see that this protein extends from the bacteria so that it is readily accessible to antibody. This protein functions as an important meningococcal virulence factor. It binds to factor H and down regulates the complement system and, therefore, limits the amount of complement-mediated lysis—the protective mechanisms against meningococci. The MenB-FHbp sequences segregate into two genetically and immunologically distinct subfamilies, A and B. Within the subfamilies, these proteins are very similar in their sequence identities, so MenB-FHbp contains two lipidated protein variants (A05 and B01), one from each subfamily to elicit antibodies that are going to recognize across those FHbps within each subfamily and thereby provide a broadly protective response [Madico et al. 2006; Schneider et al. 2006; Mascioni et al. 2009; Seib et al. 2009; Ala'Aldeen et al. 2010; McNeil et al. 2009; Jacobson, Moellig, Olcen 2009].

The following table delineates the Trumenba[®] clinical plan:

**Trumenba:
Clinical Development Plan**

Study Description	Age (Years)	Design(Control)	MenB-FHbp	Control
Trials that supported accelerated approval in the US				
Safety & Immunogenicity	18 to 40	Open Label	60	
Safety & Immunogenicity	18 to 40	Open Label	12	12
Safety & Immunogenicity	≥11 to 18	Single-blinded (saline)	198	121
Safety & Immunogenicity	18 to 64	Open Label	13	
3 Safety & Immunogenicity With Concomitant Gardasil [®]	≥11 to <18	Observer-blinded (Gardasil [®])	1982	501
4 Safety & Immunogenicity 2-Dose & 3-Dose Schedules	≥11 to <19	Single-blinded (saline at some visits)	1696	16
Safety & Immunogenicity With Concomitant Repevax [®]	≥11 to <19	Single-blinded (Repevax [®])	374	378
Safety & Immunogenicity With Concomitant Menactra [®] /Adacel [®]	≥10 to <13	Observer-blinded (Menactra [®] /Adacel [®])	1753	876
Large Scale Safety Study	≥10 to <26	Observer-blinded (Havrix [®])	3802	1901
1 Lot Consistency, Safety & Immunogenicity (B1971009)	≥10 to <19	Observer-blinded (Havrix [®])	2700	900
2 Safety and Immunogenicity (B1971016)	≥18 to <26	Observer-blinded (saline)	2475	2475
Totals			15,065*	5,530*

 *Actual numbers after study clean up. MenB-FHbp= 15,054; control: 5,525

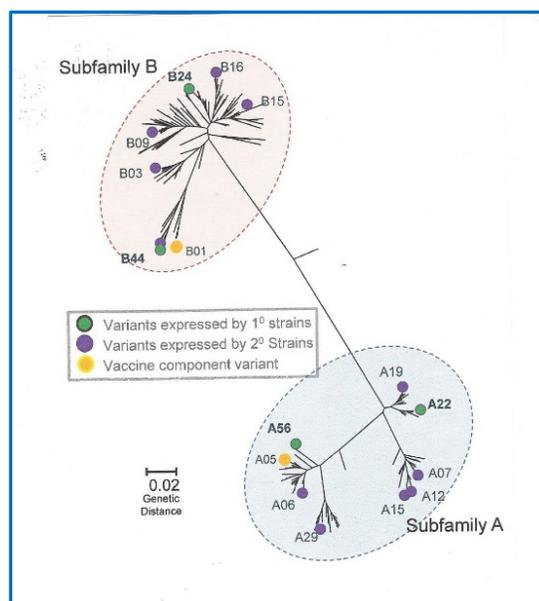
Boxed in green are the trials that supported the accelerated approval in the US. Part of the approval process was to provide ongoing studies to FDA when they are completed as post-approval commitments. As the data become available, Pfizer has been providing those data to the ACIP WG. During the considerations, data were provided to ACIP not only from the 7 licensure trials, but also from the safety and immunogenicity studies of concomitant administration of Menactra[®] and Adacel[®], the large-scale Phase 2 safety study, and antibody persistence studies from Stage 2 of an early immunogenicity study.

Dr. York indicated that during this session, she would provide an update on the two final studies within this clinical development plan for the adolescent indication: 1) a lot consistency, safety, and immunogenicity study in adolescents 10 through 18 years of age, and 2) a safety and immunogenicity study in young adults 18 through 25 years of age. She noted that she would review the immunogenicity data and compare that to data provided for licensure through two

trials, referred to as Studies 1 and 2, that provided pivotal immunogenicity, a safety and immunogenicity assessment with concomitant Gardasil® conducted in the US referred to as Study 3, and Study 4 conducted in Europe to assess 2- and 3-dose schedules. In total, there is now a large database from 11 clinical studies.

Study 1 (B1971009) is a Phase 3 immunogenicity, lot consistency, clinical safety and tolerability study of Trumenba® in healthy adolescents 10 through 19 years of age conducted in the US, Canada, and Europe. This study is comprised of approximately 3600 subjects of whom 2693 received Trumenba® and 897 received HAV/saline. Study 2 (B1971016) is a Phase 3 immunogenicity and safety / tolerability study of Trumenba® in healthy adults 18 through 26 years of age conducted in the US and Europe. This study is comprised of approximately 3300 subjects of whom 2471 received Trumenba® and 822 received saline. In both studies, immunizations were administered on a 0, 2, and 6 month schedule.

As post-approval commitment studies, Studies 1 and 2 provide the confirmatory human serum bactericidal assay (hSBA) data; that is, they are confirming the data generated in the licensure trials in Studies 3 and 4. These are confirmatory hSBA responses, which is the correlate used to predict protection against 4 MenB strains that are agreed to be representative of the prevalent strains in the US. The fHBP variants expressed by these strains are not homologous to the vaccine components. They are A22, A56, B24, and B44. This is shown on the phylogenetic tree below:



These studies also provide supportive hSBA data, meaning that hSBA responses are shown against a panel of 10 additional strains, which are referred to as secondary strains. They express variants that are prevalent and are not homologous to the vaccine components. In total, with the 4 primary strains and the 10 additional strains, these account for about 80% of the meningococcal strains that are circulating.

As a reminder, there were 5 co-primary endpoints for licensure, meaning that subjects had to achieve a 4-fold rise in hSBA titer 30 days post-dose 3 to each of the 4 representative strains (A22, A56, B24, and B44). The fifth primary endpoint was a composite response, looking at the subjects who achieved an hSBA titer of greater than or equal to 1:8 and 1:16 on the A22 strain for all 4 test strains. This shows the ability of the antibody within an individual to recognize across the diversity of the FHbp being expressed by these 4 representative strains, and inferring activity against the FHbp within the same subfamilies. A high proportion of individuals among adolescents and young adults who responded obtained an hSBA titer 4-fold rise against each of the 4 strains. Importantly, a high proportion of these individuals achieved an hSBA titer of greater than 1:8 for all 4 test strains.

In terms of comparison across the three studies, there is consistency across the responses with a high proportion of individuals who achieved the 4-fold rise in titers after receiving the third dose, and also comparable levels of individuals who have a composite response achieving an hSBA titer of greater than 1:8 for all 4 test strains. 1:8 is higher than the accepted correlate of protection of 1:4. This consistency of responses to vaccine is, in fact, observed across the Phase 1 and Phase 2 studies where this immunogenicity data is available. There are comparable responses across the studies regardless of the geographic area in which the studies were conducted. Therefore, the Phase 2 and 3 studies confirm the data that informed the licensure of Trumenba[®] and provide evidence that Trumenba[®] will provide a bactericidal response which will be active against the diverse MenB strains that are circulating and causing disease in the US.

This is supported by the data from the 10 additional strains A06, A07, A12, A15, A19, A29, B3, B9, B15, and B16. Again, a high percent of subjects attained an hSBA titer of greater than 1:8 which is above the correlate of protection. The 10 strains are distributed well across the subfamilies and across adolescents and adults, there is a consistent high response and the ability of the antibody to recognize across these variants. These are prevalent variants in the disease-causing MenB strains.

Pfizer was also asked to provide ACIP with data from an exploratory analysis performed on some diverse FHbp variants expressed by outbreak strains B24, A22, B03, B44, B228, and B153. These data are from 10 different isolates from 10 different outbreaks occurring in the US and France from 2011 through 2015. The hSBA titer of the correlate of protection was 1:4.

These 10 strains are diverse in the hSBA variants they express. They can be prevalent variants. In fact, 5 of these strains express B24. A22 and other prevalent variant B03 and B44 are also prevalent variants. There are also unique variants like B228 and B153. These data were generated with a small number of serum samples with exploratory hSBA assays, which sometimes can have challenges in development of the assay. These data demonstrate that all of the strains are susceptible to killing, and that the level of responses observed overall and in general are similar to what has been observed in the clinical studies. In the totality of the immunogenicity data to date, these data would be expected to support that Trumenba[®] would be expected to elicit a broadly protective immune response.

In terms of evaluation of safety, the safety profile demonstrated by Trumenba[®] in Studies 1 and 2 were consistent with the safety data that supported licensure, and in which the majority of local and systemic events were mild to moderate in severity and transient after each vaccination. The most common AEs were pain at the injection site, fatigue, headache, muscle pain, and chills. There was no clear pattern of potentiation with progressive dosing. The SAE

rates were comparable between Trumenba[®] recipients (1.7%) and controls (1.6%) in 4 controlled trials. In both Study 1 and Study 2, Trumenba[®] was well-tolerated in adolescents and young adults. The reactogenicity profile was consistent with the prior studies, and there is a low SAE rate overall of 1.9% versus 2.4% in the vaccine and control groups, respectively in adolescents and 1.3% for both the vaccine and control groups in young adults.

In the total safety database comprised of data from 11 clinical trials, studies have been conducted in the US, several European Countries, Canada, Australia, and Chile. Approximately 15,000 subjects who have received Trumenba[®] and approximately 5500 controls are included in the database. Approximately 3000 of these individuals are from the US. Trumenba[®] has demonstrated an acceptable safety profile. The most common local and systemic reactions were injection site pain, headache, fatigue, and muscle pain. Reactogenicity events were mostly mild and moderate and of short duration. The median duration was 2 to 3 days for local reactions and 1 to 2 days for systemic reactions, and there was no potentiation of reactions with subsequent doses. Trumenba[®] has demonstrated an acceptable safety profile when co-administered with other routinely administered adolescent vaccines like MCV4/Tdap, dTaP-IPV, or HPV4. Similar proportions of newly diagnosed chronic medical conditions, autoimmune diseases, and neuroinflammatory conditions were reported in Trumenba[®] recipients and controls. Rates of SAE are similar between Trumenba[®] recipients (1.6%) and controls (1.9%).

In summary, Trumenba[®] was designed to provide broad protection against MenB. The newly available hSBA data confirm that Trumenba[®] elicits bactericidal activity against diverse meningococcal serogroup B strains. Trumenba[®] demonstrates a favorable safety profile in adolescents and young adults. Spontaneous safety data collected post-approval supports the safety profile observed in clinical studies, with reactogenicity events being the most frequent events reported. Trumenba[®] was recently used in mass vaccination campaigns for outbreak control at two US colleges. One of the colleges with an opt-out policy and a student population of approximately 4500 had very good compliance. The other had an opt-in policy and probably less than 50% received the first dose in a target population of around 20,000. No new safety signals have been detected based on post-marketing surveillance. The data support administration with routinely recommended adolescent vaccines. In total, the data continue to support the expectation that immunization with Trumenba[®] will provide a broadly protective response against MenB disease when used both for outbreak control and prevention of endemic disease. The full public health potential of Trumenba[®] can be realized only with broad implementation in populations at risk of meningococcal disease.

Discussion Points

Regarding protection against outbreaks shown on Slide 9, Dr. Walter noted that two strains seemed to show lower protection than others and wondered whether there was something different about them.

Dr. York replied that these are small numbers. Strain-specific differences are observed, and some are more difficult to set up in the assays. In general, overall these data show that there is a possibility of killing. The trend would be toward having the kind of protection that has been observed in clinical trials.

Dr. Kempe asked whether there are any immunogenicity data on subsets who received 1 dose, or prime and booster and not the intermediate dose.

Dr. York responded that with a single dose, there is greater than a 50% response to 3 of the strains and approximately 20% to 25% to 1 of the B strains. In general, there is a response to one dose. Certainly, there is an increase in the response after receiving additional doses. There are data from one of the pivotal licensure trials in Europe comparing the 2- versus 3-dose schedule (Slide 16), which show the 4-fold response after a 3-dose schedule at 0, 2, 6 and 0, 1, 6 months and in increasing intervals of two doses at 0, 6; 0, 4; or 0, 2 months. The responses are substantial, but are not as high as if 3 doses had been received. Clearly, there is still a high level of protective response with a longer interval.

Dr. Reingold asked whether the vaccine has any effect on carriage. Dr. York responded that Pfizer is working on those data.

Noting that there had been 3 or more college outbreaks, Dr. Baker wondered whether Pfizer had done any testing with its assay against those strains.

Dr. York indicated that the 10 strains she showed include US strains as well as strains from France.

Dr. Cohn inquired about the magnitude of the response against the additional 10 strains compared to the primary 4 strains in terms of GMTs.

Dr. York responded that as might be expected, there are differences in the GMTs depending upon the strain. But, there is a comparable response within those. What is typically observed in B subfamily strains will be consistent through that, but it may be quite high as well. The GMTs are quite predictable. It is within the overall range and is not restricted to a particular subfamily.

Results of a Mass Immunization Campaign With 4CMenB Vaccine In the Saguenay-Lac-Saint-Jean Region, Quebec, Canada

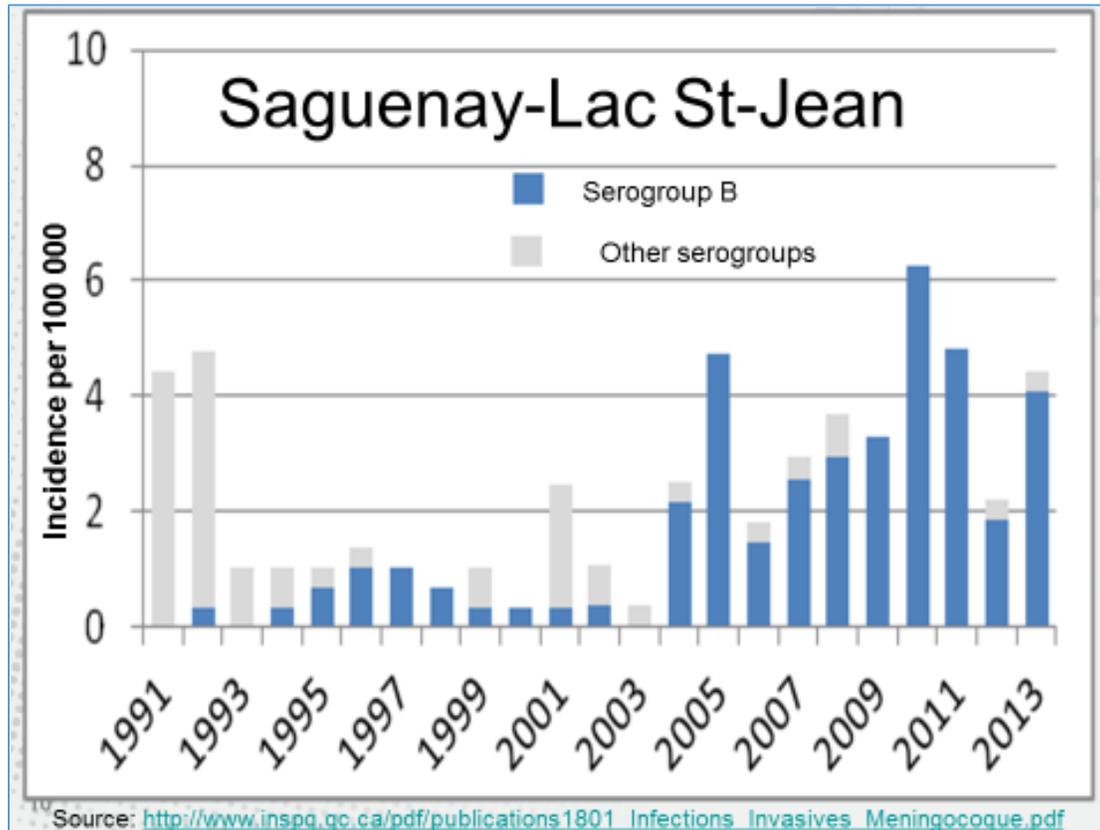
**Gaston De Serres, MD, PhD
Institut National De Sante Publique
Du Québec and Laval University**

Dr. De Serres described the Canadian experience regarding a mass immunization campaign against MenB using the 4-component meningococcal B vaccine, produced by Novartis and purchased by GSK. He indicated that the information he was presenting was funded by the Ministry of Health.

Québec has a population of approximately 8 million, but the outbreak occurred within a sub-region of the province known as Saguenay-Lac-Saint-Jean. Comparing the number of reported cases per year, Quebec has the largest number but is not the largest province. Ontario has nearly twice the population, but the number was much lower. Canada has an incidence of 0.33/100 000 and Quebec had an incidence approximately twice that level at 0.76/100 000. The highest incidence was in infants, which rapidly declined in preschoolers, was pretty low between 5 and 14 years of age, but increased in older teenagers and young adults.

In the early 2000's, the ST-269 clone emerged. This was not just a clonal complex. It was a specific clone that emerged and spread rapidly throughout the province. The Saguenay-Lac-Saint-Jean Region 2 is a small region of approximately 270,000 people with nearly 60,000 children less than 20 years of age. The incidence among those under 20 years of age during

the period 2006 through 2013 was above 10 / 100,000. For the other regions, the incidence was much lower. Even for adults, the incidence was higher among adults in Saguenay-Lac-Saint-Jean than in the rest of the regions. The following table shows all of the invasive meningococcal disease (IMD) reported in the region since 1990, with serogroup B beginning to increase from 2004, with a fairly high incidence in this region:



In the Saguenay-Lac St-Jean Region, there was high incidence in infants and teenagers. In terms of whether the strain matched the 4CMenB vaccine, nearly 90% of the isolates in that region were the ST-269 clone. None of the isolates antigens were the exact match with the MenB-4C components. Of the MenB ST-269 clonal complex, 96% were predicted to express two antigens similar to the vaccine components: factor H-binding protein (fHbp) peptide 15 (variant 1) and Neisserial Heparin-Binding Antigen (NHBA) peptide 21.

The vaccine was licensed in December 2013 and in April 2014, the Quebec Immunization Committee (CIQ) recommended vaccinating approximately 60,000 children 2 months through 20 years of age. The immunization schedule was 4 doses among children 2 through 5 months of age, 3 doses among children 6 through 11 months of age, and 2 doses for children 12 months of age and older. The campaign began in May and June 2014, during which the first dose was administered with the idea of administering the second dose during the following school year during September and October 2014. The campaign ended December 31, 2014. The vaccine was offered in schools for primary and high school children, and in public health clinics for pre-schoolers.

When the campaign was recommended, there were a lot of data regarding the reactogenicity of the vaccine. A passive VAERS is already in place that is fed by physicians. In this province, adverse events following immunization (AEFI) reporting is mandatory for all physicians. Active surveillance was added so that all vaccinees whose parents provided an email address on the consent form were sent a message one week after each dose with a link to a web-based questionnaire on a secure server. The outcomes included AEFI of sufficient severity to cause absenteeism or a medical consultation during the 7 days post-vaccination. In order to assess SAEs, another questionnaire was sent six months post-last dose. Telephone calls were made by nurses to validate the information on all hospitalizations, seizures, arthralgia, SAEs (hospitalizations, life-threatening sequelae, deaths), and other AEFIs considered severe. Coverage was good until 16 years of age, with overall coverage of 83% receiving 1 dose and 76% receiving 2 doses as shown in the following table:

Vaccine coverage as of Oct 7 2015			
Age at the 1 st dose	Target population Number	1 dose %	2 doses %
2-5 months	2990	94	92
6-11 months	1 270	93	90
1 -4 years	10 928	87	80
5-11 years	18 903	94	91
12-16 years	12 940	93	87
17-20 years	12 165	47	33
Overall	59 196	83	76

Of the vaccinees, 69% provided an email address. The participation rate was not large. For the first dose, there was a participation rate of 39% among those sent an email message and 27% among all vaccinees. For the second dose, participation was 32% among those sent an email message and 22% among all vaccinees. Six months post-last dose, participation was 23% among those sent an email message.

In terms of fever, that vaccine was associated in clinical trials with a high proportion of fever. For Doses 1, 2, 3, and 4 in infants, the onset was primarily the day of vaccination and the following day. By Day 3, fever was largely baseline. The percentage reporting an AEFI causing absenteeism or a medical consultation was consistently more frequent with the second dose than the first. Injection site reaction and general malaise were by far the most predominant reasons for absence or consultation. When the absentees attributable to fever, general malaise, or local reactions were calculated with onset on Day 1 or 2, it was 1.8% to 3.4% for those younger than 18 years of age. The province has a generous maternal leave policy, so in the first year of life, the mother is generally at home and there is no absence because of that.

However, 3.8% to just under 7% of those 6 through 16 years of age had an absenteeism due to those adverse events.

Seizures were less than what was expected based on the clinical trial, but there were 6 febrile convulsions as follows:

- 1 year old 6 hours post-dose 1
- 2 year old 8 hours post-dose 2
- 4 year old 4 hours 30 minutes post-dose 2
- 5 year old 30 minutes post-dose 2
- 6 month old 28 hours post-dose 3
- 1 year old 48 hours post-dose 3

No clustering was observed in terms of hospitalizations. The diagnoses of patients are show in the following table:

Age	Day of Hospital admission	Diagnosis
2 year old	Day 2 post dose1	Bronchiolitis
2 month old	Day 2 post dose 1	Fever and dehydration
1 year old	Day 5 post dose 1	Bronchospasm
1 year old	Day 6 post dose 1	URTI and bronchospasm
6 year old	Day6 post dose 1	Viral mesenteric adenitis
9 year old	<15 min. post dose 2	Anaphylaxis (4CMenB + Twinrix) Had similar problem with MMR
4 month old	Day 1 post dose 2	Bronchiolitis
4 year old	Day 1 post dose 2	2 episodes of febrile seizures
2 year old	Day 2 post dose 2	Bronchospasm
1 year old	Day 3 post dose 3	Febrile seizure

The most frequent SAEs requiring hospitalization were respiratory problems and other types of infections, with all SAEs shown in the following table:

	4 Months After Dose 1	6 months after dose 2	Total
Respiratory infections /problems	21	31	52
Infections (urinary, ocular, dental, etc.)	16	22	38
Surgery	11	4	15
Trauma	7	1	8
Fever /dehydration	3	2	5
Seizures	2	2	4
Renal lithiasis	0	4	4
Food allergy	2	1	3
Nephrotic syndrome	0	3	3
Anemia	0	3	3
Epilepsy	1	2	3
Crohn disease	2	1	3
Diabetes	1	1	2
Other	5	9	14

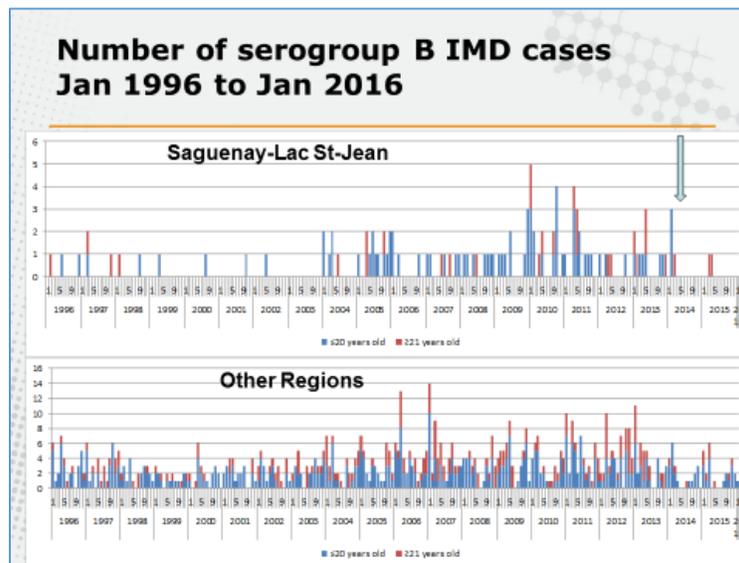
In the targeted cohort, 16 deaths occurred between May 1, 2014 and May 30, 2015. Of those, 5 deaths occurred within 6 months of a dose of 4CMenB, 4 were due to motor vehicle accidents, and 1 occurred 5 months after a single dose of 4CMenB. The death that occurred 5 months following the single dose of 4CMenB was investigated by a coroner, who concluded that the vaccine was not involved.

There were 102 AEFIs reported between May 1, 2014 and August 28, 2015. The reported rates per 10,000 administered doses were as follows:

Overall	10.3
Fever	2.9
Local Reaction	2.3
Allergic-Like Event	2.7
Seizures	0.9

There was 1 incident of Kawasaki Disease (KD) in a 4-year old child with onset 100 days post-Dose 2. In the month preceding KD, the child had received a dose of DapT-Polio (Boostrix-Polio[®]) and Flumist[®].

In terms of the impact on disease, the upper panel in the following graphic presents the region and the green arrow shows the start of the campaign, with only two cases reported after the campaign that occurred in adults:



The lower panel in the above table shows the rest of the province, in which the incidence also decreased. In terms of the two cases that occurred in the Saguenay-Lac St-Jean Region in March 2015, one case was in an unvaccinated 44 year old who had stayed in an ice fishing shelter during the week prior to disease onset. The second was in an unvaccinated 13 year old living outside the Saguenay-Lac St Jean Region that was related to the first case in that the child was in the same ice fishing shelter as the first adult case during the week prior to disease onset. Symptom onset occurred two days after those of the first case. In April 2015, a case occurred in an unvaccinated 64 year old who lived in another village in the Saguenay-Lac St-Jean Region, which was determined to be unrelated to the other cases. With regard to vaccine effectiveness, no B-IMD cases were observed among the 47,115 vaccinated residents 2 months to 20 years of age. There were 2 cases among 230,444 unvaccinated residents. Crude vaccine effectiveness was 100%, though this was not statistically significant.

In summary, because 4CMenB was recently licensed and there was a limited number of participants in the clinical trials, an enhanced surveillance for safety was set-up. Active surveillance was already set up for pandemic influenza by the Canadian Immunization Research Network (CIRN). That surveillance has the advantage to timely inform public health if there is any problem. Participation was not huge, but the hope was that if that was a problem, people would be participating and that this may over-estimate the risk but would be unlikely to under-estimate it. The passive surveillance covers all people even if they do not want to participate in active surveillance, so there were two ways to assess that. The safety profile was similar to that reported in clinical trials. There was no signal of unexpected AEFIs and no cluster of SAEs. High fever and febrile convulsions were present, but were not more frequent

than expected. A few cases of KD were reported in the clinical trials, but there was no increase in KD. Only 1 case occurred during the campaign, which was distant from the second dose. Most surprising was the rate of absenteeism of 3% to 5.7% of children and adolescents, which is quite substantial and affects the societal cost of 4CMenB.

In conclusion, the results suggest direct protection during the 18 months following the administration of the first dose of 4CMenB. There is no evidence of indirect or herd protection in adults. A decrease in incidence also occurred in the rest of the province. During the mass campaign in the Saguenay-Lac St Jean Region, the safety profile of the 4CMenB vaccine was as expected. In terms of local reactions, vaccinees complained that this vaccine was more painful than other vaccines. On the short-term, the vaccine seems to be effective. Duration of protection remains unknown.

Discussion Points

Dr. Karron wondered whether there are any data on the prophylactic use of antipyretics or non-steroidal anti-inflammatories on the safety profile and / or immunogenicity of the vaccine, given the information about absenteeism and pain.

Dr. De Serres replied that because he had just 15 minutes, he eliminated his sides about that. They recommended anti-pyretic use. Approximately 80% of children took antipyretics. Below 2 years of age, it was 90% plus. The effect reported was with antipyretics. Immunogenicity was not assessed; however, a greater impact was observed with the first dose in terms of reducing fever. The reduction was about 44% with the first dose and was smaller with the second dose. An impact was observed among different age groups, but not above 11 years of age.

Dr. York added that because this was an older age group and fever is observed a very low percentage of the time, no studies were set up to assess whether there would be reductions in immune responses based on use of antipyretics. Reporting of whether antipyretics were used was assessed, but not to that extent. Prophylactic use would not be expected in the age group in the studies.

Dr. Stephens asked for Dr. De Serres' for his thoughts about why the disease disappeared in the rest of the province, particularly given that a herd immunity effect was not observed.

Dr. De Serres said that he thought meningococcal in general and MenB in particular have epidemic cycles with long waves. It is possible that this outbreak occurred on the declining side of the current surge. However, he said he had no good explanation for why this region was specifically affected compared to other regions. Everyone has asked this question, but it is not possible to provide a sound response at this time.

Dr. Moore noted that absenteeism is intriguing to follow, but this finding is not typically reported. She wondered whether Canada had experience with other vaccines for which absenteeism following immunization was assessed to which this could be compared.

Dr. Serres replied that they do not. Because of the outcome they selected to follow with active surveillance, and they acquired this information. However, there are no data about absenteeism in the overall vaccination program.

Dr. Bennett asked whether they have baseline rates of absenteeism.

Dr. De Serres responded that they do not, but they assessed absenteeism occurring during Days 1 and 2 compared to what occurred during the rest of the week. That is an unusual way to set the baseline.

Dr. Rubin asked whether the denominators included just the people who responded from among those who provided their email address, or included the entire population.

Dr. De Serres indicated that the results he provided were for those who responded with their email address.

Regarding the data suggesting that there might be an increase of absenteeism or medical consultation post-vaccination after a subsequent dose, Dr. Rubin asked whether they were able to put some error bars around that and if that might have any implications for revaccination.

Dr. De Serres replied that they did not put the bars on this. Studies were conducted in younger children who received more than two doses, and for which there may be some answers. But it is not clear whether that would be the same in someone who received two doses as an adolescent and a booster dose 5 to 10 years later. He has not seen any data about that.

Ms. Pellegrini noted that coverage rates among children were extremely impressive. She wondered whether they were able to execute the school-based vaccination campaign with the existing infrastructure or if additional public health personnel or others were tasked for that campaign.

Dr. De Serres responded that the existing infrastructure was utilized. However, some people were engaged in other nursing work with the public health system who were rerouted for a few weeks to help out.

Considerations for Use of MenACWY Vaccines in HIV-Infected Persons

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

During this presentation, Ms. MacNeil reviewed the use of meningococcal conjugate vaccine in human immunodeficiency virus (HIV)-infected persons. She summarized the evidence of increased risk for meningococcal disease in HIV-infected persons, MenACWY vaccine response in HIV-infected adolescents, and other considerations.

In terms of background, HIV is an established risk factor for several bacterial infections. A growing body of evidence supports an increased risk of meningococcal disease among HIV-infected persons. ACIP does not currently include HIV-infected persons in the recommendations for routine vaccination of persons at increased risk of meningococcal disease. However, if an HIV-infected person aged 2 years of age or older is vaccinated, he / she should receive a 2-dose primary series.

Data on HIV and meningococcal disease has been limited historically. An analysis of surveillance data from 1988-1993 from the 8-county metropolitan area of Atlanta found that HIV-infected adults had a nearly 24-fold increased risk of meningococcal disease¹. More recently,

the Group for Enteric, Respiratory, and Meningeal disease Surveillance in South Africa's (GERMS-SA)² study reported that 45% of 308 meningococcal disease patients were HIV-infected, the age adjusted relative risk was 11.3 (95%CI 8.9-14.3), and that the case-fatality ratio among HIV-infected cases was 20% versus 11% among HIV-uninfected cases [¹Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. *Ann Intern Med.* 1995; 123:937-40; ²Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al; Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA). Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. *AIDS.* 2010; 24:1351-60].

Expanded chart reviews were completed for HIV-infected meningococcal disease cases reported through the Active Bacterial Core surveillance (ABCs) system from 2000-2008. Incidence calculations from this analysis are limited to cases that met the CDC AIDS surveillance case definition, because name-based HIV reporting was not available in all of the states during the study years. In terms of the findings, 33 HIV-infected meningococcal disease cases were reported in ABCs during 2000-2008. Of those cases, 70% were caused by serogroup C, W, or Y. In the 7 years since this review has been completed, an additional 12 cases of meningococcal disease have been reported in HIV-infected persons in ABCs during 2009-2015. Of those cases, 83% were caused by serogroup C, W, or Y [Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation*].

HIV-related clinical data were collected on meningococcal cases with HIV-infection as part of the expanded chart review. In general, patients presented with a wide range of CD4 counts and several met the CDC AIDS surveillance case definition. The majority were also currently taking antiretroviral therapies at the time of meningococcal disease presentation. Of the cases, 17 met the CDC AIDS surveillance case definition and were included in the incidence calculations. Meningococcal disease incidence among persons with AIDS was 3.5/100,000 compared to 0.3/100,000 among persons not meeting the CDC AIDS case definition, resulting in a rate ratio of 12.9. In this study, an increase in risk was observed for both HIV-infected men and women and the rate ratio among men was not significantly different than that among women [Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation*].

In New York City, meningococcal surveillance data from 2000-2011 was matched to death and HIV registries. As part of this study, an age-matched case-control analysis was also performed among HIV-infected persons and included a subset of cases with CD4 count and viral load measurements near the time of meningococcal disease. A total of 40 HIV-infected cases were reported in New York City during 2000-2011. Of those cases, 87% were caused by serogroup C, W, or Y. The incidence of meningococcal disease among persons infected with HIV was calculated. Incidence was 3.4/100,000 in HIV-infected persons compared to 0.34/100,000 among HIV-uninfected persons, for a risk ratio of 10. A higher case fatality ratio was observed among HIV-uninfected cases compared to HIV-infected cases. The risk of meningococcal disease decreased during the study period for both HIV-infected and HIV-uninfected persons in New York City. Meningococcal disease incidence among HIV-infected persons decreased from 4.7/100,000 in 2000-2002 to 1.9/100,000 during 2009 through 2011. In the case-control analysis among persons infected with HIV, patients with meningococcal disease were 5.3 times as likely as age-matched controls to have low CD4 counts and 4.5 times more likely to have

high viral loads [Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. *Ann Intern Med.* 2014; 160:30-38].

The most recent study, which is from the United Kingdom (UK), assessed risk for meningococcal disease among HIV-infected children and adults during 2011-2013. Incidence of meningococcal disease was 6.6/100,000 in HIV-infected persons compared to 1.5/100,000 among HIV-negative persons, for a risk ratio of 4.5 [Simmons RD. et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. *BMC Med.* 2015; 13: 297].

All but one of the cases in HIV-infected persons occurred in adults 16 through 64 years of age, which meant that there was a 22.7-fold increased risk for HIV-infected adults compared with HIV-uninfected adults. During 2011-2013, 14 HIV-infected cases were reported in the UK. Of these, 71% were caused by serogroup C, W, or Y. Most of the HIV-infected cases were aware of their HIV status and were receiving antiretroviral treatment. The most common clinical presentation was septicemia. Although intensive care admission was common, none of the HIV-infected patients died [Simmons RD. et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. *BMC Med.* 2015; 13: 297].

To summarize the epidemiologic data, there is an increased risk for meningococcal disease in HIV-infected persons. Among HIV-infected persons, low CD4 count or high viral load increases risk. In some studies, a similar increase in risk was observed for both HIV-infected men and women. However, overall risk is declining along with meningococcal disease incidence in the US. In HIV-infected persons, meningococcal disease is primarily due to serogroups C, W, and Y. Data on the case-fatality ratio for HIV-infected meningococcal disease cases is mixed.

Regarding vaccine response for HIV-infected persons, the data on HIV-infected adolescents is based on approximately 300 adolescents included in this study. The proportion of HIV-infected adolescents with more than a 4-fold increased risk in rSBA titers at week 4 was 52% for serogroup C and 53% for serogroup Y. For HIV-infected adolescents who received a single dose of MenACWY-D, the response was significantly lower for those with either a low CD4 count or a high viral load [Phase I/II, Open-Label Trial of Safety and Immunogenicity of Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Human Immunodeficiency Virus-Infected Adolescents. *Pediatric Infectious Disease Journal.* 29(5):391-396, May 2010].

In terms of GMTs against serogroup C at 0, 4, 24, 28, and 72 weeks, despite a second dose of vaccine at 24 weeks, response rates remained low through 72 weeks for those with low CD4 counts at study entry. For those with higher CD4 counts at study entry who received one dose of MenACWY-D, after an initial response at 4 weeks, GMTs waned rapidly. Persons with higher CD4 counts at study entry who received two doses of MenACWY-D, after an initial response at 4 weeks, GMTs waned rapidly after both Dose 1 and Dose 2. Overall, the response to serogroup Y is higher than for serogroup C, but the same pattern of rapidly waning titers is observed. Regarding the percent of subjects who still had antibodies at week 72 or approximately 1.5 years after 1 or 2 doses of MenACWY-D, the primary study endpoint was the percent of subjects with rSBA titers $\geq 1:128$. For serogroup C, titers waned to 21% to 35%. For serogroup Y, titers waned to 63% to 71%. The proportion of subjects with rSBA titers $\geq 1:8$ are slightly higher than titers of $\geq 1:128$ [Immunogenicity and Safety of 1 vs 2 Doses of Quadrivalent

Meningococcal Conjugate Vaccine in Youth Infected with Human Immunodeficiency Virus. *The Journal of Pediatrics*. 161(4):676-681. October 2012].

In summary, seroresponse to MenACWY-D conjugate vaccine in HIV-infected adolescents is suppressed compared to healthy adolescents. Low CD4 count or high viral load suppresses response further. In addition, the immune response to MenACWY-D wanes rapidly. Although a boost response is seen to a second dose, duration of protection will likely be an issue.

In addition to the evidence of increased risk for meningococcal disease in HIV-infected persons and meningococcal vaccine response, the WG also discussed other programmatic considerations for the use of meningococcal vaccines in HIV-infected persons. There are approximately 1.2 million persons 13 years of age or older living with HIV in the US¹. An additional 50,000 new HIV infections occur each year¹. Only about 50% of persons diagnosed with HIV receive regular HIV care². Of those retained in care, approximately 89% are prescribed antiretroviral therapy and 77% achieve viral suppression². For HIV-infected persons in care, HIV clinics may already be administering other vaccines recommended for HIV-infected persons. HIV-infected persons in care may be more likely to have CD4 counts and viral loads that are favorable for immunogenicity to the meningococcal vaccine [¹ <http://www.cdc.gov/hiv/statistics/overview/ata glance.html>; ² <http://www.cdc.gov/hiv/prevention/programs/pwp/linkage.html>].

Although vaccine coverage data specifically for HIV-infected adults is sparse, coverage with influenza, hepatitis B, and hepatitis A vaccine has been estimated for HIV-infected persons in care through the HIV Outpatient Study (HOPS). Among active patients in HOPS clinics, annual influenza vaccination rates were between 26% and 51% during 1999-2013^{1,2}. Additionally, 32% of eligible patients were vaccinated with at least 1 dose of hepatitis B vaccine, and 23% of eligible patients were vaccinated with at least 1 dose of hepatitis A vaccine during 1992-2002³ [¹Durham MD. Rates and correlates of influenza vaccination among HIV-infected adults in the HIV Outpatient Study (HOPS), USA, 1999–2008. *Preventive Medicine* 53 (2011) 89–94; ²Durham MD. Seasonal Influenza Vaccination Rates in the HIV Outpatient Study—United States, 1999–2013. *CID* 60 (2015) 976-7; ³Tedaldi EM. Hepatitis A and B Vaccination Practices for Ambulatory Patients Infected with HIV. *CID* 38 (2004) 1483-9].

The current consideration is for use of MenACWY conjugate vaccine only. In HIV-infected persons, risk appears to be due primarily to serogroups C, W, and Y. No safety or immunogenicity data is available for use of serogroup B meningococcal vaccines in HIV-infected persons. The current consideration includes all HIV-infected persons 2 months of age and older. Because increased risk from HIV-infection is life long, regular booster doses would be recommended for HIV-infected persons similar to other groups at increased risk.

AAP currently recommends MenACWY vaccine for HIV-infected children 2 years of age and older. Here is the language from the 2015 Red Book addressing the use of MenACWY vaccine in HIV-infected children:

- The risk of meningococcal disease in HIV-infected individuals is not well defined. People with HIV infection who are 2 years or older should receive a 2-dose primary series at least 8 weeks apart.

Current AAP and ACIP recommendations are not harmonized for HIV-infected children 2 years of age and older.

Regarding risk of meningococcal disease in MSM, of meningococcal disease cases among MSM for whom HIV status is known, the majority (59%) are HIV-infected. This makes disentangling the relative contribution of HIV and MSM status to the increase in risk challenging in MSM populations. However, vaccinating HIV-infected persons offers an opportunity also to potentially impact meningococcal disease risk among MSM.

In summary, a growing body of evidence supports an increased risk of meningococcal disease among HIV-infected persons. The incidence of meningococcal disease in HIV-infected persons is elevated and ranges from 3.4 to 6.6/ 100,000 persons. That translates to a relative risk of 4.5 to 12.9 compared to HIV-uninfected persons. In HIV-infected persons, risk is primarily due to serogroups C, W, and Y. Suboptimal vaccine response and programmatic challenges may limit the impact of vaccination on disease burden in HIV-infected persons. However, HIV-infected persons represent a relatively small, defined population who are already recommended to receive specialized medical care.

There is strong support from the WG for including HIV-infected persons in the groups at increased risk of meningococcal disease. The primary considerations for the WG included the evidence of increased risk of meningococcal disease in HIV-infected persons, the potential benefits of vaccination in the targeted group, and the fact that HIV-infected persons represent a population who are already receiving specialized medical care. However, the WG also recognizes that there is suboptimal vaccine response and likely issues with duration of protection in HIV-infected persons, which may limit the impact of vaccination in this group.

Listed below are the current recommendations for use of MenACWY conjugate vaccine in persons at increased risk for meningococcal disease:

- Routine vaccination of persons aged ≥ 2 months at increased risk of meningococcal disease, including:
 - Persons with persistent complement component deficiencies¹
 - Persons with anatomic or functional asplenia²
 - Microbiologists who are exposed routinely to isolates of *Neisseria meningitidis*
 - Persons at risk during a community outbreak attributable to a vaccine serogroup
 - Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
 - Unvaccinated or incompletely vaccinated first-year college students living in residence halls
 - Military recruits

¹Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H;

²Including sickle cell disease].

The WG proposes adding persons with HIV infection to the list of groups recommended for routine vaccination with MenACWY vaccine. Guidance for use of MenACWY for HIV-Infected persons would be as follows:

- Persons aged ≥ 2 years with HIV who have not been previously vaccinated should receive a two dose primary series of MenACWY (0, 2 months)
 - Multi-dose schedule for children aged < 2 years
- Persons with HIV who have been previously vaccinated should receive a booster dose at the earliest opportunity, and then continue to receive boosters at the appropriate interval
 - Current booster recommendations: 3 years if age < 7 years at previous dose and 5 years if age ≥ 7 years at previous dose

A cost-effectiveness analysis and a GRADE analysis for routine use of MenACWY in HIV-infected persons 2 months of age and older are currently in progress and will be shared with ACIP as they are completed.

ACIP members were asked to consider the following questions for discussion:

- In addition to the cost-effectiveness analysis and GRADE, are there additional analyses that ACIP would like to see?
- Is ACIP in agreement with the Meningococcal Vaccines Work Group proposal to consider routine use of MenACWY in HIV-infected persons ≥ 2 months of age?

Discussion Points

Based on such a dramatic decline in such a short period of time, Dr. Moore asked whether there was discussion in the WG about potentially reducing the interval for booster doses among HIV-infected adults to 3 years instead of 5 years, or if there are 5-year data on their antibody titers.

Ms. MacNeil replied that the WG did not discuss moving to a shorter interval, given that they were thinking about simplicity and harmonization with the current recommendations for other groups at increased risk. However, they could certainly discuss a shorter interval.

Dr. Messonnier asked whether there are any data on more than a single vaccination. Following the rationale Dr. Moore used, if the interval was shortened, what would be done after that. That is, are there any data on multiple doses of conjugate vaccines?

Ms. MacNeil responded that there are not. For HIV-infected adolescents, the two studies she presented are the only data they have for either vaccine.

Given the conversation, Dr. Baker (IDSA) suggested that when the cost-effectiveness study is done, boosting on a 3- or 5-year schedule should be considered. Medically, it makes more sense to have a 3-year interval. Programmatically, it is a nightmare. However, this might be informative.

Dr. Riley asked whether there are any data on co-administration with other vaccines, particularly in this population.

Ms. MacNeil responded that while there are not for HIV-infected persons in particular, there are data for healthy adolescents.

Dr. Bennett emphasized that the rates of vaccination among HIV-infected individuals were incredibly low, especially since they are among people who are receiving care. She asked whether the WG had considered how this vaccine would be implemented among those groups, given the existing poor rates.

Ms. MacNeil indicated that one reason the WG was considering HIV-infected persons was because HIV care providers are already providing other vaccines and could provide this vaccine as well. Rates of vaccination in the general adult population are relatively similar.

Dr. Romero asked whether there are any data on the AEs associated with revaccination of younger children, and why there is a lower mortality rate in HIV-infected individuals.

Dr. Messonnier responded that there are some CDC data, but it is comparable to healthy individuals.

Ms. MacNeil responded that in the two US studies and the UK, the case fatality ratio is lower for HIV-infected persons. There is a variety of reasons. It could be that people get into care more quickly, they are being treated more aggressively perhaps because they are immunosuppressed, the disease process is not as severe, et cetera.

Meningococcal Disease Among MSM in the US: January 2012-June 2015

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For this presentation, Dr. Folaranmi discussed the results of an analysis of surveillance data on meningococcal disease among MSM in the US, including instances of community-based outbreaks or clusters of invasive meningococcal disease (IMD) among MSM. The first reported outbreak of IMD among this group occurred in Toronto in 2001. The first reported US outbreak occurred in Chicago in 2003. Subsequent clusters/outbreaks have occurred in New York City (2010-2013), Los Angeles County (2012-2013), Paris (2013), Belgium (2013), Berlin (2013), and Chicago (2015). All outbreaks were caused by serogroup C ST-11 clonal complex, a common invasive strain of *Neisseria meningitidis* and a frequent cause of outbreak cases. These clusters had between a 25% to 50% case fatality ratio. These ratios were high when compared to 10% to 15% case fatality ratio seen in the general US population. Similarly, 68% and 75% of the cases in New York City and the most recent Chicago outbreak were HIV-infected. These percentages were also high compared to an HIV prevalence of 19% observed in the general US MSM population.

These instances of community-based outbreaks and clusters have raised the question as to why MSM have an increased risk for IMD. Therefore, the study objectives were to:

- Identify IMD cases reported among MSM within the observation period
- Describe IMD epidemiology and case characteristics among MSM and non-MSM
- Assess rates of IMD and prevalence of known IMD risk factors among MSM
- Estimate the relative risk of IMD among MSM compared to non-MSM
- Estimate the relative risk of IMD among HIV infected MSM compared to HIV uninfected MSM

Regarding the methods used in the analyses, meningococcal disease surveillance data are reportable in the US. All US states and territories have passive reporting that includes all confirmed and probable cases. When a meningococcal case is reported, an intensive case investigation is conducted by the health department to identify close contacts who may require prophylaxis for the disease. Information on the sex of sex partners and HIV status may be captured in case notes, but is not usually reported through surveillance.

To address the first objective to identify IMD cases that occurred among MSM, CDC posted two Epi-X calls for cases posted in May 2013 and June 2015. State health departments, including Washington, DC and New York City, were asked to review all meningococcal disease cases among men 18 through 64 years of age occurring during the study period of January 2012 through June 2015. If MSM cases were identified, case investigation and risk factor data were abstracted. If no MSM case was identified, zero report was requested. After data abstraction, all IMD cases were classified into five groups:

- MSM cases in New York City (MSM-NYC)
- MSM cases in Los Angeles County (MSM-LAC)
- MSM cases in Chicago, including those from the metro area (MSM-Chicago)
- MSM sporadic cases and all other MSM cases (MSM-Others)
- Men not known to be MSM (Non-MSM)

Cases within the three jurisdictions (New York City, Chicago, Los Angeles County) were grouped separately because they reported an outbreak or cluster during the observation period. Not all MSM cases that occurred within the three jurisdictions within the observation period were part of a cluster or outbreak. However, for analysis, all cases that occurred within each jurisdiction during the observation period were grouped together.

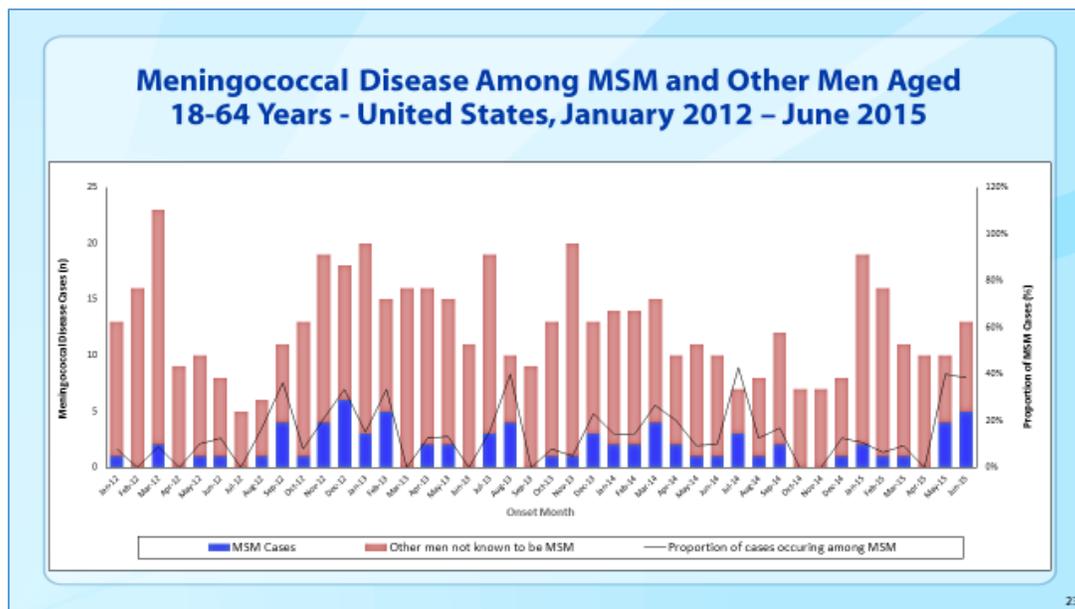
To address the other four objectives, the denominator was estimated for the disease rate calculation. MSM was defined as “sex with another man in the past five years.” Similarly, the MSM population per jurisdiction was defined as the “population of men aged 18 through 64 years X MSM prevalence.” To estimate the population of men 18 through 64 years of age, the 2012 population estimate data of the American Community Survey (ACS) was utilized. The ACS is a yearly survey conducted by the US Census Bureau. Using the survey data, the number of men 18 through 64 years of age in the US was estimated to be 96,618,006.

To estimate MSM prevalence per jurisdiction, data were used from a recent study conducted by subject matter experts (SMEs) from CDC’s Division of STD Prevention (DSTDP) and Emory University. The estimates were 6.8% for Los Angeles County, 7.3% for New York City, 6.6% for Chicago, and 3.3% for other US jurisdictions. The overall prevalence of MSM in the US was estimated to be 3.9% [Jeremy Grey, Kyle Bernstein et al, 2015. Estimating the population sizes of men who have sex with men (MSM) in the U.S. states and counties using data from the American Community Survey. Manuscripts under Review].

Estimation of the HIV-infected MSM population in each jurisdiction was based on 2012 HIV surveillance data^{1,2,3,4}. The HIV uninfected MSM population per jurisdiction was calculated using the formula: (Population of Men Aged 18-64 Years * MSM Prevalence) – Surveillance Estimate of HIV Infected MSM. MSM-Others' Cases Estimate was calculated using the formula: Total U.S. Estimate – (LAC+ NYC + Chicago Estimate). HIV status data were not available among non-MSM cases¹<http://www.nyc.gov/html/doh/downloads/pdf/dires/surveillance-report-dec-2013.pdf>;
²https://www.cityofchicago.org/content/dam/city/depts/cdph/HIV_STI/2014HIVSTISurveillanceReport.pdf;
³ <http://publichealth.lacounty.gov/wwwfiles/ph/hae/hiv/2012AnnualHIVSurveillanceReport.pdf>;
⁴<http://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-vol-25.pdf>].

Regarding the results, 527 meningococcal disease cases were identified overall among men 18 through 64 years of age reported to CDC between January 2012 and June 2015. Of these cases, 74 (14%) were identified as MSM from 17 states and 453 (86%) cases were among non-MSM from 47 states and Washington, DC. Before analyzing the data by the jurisdictional classifications described earlier, the age group and MSM status was first assessed for all case patients to understand whether the case patient would have been eligible for vaccination through the vaccination platform. Case patients 18 through 24 years of age accounted for 31% of the non-MSM cases, case patients 26 through 35 years of age accounted for 43% of the MSM cases, case patients 36 through 45 years of age accounted for 19%, case patients 46 through 55 years of age accounted for 16%, and case patients 56 through 64 years of age accounted for 1%. Overall, the median age for all MSM cases was 31 years and the median age for non-MSM cases was 34 years.

This graphic shows the frequency of meningococcal disease cases by month within the observation period:



Subsequently, the data were analyzed by jurisdiction. Of the 74 MSM cases identified in this study, 23, 14, and 11 MSM cases occurred in New York City, Los Angeles County, and Chicago, respectively. Of the cases, 26 were classified as MSM-Other because they were sporadic cases in states and geographic areas outside of the three jurisdictions.

The majority of cases in the MSM and non-MSM categories were non-Hispanic. However, an equal proportion of Hispanic and non-Hispanic cases were observed in Los Angeles County. The majority of the MSM-Others, MSM-LAC, and Non-MSM categories were White. However, Blacks accounted for a greater proportion of the cases from New York City and Chicago.

Clinically, meningitis and bacteremia were the two most common presentations. The clinical presentations reported are not mutually exclusive. About 10% of all MSM cases had both meningitis and bacteremia, or either of them and another clinical presentation such as septic shock or pneumonia. Therefore, the percentages may exceed 100%. Among the MSM cases within MSM-Others, MSM-NYC, MSM-LAC, and MSM-Chicago case fatality ratios were observed of 39%, 26%, 36%, and 27% respectively. Among non-MSM cases, the case fatality ratio was 24%.

The serogroups included in MenACWY vaccines accounted for most of the MSM cases with known serogroup information. However, serogroup C was predominated among MSM cases. On the other hand, a wide distribution of serogroups is observed among the non-MSM cases. Serogroup information for about 16% of non-MSM cases was not available. Between 36% and 65% of the MSM cases were HIV-infected. Overall, 59% of all MSM cases with known HIV status were HIV-infected. When the data were restricted to only serogroup C, W, and Y cases, the overall HIV prevalence among MSM was 58%. Across all case patients, serogroup C cases were 1.5 times more likely to have a fatal outcome. When comparing case fatality to MSM status, a significant association was not observed between them. However, outcome data was unknown in 15% of the cases of the non-MSM case patients. Similarly, a significant association was not observed between case fatality and HIV status among MSM. Similar findings were observed when data were restricted to only serogroups C, W, and Y cases.

Next, behaviors reported among the MSM cases were assessed. Of MSM case patients, 33% reported smoking; 49% reported use of recreational drugs, including marijuana; 47% reported multiple sexual partners or engaged in anonymous sex; 61% reported using dating apps or websites to meet partners; and 21% had a history of recent travel. There are variations in the number of cases assessed due to limited availability of data reporting these behaviors.

Regarding the risk of IMD among MSM and non-MSM, first the annualized incidence rates among MSM were estimated and compared those to the incidence among non-MSM within each jurisdiction. Overall, the incidence among MSM in the US was 0.59 cases/100,000. This is compared to 0.15 cases/100,000 among non-MSM. Thus, MSM have 4 times the incidence risk of IMD compared to non-MSM. MSM within the MSM-Others category have 1.8 times the incidence risk for IMD when compared to non-MSM cases. The three MSM cluster categories have a relative risk of IMD ranging from 14.6 to 23 when compared to non-MSM cases.

Next, incidence rates were compared between HIV-infected and HIV-uninfected MSM. Overall, it was observed that HIV-infected MSM had 10.1 times the risk of IMD compared to HIV-uninfected MSM cases. It was observed that MSM cases within the MSM-Others category had a higher relative risk for IMD when compared to HIV-uninfected MSM cases. On the other

hand, the relative risk for IMD among HIV-infected MSM within the three cluster categories ranged from 4.1 to 6.8 compared to HIV-uninfected MSM.

IMD annualized incidence rates among HIV-infected MSM and other men were then compared within each jurisdiction. *Other male cases* is defined as “all non-MSM and HIV-uninfected MSM cases combined.” Overall, HIV-infected MSM have 16 times the risk of IMD compared to all Other Male cases. HIV-infected MSM within the MSM-Others category have 6.7 times the risk of IMD compared to other men cases; whereas, within the cluster categories, HIV-infected MSM have a relative risk ranging from 22.5 to 34 when compared to Other Male cases. In summary of relative risk when the data was restricted to only serogroups in MenACWY vaccines, an increase was observed in the overall relative risk of IMD among MSM from 4 to 7.3 when compared with non-MSM cases having serogroup C, W, and Y infections. The relative risk for IMD among MSM compared to non-MSM in the MSM-Others category was 3.3. The relative risk for IMD among the cluster cases ranged from 21.3 to 38.9 when compared to non-MSM cases.

HIV-infected MSM with serogroup C, W, and Y infection had a relative risk of 9.2 when compared to the HIV-uninfected MSM overall. However, within the MSM-Others category, the relative risk for IMD increased to 10.3 when compared to HIV-uninfected MSM. A decline was noted in IMD risk among the cluster cases with a relative risk that ranged from 1.8 to 7.7 when compared to HIV-uninfected MSM cases. HIV-infected MSM had a relative risk of 25.7 and 6.7 in the overall and MSM-Others category respectively. Among the cluster cases, the relative risk ranged from 12.9 to 48.4 when compared to Other Men cases. Additionally, HIV-uninfected MSM were compared to non-MSM cases only. Overall, a relative risk of 3.0 was observed among HIV-uninfected MSM when compared to non-MSM cases. On the other hand, the relative risk in the MSM-Others category was 0.97 when compared to non-MSM cases. Among the cluster MSM cases, the relative risk for IMD among HIV-uninfected MSM ranged from 9.3 to 22.8. Finally, it was observed that IMD risk diminished among MSM in non-outbreak settings when HIV infection is removed from the equation as shown by the decline in relative risk from 3.3 to 0.97.

Regarding the salient issues from the analyses, MSM had a higher incidence in terms of IMD risk among MSM in both outbreak and non-outbreak settings compared to the general non-MSM male population. It was noted that serogroup C accounted for the majority of the MSM cases reported during the observation period. This is consistent with all previous outbreaks reported among MSM; however, the reason for this occurrence remains unclear.

Similarly, HIV prevalence among MSM with IMD was high at 59% when compared to the general HIV prevalence of 19% among MSM in the US.¹ It is unclear why there is no significant association observed between HIV status and case fatality among the MSM cases in the analysis. This may be related to access to HIV care and the care-seeking behavior of the case patients. Unfortunately, there are no data on viral load or CD4 count status that would allow for a stratified analysis. Based on the analyses, it was observed that being MSM combined with HIV infection conferred a higher risk for meningococcal disease than being MSM alone. Similarly, HIV infection seems to be responsible for most of the increased risk observed among MSM-Others [¹Prevalence and Awareness of HIV Infection Among Men Who Have Sex With Men—21 Cities, United States, 2008. *Morbidity and Mortality Weekly Report (MMWR)*. 2010;59(37):1201-7].

In terms of high risk behaviors among MSM with IMD, a high prevalence of recreational drug use among MSM with IMD of 48% was observed compared with a recreational drug use prevalence of 10%¹ among US adults. A high prevalence of smoking was observed among MSM with IMD of 30% compared with an 18%² prevalence among US individuals 12 years of age and older. The reasons for increased IMD risk in outbreak settings are unclear, but may include an increase in the number of contacts and/or higher-risk behaviors. MSM with these behaviors may also be at increased risk of being infected with HIV [1Jamal A, Agaku I, O'Connor E, King B, Kenemer J, Neff L. Current Cigarette Smoking Among Adults — United States, 2005–2013. (MMWR). 2014;63(47):1108-12; 2Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. 2015].

The analysis is not without limitations. Ascertainment of MSM and HIV status during case investigations is still a challenge. The estimates are conservative, and it is likely that misclassification of MSM status may underestimate the rate. Systematic collection of information on sexual behavior by health departments will help reduce misclassification in future analyses. Similarly, IMD incidence may vary depending upon the accuracy of denominator estimates. CDC recommended that all health departments routinely assess MSM and HIV status for cases that occur in men 16 years of age and older. It remains unclear how broadly and completely this recommendation has been implemented. Given the lack of a proper control population and missing/incomplete data, assessment of risk factors is difficult.

The key messages from this analysis are that MSM had increased incidence of IMD, but the overall incidence remains low in both outbreak and non-outbreak settings compared to the general population. Incidence increases with HIV infection and was higher among serogroups C, W, and Y infections in case patients. Also, most MSM case patients are in the older age groups and would not have been vaccinated as part of the current adolescent vaccination platform for MenACWY.

Considerations for Use of MenACWY Vaccines in MSM

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Centers for Disease Control and Prevention**

Ms. MacNeil presented a summary of the WG discussions on meningococcal disease among MSM. The ongoing clusters and outbreaks of meningococcal disease among MSM have increased awareness of meningococcal disease cases occurring in MSM. However, understanding the risk for meningococcal disease in MSM is challenging given the associations with HIV-infection and higher-risk behaviors and the limited data available to evaluate and tease apart these potential risk factors.

During the clusters and outbreaks among MSM in New York City, Los Angeles County, and Chicago, MenACWY vaccines were used as part of outbreak response, with local vaccination recommendations targeting either a subgroup of MSM¹ or all MSM. In these jurisdictions, vaccination recommendations for MSM continue to remain in place. ACIP recommendations support the use of meningococcal vaccines in response to outbreaks. However, these reactive vaccination campaigns often require considerable resources and effort on the part of the affected health department. Despite these challenges, the initial vaccination response was demonstrated to be cost-effective in New York City² [1MSM, regardless of HIV status, who regularly have close or intimate sexual contact with men met through an online website, digital

application ("app"), or at a bar or party; ²Simons et. al. Cost-Effectiveness of Meningococcal Vaccination Among Men Who Have Sex With Men in New York City. *J Acquir Immune Defic Syndr.* 2016 Feb 1;71(2):146-54].

As the WG reviewed the available data on the epidemiology of meningococcal disease among MSM, the key discussion points were that outbreaks of meningococcal disease continue to occur among MSM; MSM had higher incidence rates than non-MSM in both outbreak and non-outbreak settings; and in non-outbreak settings, HIV infection appears to be the main driver of increased risk for MSM. The reasons for outbreaks among MSM are unclear, but may include close social networks, an increased number of contacts, and/or higher risk behaviors.

As presented earlier, it is estimated that approximately 3.9% of the US adult male population is MSM, which translates to a population size of approximately 3.8 million people. To evaluate the potential programmatic issues and challenges for vaccinating MSM with meningococcal vaccines, the WG looked at other vaccines currently recommended by ACIP for MSM or subgroups of MSM, including HPV, Hepatitis A, and Hepatitis B vaccines. These vaccines may be administered to MSM in a variety of settings and requires disclosure of MSM status to health care providers (e.g., primary care, STD clinics, et cetera).

The National HIV Behavioral Surveillance (NHBS) surveyed over 10,000 US adult MSM in 2014. Of these, 82.2% visited a health care provider in past year¹. Among HIV-infected MSM, 97% had used health care. Among other MSM, 80% had used health care. Approximately 80% disclosed MSM activity to a healthcare provider. The locations of usual care included doctor's office or HMO (55.6%), clinic or health center (28.1%), hospital emergency room (13.5%), and other (2.4%) [¹Unpublished data, courtesy S. Oliver and E. Meites].

Many STD clinics providing health care to populations which include MSM offer vaccines, including meningococcal vaccine. In a survey from the National Coalition of STD Directors (NCSD) of 78 STD clinics from 46 US states, three-quarters stocked at least one vaccine and nearly half stocked a meningococcal vaccine [Unpublished data, courtesy E. McGinnis and NCSD].

The NHBS survey also provides estimates of HPV vaccine coverage among MSM. In the 2011 NHBS survey¹, only 5% of MSM 18 through 26 years of age reported receiving at least 1 dose of HPV vaccine, with 13% coverage among HIV-infected MSM. In late 2011, the ACIP recommendation for HPV vaccine for males and MSM was changed from permissive to routine. In the next NHBS cycle in MSM in 2014², 17% of MSM 18 through 26 years of age reported receiving any HPV vaccine, with 37% coverage among HIV-infected MSM [¹Meites, E et al. HPV vaccine coverage among men who have sex with men – National HIV Behavioral Surveillance, United States 2011; Vaccine 2014; ² Unpublished data, courtesy S. Oliver and E. Meites].

After reviewing the available data, no consensus was reached by the WG for including MSM or a particular sub-group of MSM in the groups at increased risk for meningococcal disease. The primary reasons include the low absolute risk for meningococcal disease currently in non-outbreak settings and potential programmatic challenges for implementing a vaccination program in MSM. The WG feels that continued study is needed to better understand transmission and risk factors for this population. In terms of meningococcal disease cases, the prevalence of HIV is high, with nearly 60% of MSM meningococcal diseases cases co-infected with HIV. This is compared to an overall HIV prevalence in the general US MSM population of 19%¹. Therefore, a recommendation for vaccination of HIV-infected persons could address an

important proportion of MSM meningococcal disease risk [¹Prevalence and Awareness of HIV Infection Among Men Who Have Sex With Men—21 Cities, United States, 2008. *Morbidity and Mortality Weekly Report (MMWR)*. 2010;59(37):1201-7].

MenACWY vaccines will continue to be used to vaccinate at risk populations if additional outbreaks of meningococcal disease among MSM occur. In addition, enhanced surveillance for cases of meningococcal disease in MSM and HIV-infected persons is ongoing. Updates will be shared with the WG and ACIP as additional data become available.

Discussion Points

In terms of changing the recommendations, it seemed key to Dr. Kempe to understand how much of the MSM risk is due to HIV. Dr. Folaranmi's slide 49, "Relative Risk of IMD among MSM with Serogroup C, W, and Y Infections" seemed to contain the most salient information. There are no 95% confidence intervals. The last line appeared to be the comparison between non-HIV MSM with non-MSM. She asked Dr. Folaranmi to expand on this.

Dr. Folaranmi explained that for the first line, the general MSM population was compared to the non-MSM population. The goal was to tease out the effect of HIV infection, which is why HIV-infected MSM were compared to non-MSM. The risk is almost 1, meaning that the majority of risk observed among MSM compared to non-MSM is likely due to HIV infection in the sporadic setting. That effect was not seen in the clusters. Most of the cases in the clusters were due to outbreaks.

Regarding why more is not known about risk factors for meningococcal disease in MSM and potential problems with not having proper controls, Dr. Reingold pointed out that many case-control studies have been conducted on MSM to assess numbers of partners, going to bath houses, and various other risk factors for HIV infection. He was curious as to whether or not having controls was a resource problem or if there was a plan to conduct case-control risk factor studies. In terms of this type of analysis, he suggested that it might be better to calculate population attributable risks instead of simply trying to compare relative risks in terms of trying to sort out how much of this is HIV and how much is MSM.

Dr. Folaranmi replied that the population attributable risk was not calculated, but it is something to consider for further analysis. With respect to the control group, the group referred to as non-MSM cannot be confidently said to be all non-MSM, which is why the term "Other men not known to be MSM" is used. They are not a perfect control group to use to analyze the data. He did not know of any studies that assessed risk factors between MSM and non-MSM. One study was conducted in New York City that attributed one possible risk factor, STDs in the past year before infection and HIV infection. Those two risk factors were identified in that particular case-control study. CDC's population was very small, comparing approximately 50 MSM cases to about 50 controls.

Dr. Reingold clarified that he was talking about case-control studies comparing MSM who have meningococcal versus those who do not to assess risk factors among MSM (going to bath houses, number of sex partners, condom use, et cetera). Presumably, those studies could be conducted.

Ms. Martin (SME) responded that CDC has discussed conducting a risk factor study. Part of the problem is that the number of cases is low, so it would have to be a national study. New York City conducted a study, but their comparison group is somewhat different from the case group and raises some questions pertaining to the validity of the findings.

Ms. Pellegrini said she was struggling most with the limitations of ACIP's mandate. This is a very complex population with a lot of confounding risk factors. It is not clear whether vaccine is the right public health intervention to achieve this goal. Can IMD actually be reduced by reducing HIV infection, promoting condom use, et cetera? She wondered whether their CDC colleagues could discuss how these conversations occur within the agency, because she is very concerned about potentially sending a recommendation to Dr. Frieden and putting the agency in a position of deciding whether to support the recommendation and essentially divert public health resources to this less effective intervention simply because ACIP is not tasked with determining how to reduce meningitis.

To clarify any misunderstanding, Dr. Messonnier noted that the place the WG came to on this issue was not moving toward a vaccine recommendation. Given all of the complexities, they recognize that this is not what the current science says at this point. The larger issue is an interesting one. Before meningococcal vaccines were available, a number of studies evaluated smoking as a risk factor for meningococcal disease that found that active and passive smoking had an attributable risk of 25% to 30% of cases of meningococcal disease. However, no one was going to make passive smoking regulations based on this. Fortunately, there were many other drivers of that. This is a very specific, very small subgroup and it is difficult to determine whether that is going to drive the public health conversation. The team is working with those in the STD and HIV worlds' and this is part of it. However, Dr. Reingold and Ms. Pellegrini raised another important issue as well: Given the many other issues in this population, even launching research studies focused on this or nesting the issue in other studies is difficult.

Something that troubled Dr. Bennett regarded where the estimates for the percentage of the population that engage in MSM come from and whether they are accurate. This population may or may not want to disclose, and the rates in that population are quite dependent upon the denominator. Therefore, it concerned her that the denominator may be underestimated.

With respect to the outbreak comments, Dr. Moore thought in addition to the denominator having a significant effect on conclusions, the outbreaks themselves skew the perspective as this demonstrates. There is the allusion on slide 3 of Ms. MacNeil's second presentation to the fact that the outbreak response in New York City was demonstrated to be cost-effective. She requested that Dr. Zucker from New York City discussed what sort of cost-effectiveness they observed.

Dr. Zucker (NYC) said she would need to pull up the precise numbers to bring back to the group, but recalled that it was under \$100,000 and was within or less than the cost-effectiveness range used for the meningococcal recommendations. It was surprising to her from the New York City perspective that it was clear that HIV is an increased risk factor—the data supported that. They showed, at least in that setting, that it was cost-effective to conduct the vaccine campaign in the outbreak setting. Relative to what they just heard in terms of numbers and increased risk, having a recent vote with over \$1 million to prevent one case of IMD-B, perhaps they should have GRADE numbers to show what a national campaign would look like in terms of the cost-effectiveness for vaccinating HIV-infected persons whether it is

MSM or a subgroup. She was surprised that there was not more discussion about moving toward a routine recommendation, at least for some of the subgroups.

Ms. MacNeil indicated that the cost-effectiveness analysis performed for GRADE would be presented in June 2016 for HIV-infected persons.

Dr. Duchin (NACCHO) said he wanted to further explore some of the incidence numbers in the various sub-strata presented. For the HIV-infected cohorts, particularly in the three cities, the incidence rates are much higher than they are for adolescents for whom meningococcal vaccination is routinely recommended. Even for some of the HIV-uninfected populations, they are comparable. He requested further information about what the WG thought about that issue, and whether it would be appropriate to consider vaccination where it has been established that the rate of disease is so much higher than it is for other populations for whom the vaccine is already recommended.

Ms. MacNeil responded that the three jurisdictions that had outbreaks or clusters recommended vaccination of MSM, and those recommendations remain in place for those jurisdictions.

Dr. Duchin (NACCHO) asked whether she was saying that there would be a different policy for jurisdictions in which outbreaks are occurring versus where they have not yet occurred.

Ms. MacNeil replied that the WG did not discuss this because the recommendations are already in place in response to the outbreaks.

Dr. Baker (IDSA) congratulated the presenters for summarizing information that took days for her to hear repeatedly. This is very complex and difficult to tease out. It would be great to conduct a case-control study, but it would cost a prohibitive amount. She thinks the HIV data are very clear and compelling. The AAP recommended MenACWY many years ago when the vaccine became available to drop down to two years with booster doses. HIV-infected people is a subgroup. They are a larger subgroup than children born with congenital complement deficiencies, which are on the list of high risk individuals. When attempting to add, tear apart, figure out, or analyze MSM, it is complicated. She thinks the HIV data are clear and that a policy group should not care about what proportion are being vaccinated. Does ACIP recommend influenza vaccine for everyone 6 months of age and older? Yes. Is it a good policy decision? Yes. Do we have some groups that are well below 50%? Yes. It is not bad policy. ACIP is not in charge of implementing. There is no reason not to add vaccine to public health measures to reduce risk. Influenza vaccine recommendations are added to hand-washing, cough etiquette, and other measures. It is not either / or.

Dr. Zucker (NYC) clarified that New York City is focused on HIV-positive persons. A person is MSM, but is high risk MSM high risk as defined from an outbreak cluster in terms of increased used of looking for partners on apps. It is not a routine MSM recommendation.

Public Comment

Lynn Bozof
National Meningitis Association, Inc. (NMA)

Thank you. Hi. I'm Lynn Bozof, President of the National Meningitis Association (NMA). Most of you are familiar with my story of losing my son, Evan, to meningococcal disease as a college junior. I did not originally plan to speak at this meeting because there were no mening votes

scheduled. But, I'm getting constant phone calls and emails from people with major difficulties finding serogroup B vaccines. So, I felt I needed to say something. Then with the recent outbreak at Santa Clara University and the MenB case at Yale, this is obviously an issue that we still need to think about. Thank goodness there were no fatalities from those cases. The Category B recommendations seemed like a really great place to start. We saw people that wanted to fully protect their children who would just talk to their health care provider and let them know this is important to them. Unfortunately, that is really not working out. We hear from parents that their child's doctors aren't aware of the MenB recommendations. Even fewer are carrying it, and they don't know where to send people for it. The other day, we had a workshop and one of the moms whose son contracted serogroup B at Princeton had to make 12 phone calls to find the vaccine for her younger son. We had another college-age survivor that had to make 5 phone calls to find the vaccine. These are people that are motivated. These are people that want to be vaccinated. If it's so difficult for them, what is the average person going to do? They are going to give up. So, when we have someone who wants to be vaccinated, yet can't find the vaccine, it's a bad situation. When health care providers don't know how to deal with a vaccine request, that's a bad situation. We really need to do better. Most people want to send their children off to college fully protected. We should make this easy. It should be a "no-brainer." But, it's really turning out to be a challenge to get vaccinated for serogroup B. So, I'm hoping that in the next ACIP meeting that this can be addressed again. Thank you.

Japanese Encephalitis Vaccine

Introduction

Lorry Rubin, MD ACIP, Workgroup Chair

Dr. Rubin reminded everyone that inactivated vero cell culture-derived Japanese encephalitis 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 a Policy Note was published in the *MMWR*. In 2013, ACIP approved recommendations for use of a primary series in children and an additional Policy Note was published in the *MMWR*.

The JE Vaccine WG's 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 focused on duration of protection following the primary series and a booster dose in adults, duration of protection and consideration of need for a booster dose in children, and the JE Vaccine WG's summary and plans.

Duration of Protection Following Primary Series and Booster Dose of IXIARO® in Adults

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

Dr. Dubischar reminded everyone that the IXIARO® primary series was approved by FDA in 2009 for use in persons 17 years of age and older. Initial data on antibody persistence after a primary series of IXIARO®, the immunogenicity and safety of a booster dose, and duration of protection after the booster were added to the IXIARO® prescribing information in 2010. The data were presented to ACIP and a booster recommendation was issued in 2011¹. In 2013, the IXIARO primary series indication was expanded to include children from 2 months of age, and ACIP issued a respective recommendation. Data on need for and timing of a booster in children were not available at the time. New clinical data are now available on duration of protection after primary series and after a booster dose, in both adults and children [¹MMWR, May 27, 2011, Vol. 60, No. 20].

Three clinical trials in adults provide data relevant to persistence of antibodies. New clinical data for IXIARO® are available for both antibody persistence after primary series and after booster dose:

Study	Follow-Up After Primary Series (Reviewed by ACIP)	Follow-Up After Primary Series (New Data)	Follow-Up After Booster (Reviewed by ACIP)	Follow-Up After Booster (New Data)
IC51-303	36 months	60 months	Not Done	
IC51-311	15 months		12 months (all subjects)	76 months (subgroup)
IC51-305	24 months		13 months	

Trial IC51-303 was a long-term immunogenicity and safety study. The design was a single-arm Phase 3 follow-up study, with no treatment administered. The study population was comprised of 181 subjects 18 years of age and older for the first 24 months after the first dose, with 152 subjects included in the analysis up to Month 60 after the first dose. Follow-up was at 2, 6, 12, 24, 36, 48, and 60 months after the first vaccination. There were 4 study sites in Austria, Germany, and Romania. The endpoints included:

- Primary endpoint of SCR at Month 24 after first vaccination
- Secondary endpoint of GMT at Month 24 after first vaccination
- Immunogenicity (SCR and GMT) at Months 2, 6, 12, 36, 48, and 60
- Rate of subjects with SAEs and medically attended AEs up to Month 6
- SAEs

The seroprotection rate was defined as the rate of subjects with a protective titer (PRNT₅₀ ≥1:10). There was a decrease in seroprotection from 99% down to about 80% within the first 12 months. Seroprotection then remained stable at approximately 80% for up to 5 years after the first dose. The GMT decreased markedly in the first year, then remained stable at approximately 40 for up to 5 years. The study was conducted in an area where tick-borne encephalitis (TBE) vaccine is relatively common. It was observed in the pivotal studies that a response to a first dose of JE vaccine is enhanced in people who have had a prior TBE vaccination. For that reason, a post-hoc analysis was performed to assess the impact of TBE vaccination on the seroprotection rate. Subjects were grouped by their TBE virus vaccination status at each study visit as follows:

- No TBE vaccination up to the specific time point before the JE series
- TBE vaccination prior to the first dose of IXIARO[®], but no TBE vaccination during the study
- TBE vaccination during the study after IXIARO[®] vaccination

Among the subjects without any TBE vaccination before or during the study, the seroprotection rate decreased to approximately 60% at the end of 5 years follow-up; whereas, people with prior or concomitant TBE vaccination tended to show higher seroprotection rates over time [Schuller et al 2008, Dubischar-Kastner et al. Abstract LB-2357, American Society of Tropical Hygiene 2011].

Trial IC51-311 was the main booster dose trial for XIARO[®] to assess the effect of a booster dose on long-term immunity. This was a single-arm, open-label follow-up study conducted in 198 subjects 18 years of age and older. The treatment group received a 0.5 mL booster of IXIARO[®] intramuscularly at Month 15 after primary immunization. Follow-up occurred at 1, 6, and 12 months after the booster. There were 3 study sites in Austria and Germany. The endpoints were:

- A primary endpoint of SCR at Month 12 after the booster vaccination
- Main secondary endpoints of SCR at Day 28 and Month 6 after the booster vaccination; GMTs at Day 28, Month 6, and Month 12; and solicited and unsolicited AEs up to Month 12

In this trial, the seroprotection rate dropped from 97% to 69% by 15 Months after the start of the primary series. GMT after primary immunization declined from about 170 to 23 [Eder et al, Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO[®], IC51. Vaccine 2011,29;2607–2612].

Trial IC51-305 was an open-label, Phase 3 supportive booster / long-term immunogenicity follow-up study. The objectives of the trial were to determine long-term immunogenicity, and response to a booster dose in subjects without measurable antibody titers. The study population consisted of 356 subjects 18 years of age and older who received one of three different doses / schedules of IXIARO[®] in a preceding trial. Dr. Dubischar showed only data for the standard schedule group during this session. A 0.5 mL booster of IXIARO[®] was administered to seronegative subjects only. Subjects who were seronegative at Month 6 were boosted at Month 11. Subjects who were seronegative at Month 12 were boosted at Month 23. Follow-up was at 2 years after the primary series and up to 12 months after the booster. There were 2 study sites in Germany and Northern Ireland where TBE vaccination is not practiced at all. The primary endpoint was seropositivity at Month 24. Seronegative subjects received a booster, but remained classified as seronegative for subsequent time points in this analysis.

The main secondary endpoints included seroprotection at Month 6, 12, and 24; GMTs at Month 6, 12, 24; and SAEs and medically attended AEs and local and systemic tolerability of the booster. In this trial, the seroprotection rate dropped from 97% to 58% by Month 12 after start of the primary series. By Month 24 after the primary series, only 48% of the subjects retained protective titer levels. A stronger decline was observed in the GMTs from 219 to 16 by Month 24 [Dubischar-Kastner et al Vaccine 2010].

For Trial IC51-311, the main booster dose trial, neutralizing antibodies also were assessed at 1, 6, and 12 months after booster. The seroprotection rate increased from about 70% at the pre-booster time point to 100% within 1 month of the booster dose, and remained at 99% for at least 12 months after the booster dose. There was about a 40-fold increase in GMTs with the booster dose. Up to about Month 12 after the booster dose, GMTs were retained at higher levels than observed after the primary series.

A study was conducted as an extension of the IXIARO[®] main booster trial that assessed neutralizing antibodies 6 years after the booster dose in a subset of the original study population at 2 of the 3 original study centers. For this study, the investigators were able to call back 67 of the original 198 subjects from main booster trial for serological sampling on average 76 months from their booster dose. Among these subjects, the seroprotection rate remained at 96% approximately 6 years after the booster dose and the GMTs were about 150. The data from that study also were used for mathematical modeling of the antibody decline. A PRNT₅₀ titer of 1:10 was defined as the limit for protection. Duration of protection depends upon the titer level after the booster dose. The modeling estimated that about 75% of subjects will be protected for a minimum of 10 years. The average duration of protection is projected to be 14 years, with a range 2 to 25 years. The authors concluded that a second booster dose should be scheduled after 10 years for this vaccine [Paulke-Korinek et al, Persistence of Antibodies Six Years after Booster Vaccination with Inactivated Vaccine against Japanese Encephalitis. Vaccine 2015].

To summarize the data on boosting in adults, based on waning neutralizing antibody titers and a seroprotection rate range of 83% to 58% in the clinical trials, a booster of IXIARO[®] should be considered or recommended at 12 months after the primary series. Clinical data demonstrate that a booster dose of IXIARO[®] will elicit a memory response at least until 23 months after the primary series. After an IXIARO[®] booster dose, clinical data demonstrate high levels of seroprotection for 6 years. Mathematical modelling suggests seroprotection may persist for at least 10 years after the booster dose of IXIARO[®] in 75% of vaccinees. Safety data for a booster dose of IXIARO[®] were presented to ACIP for the booster recommendation vote in 2011. No safety concerns were identified, and the AE profile was in-line with the primary series.

In conclusion of the discussion regarding an adult booster dose, Dr. Dubischar presented information about the regulatory status and outlook for an IXIARO[®] booster dose recommendation in adults.

In Europe, the Summary of Product Characteristics gives clear guidance for HCP for the first booster dose:

“A booster dose (third dose) should be given within the second year (i.e., 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV. Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization.”

A recommendation for a second booster dose after 10 years is currently under review by the EMA.

In the US, both the Prescribing Information and the ACIP recommendations use less prescriptive language than Europe for first booster dose:

“Individuals 17 years of age and older: If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.”

FDA indicated that without actual safety and immunogenicity data instead of mathematical modeling, no recommendation for a second booster would be granted in the label. Therefore, Valneva has no current plans to submit additional antibody persistence data for IXIARO® to FDA.

Duration of Protection and the Need for A Booster Dose of IXIARO® in Children

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

Dr. Dubischar next presented an overview of clinical data pertaining to duration of protection after a primary series and booster dose of IXIARO® in children. Two clinical trials in children provide data relevant to persistence of antibodies, and one clinical trial provides data on antibody persistence following a booster dose. This presentation provided a comprehensive summary of the following available clinical data on primary series and booster:

Study	Region	Duration of Follow-Up Initial Study*	Duration of Follow-Up Extension Study*	Follow-Up After Booster	Trial ID
IC51-322 / IC51-324	JE Non-Endemic	7 months	36 months (subgroup)	None administered	IC51-322 / IC51-324
IC51-323 / IC51-325	JE Endemic	7 months	36 months (subgroup)	24 months (subgroup), booster given at month 12	IC51-323 / IC51-325

...safety and immunogenicity study of IXIARO® in a JE vaccine naïve, pediatric travelers population comprised of children and adolescents 2 months or older through less than 18 years of age. This was an open-label, single-arm trial with an extension study and 100 children were evaluated for safety and 64 children were evaluated for immunogenicity. There were 23 children enrolled in the extension study IC51-324. The treatment group was comprised of 12 children less than 3 years of age who were given a 0.25 mL dose of IXIARO®, and 88 children 3 years of age to 18 years of age who were given a 0.5 mL dose of IXIARO®. Follow-up was at Day 56 and Month 7 in the parent study and at Months 12, 24, and 36 in the extension trial. There were 15 study sites in Australia, Germany, USA, Denmark, and Sweden. The parent study primary

endpoint was rate of SAEs and medically-attended AEs until Day 56. The secondary endpoint was immunogenicity (SCR/ GMT) up to Month 36.

Long-term data are limited in traveling children due to recruitment issues. In children aged 3 years of age or less at primary immunization, the seroprotection rate decreased in the first 6 months, then remained stable at approximately 90% for up to 3 years. One child less than 3 years of age was enrolled in the extension study, and retained a protective titer. The GMTs declined in the first 7 months, and then remained fairly stable over time [Dubischar-Kastner et al., Abstract P 2.7, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway; and Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada].

Trial IC51-325 was an antibody persistence / booster study in Philippine children to assess long-term persistence of immunity and the safety and immunogenicity of an IXIARO[®] booster dose in children from JE endemic regions. The study population was comprised of 300 children and adolescents 2 months through 17 years of age who were vaccinated in a preceding trial.. This was an open-label, randomized, Phase 3 study. Subjects were randomized 1:1 into a booster group (12 months after first vaccination) and non-booster group of 150 subjects each. Follow-up occurred at Month 13 after the first immunization (4 weeks after booster dose) and Month 24 for safety and immunogenicity. There were 3 study sites in the Philippines. The primary endpoint was seroconversion rate at 1 month after the booster dose. The secondary endpoints included GMTs at 1 month after the booster dose and SAEs and medically attended AEs 1 month after the booster dose.

Of the children in this study, 149 were followed for a maximum of 3 years with a mean age of 4.6 years at the time of primary vaccination. The seroprotection rate decreased in the first 6 months, then remained stable at approximately 90% for up to 3 years based on combined data for all ages / doses. Though marginal, there was a constant increase in GMTs. Looking at the individual titers of the subjects, titer increases that were suggestive of natural boosting were observed in 24 of 150 children during follow-up. Children 1 to less than 3 years of age and 3 to less than 12 years of age showed a stronger decline in seroprotection rate down to approximately 80% at Month 7, although the numbers are limited in some of the age cohorts. A booster dose was received by 148 children 12 months after the primary series, with a mean age of 5.6 years at the time of the booster. The booster increased the seroprotection rate to 100% and this level was sustained for 2 years. As in adults, GMTs increased about 40-fold after the booster, and remained higher compared with GMTs 2 months after the primary series.

In terms of safety, the booster dose in children was very well-tolerated. Most AEs were mild or moderate, and the AE rate with the booster was lower than with the primary series. The most common AEs were local reactions, fever, loss of appetite, and headache. All of these were reported in less than 10% of children. Two SAEs occurred within 4 weeks after booster, including an abscess of the right flank and dengue fever) [Dubischar-Kastner et al., Abstract P 2.8, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway; Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada].

In summary, in a small, mainly adolescent pediatric cohort from JEV non-endemic regions, antibody titers declined considerably up to Month 36 after vaccination with IXIARO[®], but the seroprotection rate was still high at 89.5% in 17/19 subjects. In a larger pediatric cohort from a JEV-endemic country, antibody titers also declined considerably up to Month 36.

Seroprotection rates remained greater than 80% in all age groups. Natural boosting through JEV virus exposure may have contributed to persistence of antibodies in this trial. Together, data suggest that booster dose administration may not be absolutely necessary in any pediatric age group for a minimum of 3 years after the primary series. However, titers in children declined substantially within the first year after the primary series, and the long-term seroprotection rate was enhanced by a booster dose, which was well-tolerated. Valneva considers administration of a booster dose in children 12 months after primary series justified for programmatic reasons in terms of uniformity of medical use for adults / children and optimization of long-term protection.

In Europe, a first booster recommendation for IXIARO[®] in children is currently under regulatory review. There is indication that the adult booster recommendation will be extended for children:

“A booster dose (third dose) should be given within the second year (i.e., 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV ...”

In the US, the FDA is currently reviewing the pediatric booster data on IXIARO[®], which were submitted as part of the post-marketing commitment. Valneva plans to file a supplemental BLA with the FDA in 2016 with proposed edits to the prescribing information for a first booster dose of IXIARO[®] in children. The proposed wording for a pediatric booster dose of IXIARO could resemble the adult language in the prescribing information:

“If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.”

In Europe and the US, there will not be a recommendation for a second booster dose of IXIARO[®] in children.

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.

As a reminder, ACIP approved the JE-VC booster dose recommendation in 2011 which states:

“If the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure.”

Data supporting the booster dose recommendation came from three clinical trials that provided data on persistence of protective neutralizing antibodies after a primary 2-dose JE-VC series. At 12 through 15 months after the 2-dose primary series, 58% to 83% of subjects were seroprotected based on these 3 studies. At 24 months after the 2-dose primary series, 48% to 82% of subjects were seroprotected in the 2 studies with data. Thus, the results of the percentage of subjects with protective JE titers were quite variable. In the study that had an 82% seroprotection rate at 24 months, subjects were followed up for 60 months. At 5 years, 82% (124/152) of subjects were seroprotected. The neutralizing antibody GMT was 43. In addition, a post-hoc analysis was done for this study that stratified subjects by TBE vaccination status. Seroprotection rates and GMTs were higher if TBE vaccine was administered after commencement of JE-VC vaccination. The seroprotection rate at 24 through 60 months was 90% to 100% in the TBE vaccine group and 64% to 72% in the vaccine group who did not receive TBE vaccine. GMTs in the TBE vaccine group were significantly higher than GMTs in the non-TBE vaccine group at 24, 36, and 48 months.

The WG reviewed and assessed these data. The WG's assessment and summary of the duration of protection following a JE-VC primary series in adults are that after a 2-dose primary series, long-term seroprotection rates and GMTs are lower in those not administered TBE vaccine compared with those administered TBE vaccine. TBE vaccine is not available in the US and other flavivirus vaccines, such as YF vaccine, are not routinely administered with JE-VC. Therefore, JE seroprotection rates and GMTs for US travelers are likely to be most similar to the lower rates and GMTs in the study group not administered TBE vaccine. Following the WG's review, two options were considered. The first was to make no change to the current booster dose recommendations. The second was to strengthen the existing permissive ACIP recommendation from 2011. The WG concluded that the data were sufficient to consider a strengthened booster dose recommendation. The suggested recommendation would be as follows:

“If the primary series of JE-VC was administered >1 year previously, a booster dose should be given before potential JE virus exposure.”

The WG would be interested in feedback on this suggested change. Depending upon feedback, the WG would consider putting the recommendation up for a vote during the next ACIP meeting.

The second topic presented by Dr. Dubischar regarded new data on duration of protection following a booster dose in adults. In summary, in observational study, at approximately 6 years after booster dose, 96% (64/67) of subjects were seroprotected and the neutralizing antibody GMT was 148. This study was conducted in areas where TBE vaccine is not routinely administered. In one modeling study, and estimated 75% of subjects would be seroprotected at 10 years or later.

The WG reviewed and discussed these data and its assessment was that after a 2-dose primary series and a booster dose, seroprotection rates were high for at least 6 years. In addition, FDA has indicated that there will be no recommendation for a second booster dose as there are no immunogenicity and safety data to support such a recommendation. Following the WG's

review, two options were considered. The first was to make an off-label recommendation for a second booster dose. The second was no off-label recommendation, but incorporation of the data into an updated *MMWR Recommendations and Report* document to make information available for vaccine providers. The WG concluded that the data were not sufficient to support an off-label recommendation for a second booster dose. The plan is to incorporate the data into an updated *MMWR Recommendations and Reports* document.

The final topic presented by Dr. Dubischar pertained to duration of protection following a 2-dose primary series in children. One study was conducted among pediatric travelers from non-endemic countries. The long-term study cohort included only 23 children, including 1 child in the 2 month to 2 year age group who received two 0.25mL doses of vaccine, 3 children in the 3 to 11 year age group who were administered two 0.5mL doses of vaccine, and 19 children in 12 to 17 year age group who received two 0.5mL doses of vaccine. At 36 months, 89% (17/19) children were seroprotected and the GMTs were 58. Although seroprotection rates and GMTs decreased between 1 and 6 months following the primary series, seroprotection rates and GMTs were then maintained at similar levels from Months 6 through Month 36. In the long-term duration of protection studies, seroprotection rates at 36 months were higher in the pediatric study compared with the adult study. At 36 months, 89% (17/19) were children seroprotected compared with 72% (41/57) of adults in the non-TBE vaccine group in the adult study.

Data on duration of protection in children were also available from one study conducted among children in the Philippines, which is a JE-endemic country. At 36 months after a 2-dose primary series, 90% (128/142) of children were seroprotected and the GMT was 59. While seroprotection rates were variable by age group, in all age groups at least 81% of children were seroprotected. At 24 months after a booster dose, 100% (143/143) of children were seroprotected and the GMT was 350.

The WG discussed these data from the pediatric studies. The WG's assessment and summary of the need for a booster dose in children was as follows. There are limited safety and immunogenicity data on the need for a booster dose in children. The available data suggest high seroprotection rates at 3 years following a 2-dose primary series. The data have been submitted to FDA and are under review. Following the WG's review, two options were considered. The first was an off-label recommendation for a booster dose while awaiting FDA review of data. The second was no off-label recommendation, but incorporation of the data into an updated *MMWR Recommendations and Reports* document while awaiting FDA review of data. The WG concluded that no off-label recommendation would be requested. The plan is to incorporate the data into an updated *MMWR Recommendations and Reports* document to make the information available for providers, and to await FDA review of the data.

To complete the ACIP JE Vaccine WG objectives, the following topics will be addressed during future ACIP meetings:

- A presentation of updated post-licensure safety data
- 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 the updated safety, immunogenicity, and traveler data presented to ACIP during this and previous ACIP meetings
- A presentation of a draft of the updated *MMWR Recommendations and Reports* document

In conclusion, Dr. Hills noted that a new WG member and Chair will be identified to replace Dr. Lorry Rubin. She thanked Dr. Rubin for his substantial input to the ACIP JE and YF Vaccines WG.

Influenza

Introduction

Ruth Karron, MD Chair, Influenza Work Group

Dr. Karron reported that since the October 2015 ACIP meeting, the Influenza WG has considered recent data pertaining to duration of protection following vaccination, and discussion of recommendations regarding timing of vaccination; data pertaining to egg allergy and influenza vaccination, particularly use of live attenuated influenza vaccine (LAIV) for egg-allergic persons; and clinical data for quadrivalent recombinant influenza vaccine (RIV4). She indicated that the topics for this session would focus on an influenza surveillance update, RIV4, influenza vaccination and egg allergy, and proposed recommendations for 2016-2017.

Influenza Surveillance Update

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

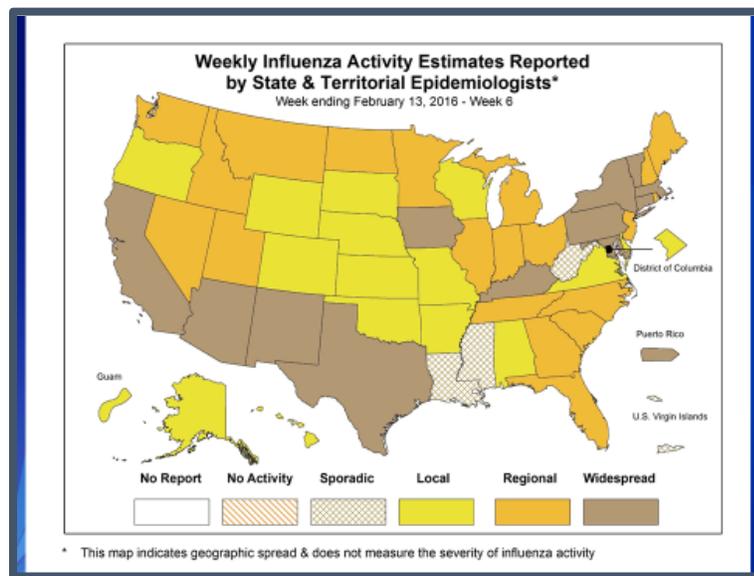
Ms. Brammer presented an influenza surveillance update and interim estimates of 2015–2016 seasonal influenza VE against medically-attended influenza from the US Flu VE Network. In terms of the number and percent of specimens testing positive for influenza at approximately 250 clinical laboratories across the country that report to CDC each week, the most recent week was Week 6 that ended on February 13, 2016. At that time, 12% of specimens tested were positive for influenza. The previous week, it was about 2.5%. To put that into perspective, activity is still very low. At the peak of influenza activity last year, 27% of clinical laboratory specimens tested positive for influenza. To date for this season, 75% of the influenza tests at public health laboratories were influenza A viruses and 25% were influenza B viruses. Among the influenza A viruses tested, 71.5% were A (H1N1)pdm09 viruses. The remainder of the As were A (H3N2) viruses. Among the influenza B viruses, 75% of those tested for lineage were in the B/Yamagata-lineage and the remaining 25% were in the B/Victoria-lineage.

The public health laboratories sent a subset of the viruses they tested to CDC for further characterization. Among those viruses, all 181 influenza A (H1N1)pdm09 viruses were antigenically characterized as A/California/7/2009-like contained in the current vaccine. All 228 H3N2 viruses genetically sequenced belonged to genetic groups for which a majority of the viruses antigenically characterized were similar to the cell-propagated A/Switzerland/9715293/2013 contained in the current vaccine. A subset of 107 H3N2 viruses were also antigenically characterized, and 100 (93.5%) were A/Switzerland/9715293/2013-like by HI testing or neutralization testing. All 88 B/Yamagata-lineage viruses antigenically characterized were B/Phuket/3073/2013-like, which is included as an influenza B component of the 2015-2016 Northern Hemisphere trivalent and quadrivalent influenza vaccines. All 35 B/Victoria-lineage

viruses antigenically characterized were B/Brisbane/60/2008-like, which is included as an influenza B component of the 2015-2016 Northern Hemisphere quadrivalent influenza vaccines.

CDC receives reports of outpatient illness from approximately 2000 primary care sites across the country. During Week 6, 3.1% of those visits were for influenza-like illness (ILI). This year has been later with less activity than the previous two seasons, but not as mild as the 2011-2012 influenza season. Hospitalization data reported through FluServ-NET reflect a similar picture. The current rate of hospitalizations is 4.1/100,000, which is much lower than observed during the previous three seasons and just slightly higher than the 2011-2012 influenza season. As would be expected given the low rate of hospitalizations and illness, influenza-associated pneumonia and influenza mortality reported to the National Center for Health Statistics (NCHS) has also been relatively low. The percentage of deaths that had pneumonia or influenza listed anywhere on the death certificate that occurred as of the week ending January 30th was 6.5%, which is well below the epidemic threshold of 7.6%. Influenza-associated deaths in children less than 18 years of age is a nationally notifiable condition. Thus far this year, 13 influenza-associated pediatric deaths have been reported to CDC.

The following map shows the geographic distribution of influenza within states and territories, which is reported to CDC by state and territorial epidemiologists or their designees:



The map shows that influenza activity across the US has not been simultaneous this year. There has been more widespread activity in the Southwest and Northeast, and less activity in the center of the country thus far. However, that is expected to progress in the coming weeks.

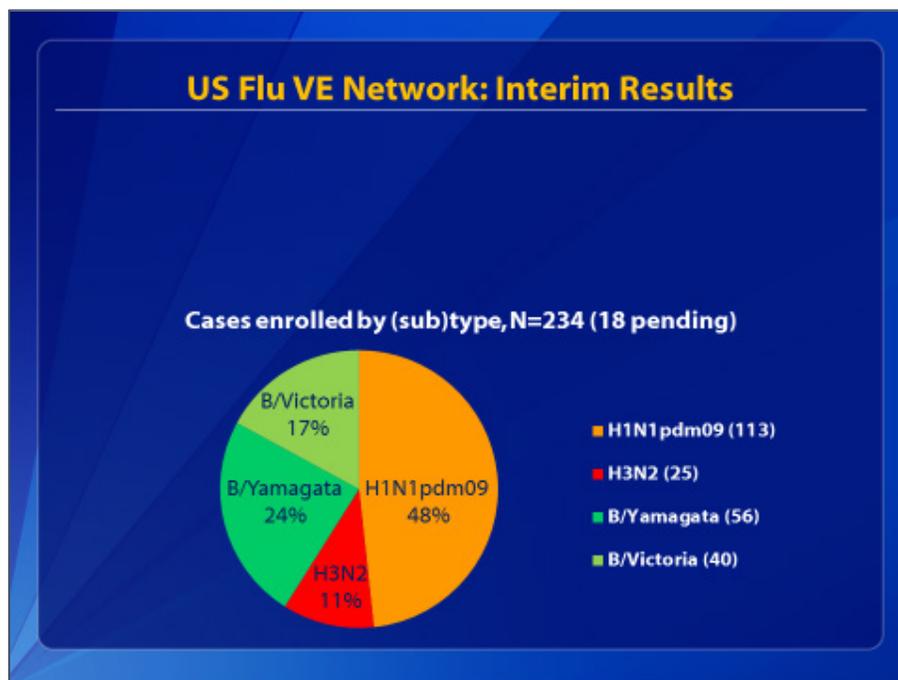
Regarding next season, the WHO Consultation on the Composition on Influenza Virus Vaccines for the Northern Hemisphere 2016-2017 is being held February 22-24, 2016. Announcement of their decision will be made on February 25, 2016. FDA's VRBPAC will meet on March 4, 2016 to make recommendations on the selection of vaccine virus strains for the US vaccines.

In summary, influenza activity to date is low compared to the previous three seasons. The rate of influenza associated hospitalizations is low, and pneumonia and influenza mortality have not exceeded threshold levels. Influenza A (H1N1) viruses have predominated, but A (H3N2) and B

viruses of both lineages have co-circulated. The majority of circulating viruses are similar to the vaccine strains.

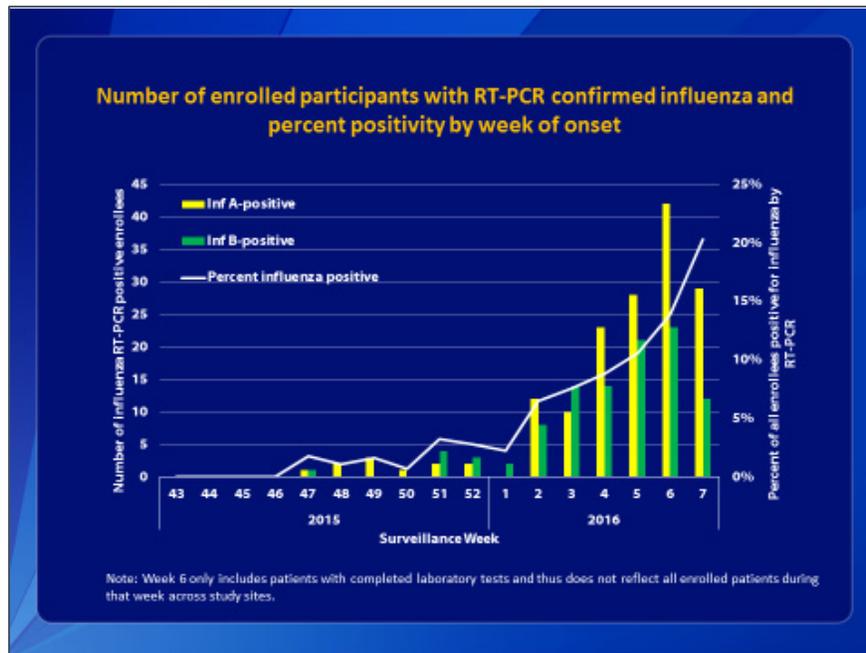
Interim estimates of influenza vaccine effectiveness for this season were presented to ACIP, but have not been published. These interim estimates included patients enrolled from November 2, 2015 through February 12, 2016. The methods are similar to previous years and have been described previously. Methods used to produce these interim estimates were the same as those used for interim estimates in previous seasons. Briefly, outpatients 6 months of age and older with acute respiratory illness and cough of 7 or fewer days duration were enrolled at five US Flu VE Network sites from November 2, 2015 through February 12, 2016. A test-negative design was used to estimate vaccine effectiveness by comparing vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls. Vaccination status was defined as “receipt of at least one dose of any 2015-16 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report.” Vaccine effectiveness is estimated as one minus the adjusted odds ratio times 100. Variables included in the models for adjustment are study site, age, self-rated general health status, race/Hispanic ethnicity, interval (days) from onset to enrollment, and calendar time.

From November 2, 2015 through February 12, 2016, a total of 3,333 outpatients were enrolled at the five network sites. Of those, 92% (3,081) were RT-PCR negative for influenza and 8% (252) of enrolled patients were influenza-positive. The contribution of each of the viruses detected in this study is shown in this pie chart:



Both influenza A and B viruses circulated, with a majority of influenza A viruses being H1N1pdm09 and a majority of B viruses belonging to the Yamagata lineage.

The following epi curve shows the number of enrolled participants with RT-PCR-confirmed influenza A or B by epidemiologic week of enrollment and the percent positivity for any influenza type by week. Note that laboratory testing is incomplete for patients enrolled during the most recent week, but the percent positivity continues to increase. Very few positive cases were enrolled before the first week of January, with a low percentage of those enrolled testing positive for influenza A or B during most weeks:



Interim adjusted estimates of VE against medically-attended influenza for all patients aged 6 months and older was 59% with a 95% confidence interval from 44% to 70%. Interim adjusted VE against H1N1pdm09 for all ages combined was 51%, with a 95% confidence interval from 25% to 69%. Adjusted estimates of VE against influenza B for all ages combined was 76%, with a confidence interval from 59% to 86% and was similar against B/Yamagata lineage viruses with an adjusted VE of 79%.

In summary, interim results from the US Flu VE Network for the 2015-2016 season through February 12, 2016 indicate that VE was 59% against medically-attended influenza. The interim estimate for this season is similar to previous seasons when vaccine was well-matched to circulating influenza viruses. Significant protection against circulating influenza H1N1pdm09 and B viruses was observed for all ages combined, while VE was not estimated against H3N2 viruses due to the small number of cases. The enrollment in VE studies for this year continues. Interim estimates may be less precise due to low numbers of flu cases enrolled, and the end-of-season VE estimates may differ from interim estimates.

Discussion Points

Dr. Reingold asked whether there was any suggestion so far regarding whether the LAIV vaccine is performing any better this season.

Ms. Brammer replied that there are not enough data at this point to know.

Quadrivalent Recombinant Influenza Vaccine

Wayne Hachey DO, MPH Protein Sciences

Dr. Hachey reported on a recent study that demonstrated the improved efficacy of a recombinant influenza vaccine versus an inactivated vaccine during the influenza season marked by a vaccine mismatch. The study was designed to demonstrate the clinical efficacy and safety of Flublok® Quadrivalent (RIV4) versus an inactivated quadrivalent vaccine (IIV4 Fluarix® Quadrivalent).

Flublok® is the first licensed recombinant hemagglutinin protein influenza vaccine. Because it does not require passage in eggs and therefore does not require an egg-adapted strain, the HA for recombinant influenza vaccines matches the wild type of the FDA-specified strain. The 2014-2015 influenza season was particularly unpleasant for adults 65 years of age and older. This was primarily due to widespread circulation of an H3N2 strain that was not antigenically matched to the vaccine, with over 80% of the identified H3N2 strains representing this mismatch. This mismatch led to low vaccine effectiveness estimated at less than 20% overall, as well as high rates of laboratory-confirmed hospitalizations for pneumonia and influenza. During this poor season, Protein Sciences conducted a double-blind RCT that compared Flublok® Quadrivalent (RIV4) versus a licensed quadrivalent inactivated vaccine (Fluarix® Quadrivalent).

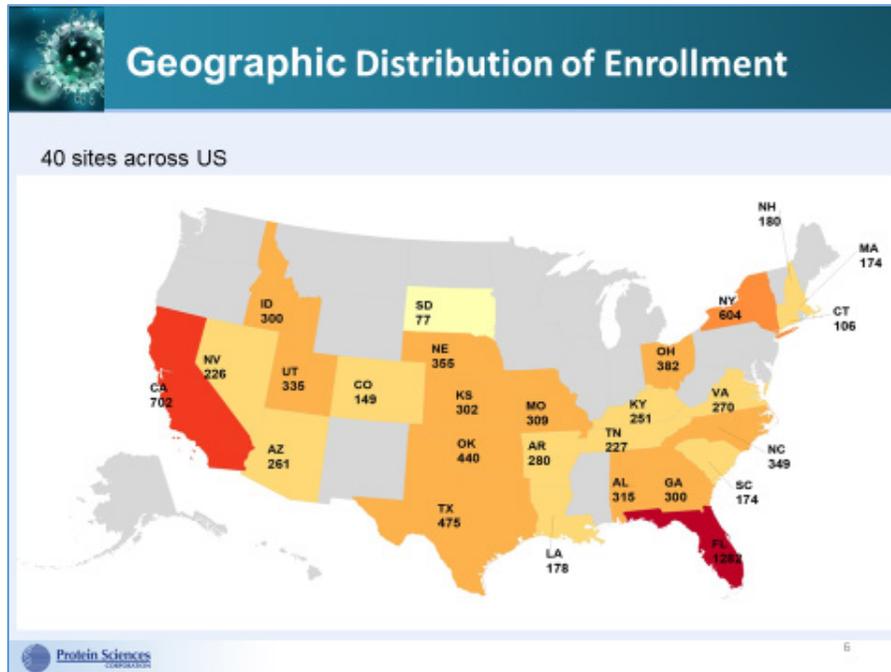
Flublok® quadrivalent attack rates were significantly lower than the IIV comparator at 2.2% versus 3.3%. These lower attack rates persisted throughout the season. Although viral cultures did not yield sufficient titers to test for antigenic similarity, the improved efficacy in the face of a mismatch is inferred from the fact that more than 80% of the circulating H3N2 viruses in that season were antigenically mismatched to the vaccines. In regard to safety, AEs were similar for both vaccines, with the exception of a lower incidence of local reactions, specifically pain and tenderness at the injection site in the Flublok® Quadrivalent group.

The study hypothesis was that the relative vaccine efficacy for Flublok® Quadrivalent would be non-inferior to that of IIV4 in adults 50 years of age and older. Non-inferiority was specified by the lower bound of the 95% confidence interval for relative VE to be greater than -20%. Superiority determined in pre-specified exploratory analysis was determined by the threshold of the lower bound of the 95% confidence interval for relative VE at greater than 9%. Sample size was powered for the primary endpoint as well as pre-specified secondary analysis of subgroups. Between October 22 and December 23, 2014 9003 subjects were vaccinated. They were subsequently followed through May 22, 2015. ILI symptomatic subjects had nasopharyngeal (NP) swabs for both PCR and culture. The protocol-defined ILI required at least one respiratory symptom and at least one systemic symptom (temperature >99, chills, fatigue, headache or myalgia) occurring at least 14 days after vaccination. The protocol definition was identical to that used for the High Dose IIV3 study in adults 65 years of age and older. HAI serology was tested in 613 subjects, reactogenicity was monitored for 7 days post-vaccination, and safety monitoring continued for 6 months post-vaccination.

The antigenic composition of Flublok® Quadrivalent was 45 mcg per antigen of H1N1: A/California/07/2009, H3N2: A/Texas/50/2012, B/Massachusetts/2/2012 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). The antigenic composition of IIV4 was 15 mcg per antigen of H1N1: A/Christchurch/16/2010 (an A/California/7/2009-like virus), H3N2:

A/Texas/50/2012, B/Massachusetts/2/2012, and B/Brisbane/60/2008. Both vaccines contained the HAs representing the strains selected by the WHO and VRBPAC for the 2014-2015 season. However, the Flublok® Quadrivalent contained a strain that was matched to the reference strain wild type.

This map depicts the geographic distribution of enrollment and shows the wide distribution across the US:



A total of 9003 participants were enrolled. After exclusions, the RIV4 group was comprised of 4303 (96.2%) in the efficacy population, 314 (7%) in the immunogenicity population, 4328 (96.7%) in the safety population, and 4228 (94.5%) completing the study. The IIV4 group began with 4489. Of those, 4301 (95.8%) were in the efficacy population, 300 (6.7%) were in the immunogenicity population, 4344 (96.8%) were in the safety population, and 4236 (94.4%) completed the study. Withdrawals were relatively rare and were evenly distributed between the two study populations.

In terms of demographics, the study included adults 50 years of age or older. Subjects were stratified to age categories of 50 through 64, 65 through 74, and 75 and older prior to being randomly assigned in a 1:1 ratio to receive a single dose of either vaccine. Distribution was even in terms of gender race and ethnicity.

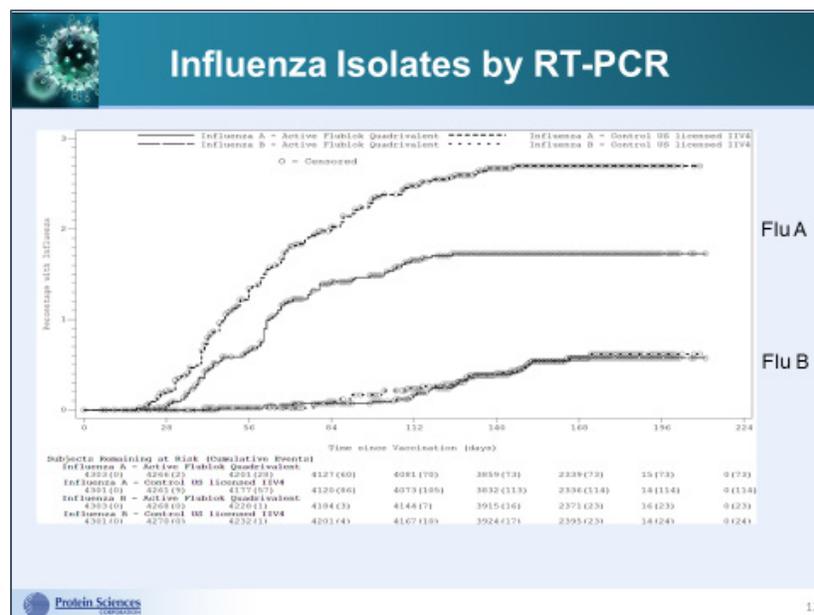
Post-vaccination HAI antibody GMTs at Day 0 and Day 8 for A/H1 and B/ Massachusetts and B/Bisbane were comparable between the two vaccine groups, with the B/Brisbane titers being quite low for both vaccine groups. HAI antibody GMTs were significantly higher for the H3 component after vaccination with Flublok® RIV4 than with IIV4.

For efficacy against rtPCR-confirmed protocol-defined ILI, 234 participants met the primary endpoint representing 96 or 2.2% of the RIV4 subjects and 138 or 3.2% of the IIV4 recipients. Specifically, those positive for H3N2 were a total of 187 with 73 in the RIV4 group and 114 in

IIV4. B strains represented rather small number of individuals at 23 and 24 subjects, respectively. Of the 102 individuals with culture-confirmed ILI, 38 were in the RIV4 group and 64 were in the IIV4.

The efficacy of RIV4 relative to the traditional IIV4 for the primary endpoint was 31% with a lower bound of the two-sided 95% confidence interval for relative vaccine efficacy of 10%, which satisfied the non-inferiority and superiority criteria. As the predominant circulating strain was H3N2, a post-hoc analysis of VE against influenza A and B was conducted. Relative VE of RIV4 versus IIV4 was 37% for type A and 17% for type B. Efficacy against cell culture-confirmed influenza was important to evaluate since this was a more rigorous assessment of the true cause of ILI. Relative VE of RIV4 versus IIV4 was more pronounced at 43%. Of note is the wide confidence intervals for the B stains due to the relatively small number of individuals.

This Kaplan-Meier curve presents the cumulative incidence of RT-PCR confirmed influenza over the season and displays the relative efficacy of the two study vaccines for influenza types A and B, with the protective effect of RIV4 in comparison to IIV4 apparent throughout the influenza season:



In a review of the primary and secondary endpoint analyses for PCR-confirmed protocol-defined ILI for all types of influenza, relative VE was about 31%. For those 50 through 64 years of age, VE was 41%. For those 65 years of age and older, VE was 0.17. However, the more rigorous culture-confirmed protocol-defined ILI for those over 65 was 0.43 and remained significant. Of note is the enhanced protective effect in individuals who have not received a prior influenza vaccine, although this cannot be explained thus far.

Moving to safety, individuals were followed for 6 months post-immunization. Medically-attended ILI included 19 individuals, 6 in the RIV4 group and 13 in the IIV4 group. Hospitalizations were rare with a total of 4, 1 in the RIV4 group and 3 in the IIV4 group. No SAEs or AEs were vaccine-related for either vaccine group. The most common AEs were comparable in each

vaccine group and included cough, ILI, oropharyngeal pain, headache, upper respiratory tract infection, fatigue, myalgia, and productive cough.

In terms of reactogenicity, the study participants were particularly compliant with reporting whether they experienced specifically solicited reactions to the vaccine. Memory aids that included both local and systemic reactions were returned by more than 96% of subjects in both treatment groups. The only difference between the two vaccine groups was with respect to local injection site pain and tenderness that were reported significantly more frequently by the IIV4 recipients, and injection site erythema was more commonly reported by RIV4 recipients.

In conclusion, Flublok[®] Quadrivalent met criterion for non-inferior efficacy against PCR-confirmed ILI, as well as the pre-specified criterion for superior efficacy over IIV4. Superiority possibly was driven by the efficacy against largely antigenically drifted influenza A. This is inferred because more than 80% of the circulating H3N2 viruses in 2014-2015 were antigenically mismatched to the vaccines. Efficacy against influenza B was similar to IIV4, which was observed with the trivalent vaccine. HAI antibody responses after Flublok[®] were especially high for A/H3, which is also consistent with previous trivalent vaccine data. Both vaccines had similar safety profiles. Injection site pain and tenderness were significantly less with Flublok[®] Quadrivalent group. There were no vaccine-related SAEs or medically-attended AEs.

Discussion Points

Dr. Moore noted that in the study, vaccination occurred during the influenza season and the relatively early arriving influenza season. She wondered if Dr. Hachey could address how the study design prevented any confounding due to prior influenza infection among those who were enrolled, or particularly geographic differences in influenza disease activity during the period of vaccination with IIV4 or RIV4.

Dr. Hachey explained that the individuals were medically screened before entering the study, so anyone with any febrile or any illness at that time was excluded from enrollment. If asymptomatic at the time of enrollment, it is possible that someone could have had influenza already prior to enrolling in the study.

Dr. Belongia noted that there is not a clear understanding of the relative importance of egg-induced mutations and how that might impact clinical effectiveness. There was a unique opportunity in a season with a mismatch and a vaccine not based on an egg-adapted virus. There was some suggestion that even in a mismatch, virus circulating relative to the vaccine strain that egg-induced mutations perhaps might make an additional contribution. He thought they had a gold mine of data in terms of evaluating the viruses from the H3N2 cases in the RIV4 and IIV4 groups. He thought it would be interesting to sequence those viruses to assess the HA and specifically evaluate the people who received RIV4 versus IIV 4 to see if there are different clades, and also to look at the people who received the prior vaccine and those who did not to look for any differences that could help to better understand what is occurring.

Dr. Ornstein (NVAC) said striking to him was the improved immunogenicity against the H3N2 component with RIV4 versus IIV4. He wondered whether they had been able to study any of the drifted strains and done any serology to determine whether there are differences in immunogenicity against the actual drifted strains that occurred during that season.

Dr. Hachey responded that while they did not characterize the viruses, they do know that at least 80% of them were drifted. In previous studies with trivalent vaccine, also during mismatched years, particularly with H3 strains, vaccines tended to do much better. This was approximately 5 years ago.

Dr. Ornstein (NVAC) said he thought it would be helpful to run HAI titers on those drifted strains to determine whether there were large differences there as well.

Dr. Bresee (SME) asked whether a similar study was planned for next year and in future years to have more than a single year of data. He agreed that characterizing these strains antigenically would be important to better understanding the data.

Dr. Hachey replied that they would be willing to conduct more studies if they were funded to do so. This study was part of the requirement imposed by FDA as part of the licensure process for individuals 50 years of age and above. It just happened to occur during a mismatch year.

Dr. Gemmill (NACI) asked whether it might be possible to expect or hope for a vaccine that offers broader coverage generally for more strains, or if they were just looking at a vaccine that helped to avoid eggs and offers more antigen in each dose. He thought the ideal vaccine would be one that lasts a long time and has coverage of all of the strains that might be circulating.

Dr. Hachey responded that everybody hopes for a universal vaccine. Unfortunately, that has eluded everyone thus far. One nice thing with recombinant technology is that a vaccine can be developed quickly in a matter of weeks that would represent a drifted strain. At this point, they are limited to about 6 million doses of vaccine. That is clearly not enough for the US population. For example, that particular year, they could have easily produced vaccine for the drifted strain. However, it would have been in limited amounts.

Dr. Decker (Sanofi Pasteur) referred to a slide showing HAI immune response Days 0 and 28 GMTs. He did not understand why for three of the four strains included in the vaccine, the Flublok[®] antibody response was actually lower than the IIV response—not significantly, but numerically lower. It was materially higher for H3N2, but not for any of the other strains. He wondered if Dr. Hachey had any idea why that might be.

Dr. Hachey responded that historically, Flublok[®] has been statistically comparable, but not any better, than the inactivated vaccine for B strains. In prior studies, the serologies for the H1 strains were better than the reference strains. However, it is important to keep in mind that with this particular season, essentially all of the A strains were H3N2. There were 6 non-typeable A strains. Other than that, the H1N1 was grossly under-represented. It may be a question of the number of samples.

Dr. Decker (Sanofi Pasteur) noted that Flublok[®] was superior to IIV4 for those 50 through 64 years of age, but not for those 65 years of age and older. He wondered whether Dr. Hachey had any thoughts on that.

Dr. Hachey responded that this was true for PCR-defined. The culture-confirmed is a much more stringent test and showed a relative efficacy of 43%. In an assessment of a subgroup of subjects 75 years of age or older, efficacy continues even with the PCR-confirmed.

Dr. Decker (Sanofi Pasteur) noted that for all four strains, Flublok[®] includes 45 mcg of protein and Dr. Hachey referred to that as a high-dose vaccine.

Dr. Hachey clarified that he called it a “higher than the standard dose vaccine.”

Dr. Decker (Sanofi Pasteur) said he was not sure how dose was measured, but looking at immunogenicity, standard IIV egg-based has 15 mcg. He wondered why it takes three times as much of the synthetic protein to get more or less the same response as with the egg-based protein.

Dr. Hachey responded that the RIV4 does get a better response than the egg-based. In the initial clinical trials with the trivalent vaccine, there were statistically superior responses to the H1 and H3 strains. Particularly in the 65 years of age and older group, when Fluzone[®] standard dose is compared with Flublok[®], the improvement in serology, particularly in the elderly population, is almost identical to the high-dose Fluzone[®] vaccine. The two results are essentially the same.

Dr. Decker (Sanofi Pasteur) said that he did not have those results in front of him and was looking at the results just presented.

Influenza Vaccination and Egg Allergy

John M. Kelso, MD
Division of Allergy, Asthma and Immunology
Scripps Clinic, San Diego and
Clinical Professor of Pediatrics and Internal Medicine
University of California San Diego School of Medicine

Dr. Kelso presented information on the use of influenza vaccines in egg-allergic recipients, emphasizing that he has a particular interest in adverse reactions to vaccines. During this session, he discussed the risk of withholding influenza vaccine and the safety of IIV in egg-allergic recipients, current guidelines regarding IIV and LAIV in egg-allergic recipients, new studies on administration of LAIV to egg-allergic recipients, and his personal recommendations.

Regarding the risk of withholding vaccine, an average of 294,128 persons are hospitalized each year in the US because of influenza, including an average of 21,156 hospitalizations in children less than 5 years of age. An average of 23,607 deaths occur each year in the US as a result of influenza, including an average of 124 children. Egg allergy is believed to affect 1.3 % of children and 0.2 % of adults¹. There are 73.7 million children in the US², meaning that there are approximately 1 million egg-allergic children [¹The Center for Food Safety and Applied Nutrition Food and Drug Administration US Department of Health and Human Services; ²www.childstats.gov/americaschildren].

Most influenza vaccines are still grown in eggs, literally, and contain measurable quantities of egg protein, typically measured as ovalbumin—the particularly allergenic egg protein that is in the vaccine. There is clearly a theoretical risk of giving something that contains egg protein to

someone who is allergic to egg protein. In terms of whether giving influenza vaccine causes systemic reactions when injected into egg-allergic patients, 27 studies have now been published on this that have collectively involved over 4100 egg-allergic subjects receiving influenza vaccine without any serious reactions, including respiratory distress or hypotension. There has been a very low rate of minor reactions (hives, mild wheezing), but this was exactly the same as in non-egg-allergic recipients [Des Roches A, et al. Egg-allergic patients can be safely vaccinated against influenza. *J Allergy Clin Immunol* 2012;130:1213-1216].

Thus, the occasional child who receives an influenza vaccine may have a couple of hives or may wheeze a little, but whether they are egg-allergic does not determine the rate of those reactions.

Regarding the subset of children who have particularly severe egg allergy, most studies have specifically included patients with histories of severe anaphylaxis (n = 513) with egg ingestion, and these patients also tolerate the vaccine. So, it appears that even severely egg-allergic patients can safely receive IIV.

In terms of why no serious reactions are being reported, manufacturers of injectable IIV report that the maximum amount of ovalbumin is less than 1 µg per 0.5 mL dose. The measured amounts in independent laboratories are usually much lower than the claimed amounts. Thus, the vaccine does not appear to contain enough ovalbumin to cause a reaction.

In terms of the current state of US allergy guidelines, allergy guidelines are typically published by the Joint Task Force on Practice Parameters. The current US guidelines state the following [Annals of Allergy, Asthma & Immunology 2013; 111:301-2]:

“All patients with egg allergy of any severity, including anaphylaxis, should receive IIV annually, using any age-approved brand of IIV in an age-appropriate dose.”

“Special precautions regarding medical setting and waiting periods after administration of IIV to egg-allergic recipients beyond those recommended for any vaccine are not warranted.”

“Language that describes egg-allergic recipients as being at increased risk compared with non-egg-allergic recipients or requiring special precautions should be removed from guidelines and product labeling.”

Dr. Kelso shared a draft document, the International Consensus (ICON) on Allergic Reactions to Vaccines, for which he had been given permission to share excerpts from current international allergy guidelines on allergic reactions to vaccines that includes the following allergy organizations: World Allergy Organization (WAO); European Academy of Allergy and Clinical Immunology (EAACI); American Academy of Allergy, Asthma, and Immunology (AAAAI); and American College of Allergy, Asthma, and Immunology (ACAAI). This document will state the following:

“Egg allergy does not impart increased risk of anaphylactic reaction to immunization with either inactivated or live attenuated influenza vaccines”

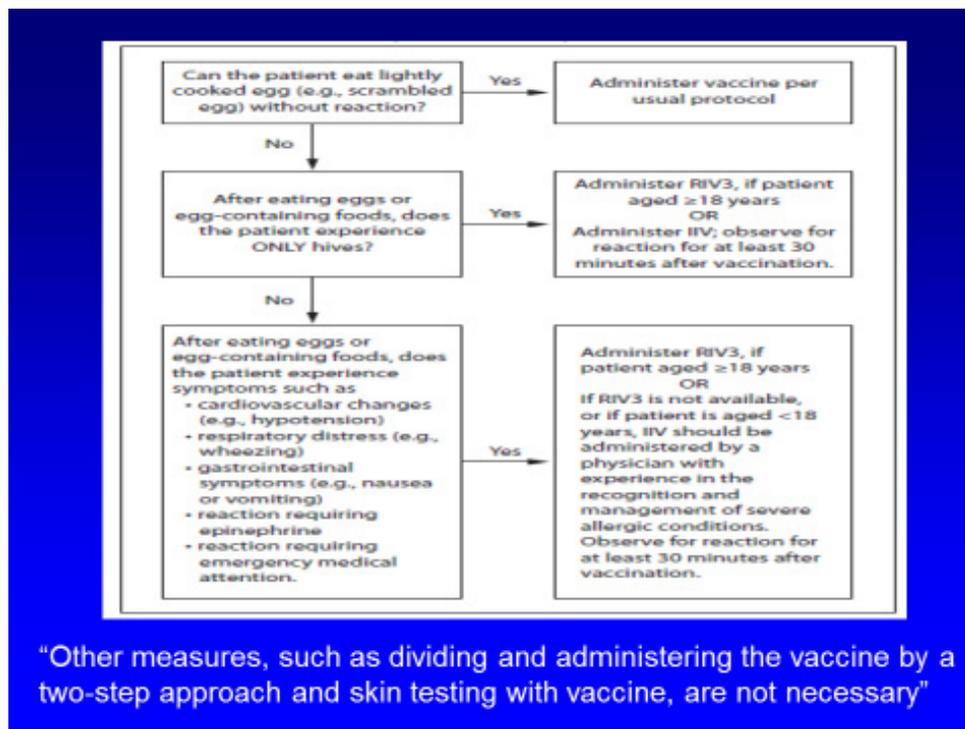
“Although cases of immediate hypersensitivity reactions such as urticaria may occur, they are no more common in egg-allergic than non-egg-allergic vaccine recipients.”

In terms of vaccine guidelines, the current National Advisory Committee on Immunization (NACI) guideline states the following:

“Regarding administration of influenza vaccine to egg allergic persons, after careful review, NACI has concluded that egg allergic individuals may be vaccinated against influenza using TIV without prior influenza vaccine skin test and with the full dose, *irrespective of a past severe reaction to egg and without any particular consideration, including immunization setting.*”

These guidelines have been in place in Canada since 2014, and they have not observed any uptick in adverse reactions or safety signals in monitoring since putting these recommendations in place where they removed any precautions regarding administration of influenza vaccine to egg-allergic patients.

The current ACIP guidelines include this algorithm:



This algorithm basically says that if someone can eat eggs and nothing happens, they are not allergic and can get an influenza vaccine. If someone eats eggs and just gets hives, they can get an influenza vaccine, but it has to be administered in a physician’s office and they have to be monitored for 30 minutes following vaccine. Alternatively, such patients can receive the recombinant vaccine that does not contain egg protein. The algorithm goes on to say that those who have had a more severe reaction to the ingestion of eggs, should go to an allergist’s office to receive the vaccine and be monitored for 30 minutes.

The ACIP guidelines go on to pay particular attention to LAIV to state that, “ACIP will continue to review safety data for use of LAIV in the setting of egg allergy.” There are several studies pertaining to this issue. The first of these included 68 children 2 through 16 years of age with egg allergy defined as a history of having not only an allergic reaction to the ingestion of eggs, but also the presence of IgE allergic antibody to eggs. Importantly, 40% of children were laboratory and clinically allergic to egg and had a history of anaphylactic reaction to egg. In addition, 55 children without egg allergy were included in this study. Participants were administered LAIV FluMist® in the usual manner, which contains less than 0.24 µg of ovalbumin per dose, and were observed for 1 hour. No patients developed an allergic sign or symptom during the hour of observation. These authors concluded that, “LAIV is a safe alternative to TIV in children with known egg allergy. It was not surprising that there were no immediate IgE-mediated reactions after vaccination of the children with egg allergy because the quantity of ovalbumin in LAIV is comparable with that of TIV, which has previously been shown to be safe in patients with egg allergy” [Safe vaccination of patients with egg allergy by using live attenuated influenza vaccine; Des Roches A, Samaan K, Graham F, Lacombe-Barrios J, Paradis J, Paradis L, et al. *J Allergy Clin Immunol Pract* 2015; 3:138-9].

The next study included a larger number of children—this time 282 children 2 through 17 years of age with egg allergy. The reason that most of these studies include children is because egg allergy is much more common in children. Egg allergy in this study is defined either as: 1) positive food challenge result to egg within the last 12 months under medical supervision; 2) previous convincing clinical reaction within 12 months and current sensitization (skin test or specific IgE); or 3) current sensitization with a greater than 95% likelihood of clinical reaction even if they had never eaten egg. Of the participants, 115/282 (41%) had prior anaphylaxis. Participants were administered LAIV FluMist® containing less than 0.24 µg of ovalbumin per dose in the usual manner, and were observed for 1 hour. In this case, 151/282 received a second dose 4 weeks later for a total of 433 doses given. No anaphylaxis occurred. Possible allergic reactions occurred in 8/282 (2.8%) within one hour of vaccine receipt. These included 6 rhinitis, 1 localized urticaria, and 1 gastrointestinal discomfort. All of these reactions were mild and self-limiting. The authors concluded that, “These data have demonstrated a safety profile in terms of systemic allergic reactions to LAIV in children with egg allergy, including those with a prior history of anaphylaxis, similar to that previously reported for children without egg allergy” [Safety of live attenuated influenza vaccine in atopic children with egg allergy; Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M, Doyle C, et al; *J Allergy Clin Immunol*; 2015; 136:376-81].

Finally, the largest of these studies included 779 children 2 through 18 years of age with a current doctor diagnosis of egg allergy. Of these children, 270 (34.7%) had a history of anaphylaxis to egg. Participants were administered LAIV in the usual manner and were observed for 30 minutes. No systemic allergic reactions occurred. Possible allergic reactions occurred in 9/779 (1.2%) within 30 minutes. These included 4 rhinitis, 4 localized/contact urticaria, and 1 oropharyngeal itch. Again, all were mild and self-limiting. The authors concluded that, “Children with an egg allergy can be safely vaccinated with LAIV in any setting” [Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M. ; *BMJ* 2015;351:h6291; *BMJ* 2015;351:h6291].

Collectively, of the three studies just covered, published reports now describe 1129 children with confirmed egg allergy, including 412 with a history of anaphylaxis to egg ingestion, who have been given LAIV without any immediate systemic reactions. As with the data on the IIV, the injectable vaccine, this is likely due to the very low amount of egg protein in the vaccine.

To put this in perspective, in the allergy world where the ingestion of allergenic foods and the likelihood of causing a reaction are contemplated, the lowest observed-adverse effect level (LOAEL) is taken into consideration. The LOAEL is the lowest amount of the offending food that would elicit mild, objective symptoms (e.g., mild urticaria, erythema, and oral angioedema) in the most sensitive individuals. It has been determined that 0.35% of patients allergic to egg may react to 130 µg of egg-white proteins. This is more than 100-fold more than the amount in influenza vaccine. Injecting and ingesting vaccine are different, but to put this in to perspective, it would take a lot more ovalbumin by ingestion to provoke symptoms, even in the most exquisitely allergic patients [Taylor SL, et al. Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J Allergy Clin Immunol* 2002;109:24-30].

On the other end of the spectrum is allergic reactions after egg-free recombinant influenza vaccine reported to VAERS. A report was published last year of 12 patients who described signs and symptoms that were consistent with acute hypersensitivity reactions after administration of RIV3, which cannot possibly contain any ovalbumin. The cases were all considered to be possible anaphylaxis. Just like all other vaccines, about 1 per million cases of anaphylaxis occur after influenza vaccine regardless of whether the recipient is egg-allergic or whether the vaccine contains egg. A patient with a history of a prior allergic reaction to influenza vaccination, not egg, should be evaluated prior to subsequent vaccinations [Allergic reactions after egg-free recombinant influenza vaccine: reports to the US Vaccine Adverse Event Reporting System; Woo EJ; *Clin Infect Dis* 2015;60:777-780].

In terms of what precautions are advised to mitigate the risk of anaphylaxis with any vaccine, ACIP's General Recommendations currently state as they always have that:

“Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management. All vaccination providers should be familiar with the office emergency plan and be currently certified in cardiopulmonary resuscitation. Epinephrine and equipment for maintaining an airway should be available for immediate use.”

These recommendations are not peculiar to influenza vaccines or egg allergies. These are recommendations that have always been made for any vaccine.

Turning to his more personal thoughts, Dr. Kelso said that he wondered whether the algorithm is needed. It implies that egg allergy increases the risk for an anaphylactic reaction after influenza immunization, but an extensive body of data says this is not the case. It implies that children with severe reactions to egg ingestion are at increased risk for reactions, but hundreds of such children have been vaccinated uneventfully. It implies that RIV is safer than IIV or LAIV for egg-allergic recipients, but all vaccines rarely cause anaphylaxis. It is inconsistent with US and international allergy guidelines. It is inconsistent with Canadian vaccine guidelines. It is an unnecessary barrier to immunization. Egg-allergic children and some adults are going unimmunized because practitioners do not want to take the risk. Many hospitalizations and some deaths occur among the unimmunized. With that in mind, Dr. Kelso indicated that his personal recommendations would be as follows:

1. No restriction on the use of the LAIV in egg-allergic recipients (i.e., treat LAIV like IIV);
2. No special precautions for the administration of any influenza vaccine (IIV or LAIV) to any egg-allergic recipient (i.e., no special medical setting or waiting period beyond those recommended for any vaccine recipient); and
3. No algorithm.

Discussion Points

Dr. Karron clarified what is done with a child who has a history of anaphylaxis to egg. The guidance does not recommend sending that child to an allergist. Instead, it says that such a child should be vaccinated by someone who is comfortable dealing with anaphylaxis. The argument can be made that anyone who offers vaccines anywhere, anytime should be prepared to deal with anaphylaxis. She said she thought that if the algorithm set up a barrier at all, it set up a barrier for those highly allergic children who have had an anaphylactic event. She would hope that those children are under an allergist's care. Whether they need to receive their vaccines under that supervision is a different issue. For the average child who has had a mild event, the guidance is to go ahead and vaccinate.

Dr. Kelso agreed that the guidance states that a physician with experience in treating severe allergic reactions, which he thought most people would translate to mean allergist. If in fact it does not mean anything beyond the expertise that any vaccine provider can offer, he would argue that it can be covered by the General Recommendations rather than a special box.

Dr. Kempe asked how many of these studies assessed younger children, and how much experience there is in Canada with repetitive immunization in children with anaphylaxis.

Dr. Kelso responded that most of these studies went down to age 2. Some of the 27 studies on injectable vaccines included infants. Because many of the studies included children, they also included children who needed a booster dose a month later. So, in many of the injectable vaccine studies and at least one of the LAIV studies, the investigators specifically assessed booster doses given at least a month later and did not observe a risk with that.

Proposed Recommendations for 2016-2017

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

Dr. Grohskopf reiterated the core influenza recommendation, with no changes proposed by the WG:

Annual influenza vaccination is recommended for all persons of persons 6 months of age and older.

- A licensed, age-appropriate influenza vaccine should be used
- Recommendations for different vaccine types and specific populations discussed in the ACIP statement

In the past four months, the WG has discussed timing of vaccination and decided that the available data did not indicate that the language should be changed substantially. The previous language in 2015-2016 read:

Optimally, vaccination should occur before onset of influenza activity in the community. **Healthcare providers should offer vaccination by October, if possible. Vaccination should continue to be offered as long as influenza viruses are circulating.** Children aged 6 months through 8 years who require 2 doses (see "Vaccine Dose Considerations for Children Aged 6 Months through 8 Years") should receive their first dose as soon as possible after vaccine becomes available, and the second dose ≥ 4 weeks later.

The statement that "Healthcare providers should offer vaccination by October, if possible. Vaccination should continue to be offered as long as influenza viruses are circulating" was clarified in the proposed 2016-2017 language as follows:

Optimally, vaccination should occur before onset of influenza activity in the community. Healthcare providers should offer vaccination **by the end of October, if possible.** Children aged 6 months through 8 years who require 2 doses (see "Vaccine Dose Considerations for Children Aged 6 Months through 8 Years") should receive their first dose as soon as possible after vaccine becomes available, and the second dose ≥ 4 weeks later. **Vaccination should continue to be offered as long as influenza viruses are circulating and unexpired vaccine is available.**

Some WG members were concerned that people would interpret "by October" to mean August or September while the spirit of the recommendation was October. The other change shown in red is a minor modification to the duration of the time during which vaccination should be offered.

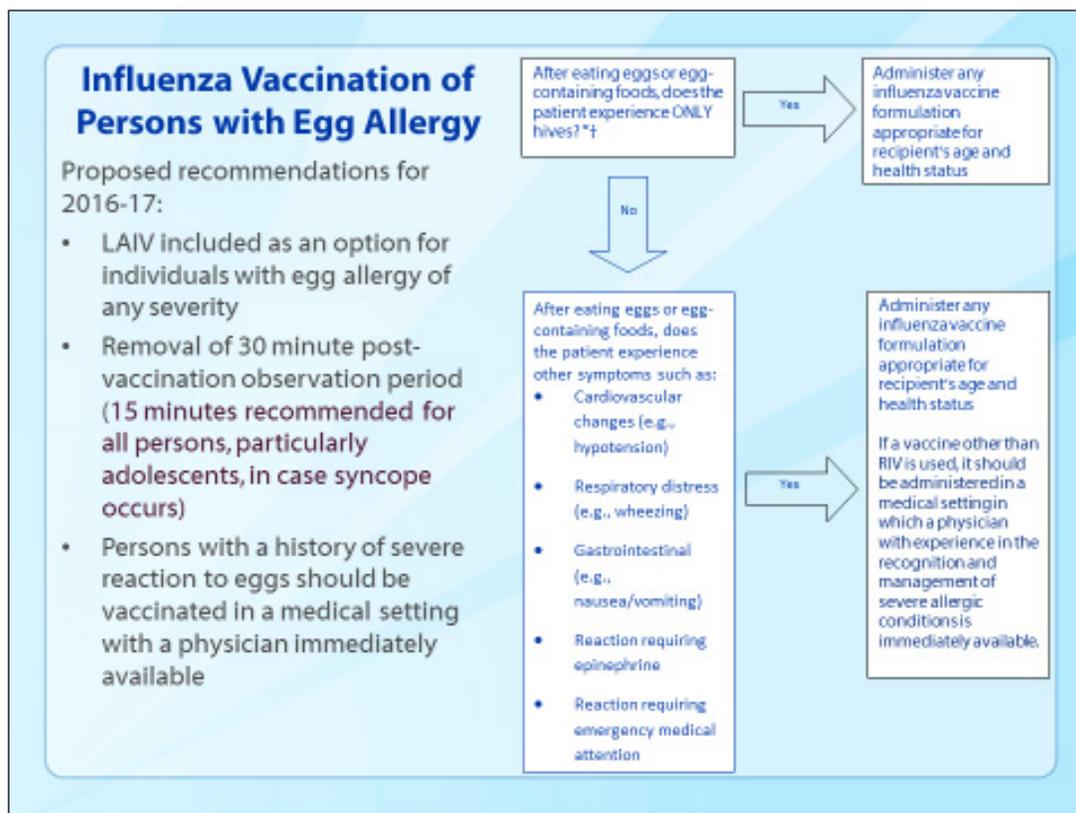
With regard to egg allergies, the 2015-2016 recommendations takes a stratified approach based on symptoms following egg exposure as follows [MMWR 2015; 64(30):818-825]:

- Hives only to eggs = mild allergy
- Any other symptoms = severe allergy
- LAIV is not recommended for egg allergy
- Until recently, there have been limited specific data on LAIV in this population
- A 30-minute post-vaccination period has been recommended since 2012 to observe for signs of allergic reaction, based largely on other allergy literature rather than post-vaccination AEs

In terms of the discussion within the WG over the course of several calls to explain the proposed language and the published data, including data discussed by Dr. Kelso earlier in the session, and potential language discussed in the Influenza WG and with investigators of the Clinical Immunization Safety Assessment (CISA) project. Major considerations included the overall rarity of anaphylaxis following vaccination in general, and because it is a rarity, events may be missed in small studies. For example, a paper by McNeil (2015) which describes VSD results noted 33 anaphylaxis cases after 25,173,965 doses of all vaccines combined for a rate of about 1.31 (95% CI 0.90-1.84) per million doses. In this paper, 10 anaphylaxis cases occurred after IIV3 was administered alone. With over 7,434,628 doses, the rate was 1.83 (95% CI 0.22-6.63) per million doses. That speaks to the relative rarity of these events in general. The 30-minute post-vaccination observation period was also discussed by the WG.

Some members thought it resulted in a false sense of security as severe reactions can occur after 30 minutes. In the same study by McNeil, the onset of symptoms was within 30 minutes in only 8 of 33 cases [McNeil MM et al, J Allergy Clin Immunol 2015]. Also discussed was the fact that since the recommendations were changed for the 2011-2012 season, there continue to be occasional VAERS reports of anaphylaxis following influenza vaccination of egg-allergic individuals. In not all cases is it known that this was due to egg, and it is probably not always possible to know that for certain. A stepwise approach such as has been taken in the past permits assessment of additional reports over seasons subsequent to change in recommendations. Similar to last time the WG discussed changing the recommendations, the discussion for those who are most severely allergic, the understanding was that these events are very rare and are probably not terribly likely. However, in the event that something happens, the feeling was that those with more severe allergy perhaps should be in a medical setting. This is the reason for the proposed recommendations.

In terms of the proposed recommendations for 2016-2017, the WG agreed that LAIV appears to be a low risk similar to that of inactivated vaccine and based on the data probably should not be treated differently from other vaccines. The proposed changes and algorithm follow:



A number of WG members wanted to call attention to the fact that the 15-minute waiting period recommended for all persons still applies, particularly adolescents, in case syncope occurs. This is pointed out in the current draft of the egg allergy language and would be pointed out in the general section about general precautions for vaccination.

In terms of the language that would accompany the algorithm, the first two points would not change from the previous recommendations

1. Regardless of a recipient's allergy history, all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available.
2. A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.
3. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Any licensed influenza vaccine (i.e., any form of IIV, LAIV, or RIV) that is otherwise appropriate for the recipient's age and health status may be used.
4. Persons who report having had reactions to egg involving symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may similarly receive any licensed influenza vaccine (i.e., any form of IIV, LAIV, or RIV) that is otherwise appropriate for age and medical conditions. The selected vaccine should be administered in a medical setting in which a healthcare provider with experience in the recognition and management of severe allergic conditions is immediately available.
5. A 30 minute post-vaccination observation period, previously recommended following vaccination of egg-allergic recipients, is no longer recommended. However, regardless of allergy history, vaccine providers should consider observing all patients, particularly adolescents, with patients seated or lying down for 15 minutes after vaccination to decrease the risk for injury should syncope occur (24).
6. For persons with no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, the recommendations in 3) immediately above may be followed.

Items 3, 4, and 5 reflect the changed language in the algorithm. With regard to retention of the algorithm, it has been found in the past that generally people seem to want one. It is possible to represent these recommendations wholly in text, but the reaction that tends to occur when discussing not having an algorithm for this and the 1- versus 2-dose question for young children has typically been that people like to have the algorithm to place in the ED or wherever else a quick visual reference is required.

Discussion Points

Dr. Moore said she was struggling with the idea of what the endpoint would be at which one would determine that an algorithm is no longer necessary. A number of studies have been presented with evidence of absence of an issue. VAERS is great for hypothesis generation, but does not suggest anything causal as is well-known from all sorts of things that can be reported to VAERS. She wondered at what point they decide there is enough evidence of absence of a problem specific to egg, at which point ACIP would be comfortable eliminating the algorithm.

Programmatically, the algorithm results in many people not getting vaccinated either because they are afraid of getting vaccinated because they have an egg allergy and they have heard that it is dangerous to get the influenza vaccine, or mass clinics, pharmacies, and school-located clinics have to spend a tremendous amount of time evaluating for this and then determining what to do. Many of them simply do not do that and decide that if there is an egg allergy question, they will skip it. This becomes quite a barrier to access for those folks.

Dr. Grohskopf replied that if a recommendation treated everyone the same way, an algorithm is probably not needed. In terms of getting to that step, the issue is that while there are data, the studies are relatively small and this is already known to be a rare event. While VAERS has obvious limitations, there has been a small number of cases in several seasons since the recommendations were originally changed in 2011-2012. Not enough to consider changing the recommendations back, but some of those cases have been discussed and it could never be determined with certainty whether those cases had more of a likelihood to do with egg than not. The general philosophy of the approach since 2011-2012 has been a season of data is reviewed, and perhaps a change is made. These particular recommendations, at least as they are presented at this point, there is no longer a waiting period which is an important barrier in a lot of clinical settings. Also, it still means that everybody can be vaccinated and not even an allergy-experienced person would be required to be there.

Dr. Kempe pointed out that this is basically a power issue and the confidence intervals are needed around the estimates. To her knowledge, nobody has assembled these data in a systematic review. That is why she was asking about the Canadian experience and whether there is anything where this has been done routinely that could help ACIP with larger numbers.

Dr. Gemmill (NACI) indicated that the work was done primarily in the province of Quebec, by Dr. De Serres who presented earlier on meningococcal B, in conjunction with the Quebec Association of Allergists. He said they feel very confident that they made the right decision so far. While the trickle down has not happened completely yet because it takes a while for practice to change once a recommendation has been made, there have been absolutely no signals. They have been in touch with their safety representatives to confirm that point. Perhaps more details can be provided in writing at a later time.

Dr. Byington (AAP) noted that the language regarding *physician* versus other providers may be very limiting in some cases if nurse practitioners, physicians assistants, et cetera are administering the vaccine. She wondered if *provider* could be substituted or *physician* was required.

Dr. Grohskopf responded that the WG discussed this at length and the final thinking was to include the word *physician*.

Dr. Karron added that there was a diversity of opinions among the WG members.

Regarding the power issue raised by Dr. Kempe, Ms. Pellegrini said that if they are looking for reactions that are literally 1 in a million, it seemed to her that there is simply no way to conduct a study that is going to turn those up in a methodical way. Furthermore, there is no way to write an algorithm that is going to effectively screen for a 1 in a million event. Therefore, it was not clear whether they should bother with an algorithm.

Dr. Kempe said she did not think they were looking for 1 in a million. If they had the numbers from Canada, an assessment could be done over a reasonable period what the point estimate could be with that number of people, and then make a more rational decision.

Dr. Grohskopf noted that something raised in the past when recommendations are changed, prior to changing there may be less use of something because it was not recommended to use it. This was brought up when it was recommended to start using the inactivated vaccine. Might more cases be seen in VAERS once it is recommended that it is okay to give the vaccine. One point that was raised was that LAIV is currently not recommended, so there may be more use and more reports in VAERS as a result.

It sounded to Dr. Messonnier that there may be more data that might be helpful to the ACIP members in thinking this through. The WG seemed to be suggesting a stepwise approach, gather additional data, and then reassess. There are other data that could be assembled, such as missed opportunities, to give the members some kind of confidence intervals. Because the data were not available during this meeting, the group could opt to table the recommendation until the next meeting when those data could be provided. Alternatively, they could take the incremental steps at some level that the WG was recommending, and hear further data at the next meeting or the meeting after that. Or, they could go all the way during this meeting.

Dr. Karron said that if they kept some type of algorithm, she would suggest removing the language “if a vaccine other than RIV is used” for two reasons: 1) RIV is not used in children, and 2) anaphylaxis can occur with RIV.

Dr. Kimberlin (AAP) said he was reading Item 4 on slide 9 as meaning that people with reactions to egg involving angioedema and so forth *may* receive the vaccine, and he would consider someone needing epinephrine or another emergency medical intervention to be pretty severe. Item 2 states “A previous severe allergic reaction to influenza vaccine, regardless of the component suspected” which might mean egg allergy or egg protein is a contraindication to receive the vaccine in the future. This seemed like a discrepancy to him.

Dr. Grohskopf clarified that Item 4 reflects symptoms following exposure to egg, while Item 2 reflects symptoms following exposure to vaccine. Regardless of allergy history, having a previous severe reaction to a vaccine is a contraindication for further receipt of that vaccine. This point does not refer specifically to egg, but has been in the recommendations since 2011-2012 because it was felt important to remind people of that. There was a specific request to insert that. Contextually, since most of the section talks about egg allergy, it probably does not fit as well.

Due to a time constraint pertaining to the Zika Virus session, Dr. Bennett suspended the conversation until later in the day.

Upon returning to the influenza discussion, Dr. Bennett reported that in speaking with the WG, putting the vote off until June would not be suitable due to the *MMWR* publication timeline. Moreover, it is unlikely that any additional information would be available by June. As a result, she asked whether anyone had a motion regarding the 2016-2017 recommendations.

Dr. Karron indicated that during the break, she caucused among the other ACIP Influenza WG members and the WG wished to propose the following changes based upon the earlier discussion:

- 1) Remove the algorithm figure entirely
- 2) Retain Items 1, 2, and 3 because they are just making general statements that are not controversial and merely reiterate what ACIP has said often
- 3) Retain Item 4, but strike the phrase “if a vaccine other than RIV is used,” state “The selected vaccine should be administered in a medical setting in which a healthcare provider with experience in the recognition and management of severe allergic conditions is immediately available,” and change *physician* to *healthcare practitioner*
- 4) Eliminate Item 5 in its entirety, because observation of people following influenza vaccine should not differ from the General Recommendations and is redundant here
- 5) Eliminate Item 6 because this was added due to one famous case in the CISA literature in a child who was not suspected of being egg-allergic; that child had anaphylaxis and then was discovered upon skin testing to be egg-allergic and it was hypothesized that the vaccination sensitized the child, so that child would not have been discovered following this recommendation

Dr. Baker said that as a pediatrician, but not representing the AAP, she thought the suggested changes were perfect and that it should be kept simple. While it would be nice to have more data in the future, the data presented during this session were enough at this point.

Dr. Weber (SHEA) noted that if RIV is allowed, it could be given by anyone. If there is a requirement that a trained physician must be present to deal with anaphylaxis, that may mean someone who is approved to intubate a patient, which means it is going to be limited to ED and the intensive care unit (ICU) physicians. It would eliminate all family practice physicians, nurses, and clinics in his facility who are not licensed for intubation.

Dr. Bennett clarified that the recommendation was to change *physician* to *healthcare provider*.

Dr. Moore thought the changes were wonderful and would make implementation much easier programmatically. In terms of the statement regarding administration in a setting where people can handle anaphylaxis, in general anyone who gives an immunization should be capable of responding and reacting to someone who has signs of anaphylaxis because any vaccine can cause that. She wondered whether something specific should be called out here, similar to Item 6 which is already in the General Recommendations making it redundant to say it again here. Perhaps it would not be necessary to restate the provision here, because any vaccine can cause anaphylaxis.

Dr. Karron pointed out that this would be a major change to the existing language, and this would provide a way to do it in a stepwise manner. It may be that over time, there are no specific recommendations around this. That would be a radical change for now.

Dr. Moore clarified that, for example, a pharmacy that is equipped to respond to someone who has anaphylaxis after administration of a drug should not be administering to this person. She was concerned about how to translate that to people who want to know where someone should go.

It was noted that the intent of the discussion in the WG was that it be in a healthcare setting where there is someone who can manage it, not in a local drug store.

In particular, Dr. Karron noted that the WG talked about the fact that they did not necessarily want children with a previous history of anaphylactic responses to be vaccinated in the school setting.

Dr. Ezeanolue suggested saying “go to a healthcare setting.” This was not clear to him based on the language.

Dr. Moore suggested clarifying the language by stating “inpatient or outpatient medical setting.”

Dr. Harriman thought Item 1 addressed emergency management and that it did not need to be in both places.

It was noted that perhaps some language could be borrowed from the General Recommendations to be put in that area.

Dr. Grohskopf replied that they plan to add the list from the General Recommendations once that is further along.

Dr. Kempe thought it would be hard for doctors to understand this change without any explanation. She wondered if they should state “based on more recent data” to set the ground work for a change that is based on something.

Dr. Bennett thought that was a good suggestion, but pointed out that the group did not have to vote on that specifically. It could be part of the narrative.

Dr. Grohskopf noted that that is a substantial part of the narrative before these bullets.

Dr. Savoy (AADP) asked if they were suggesting that the local CVS that has an office where there is a nurse practitioner who potentially has the equipment needed could or could not give a vaccine to an egg-allergic child. It sounded like some people were saying “yes” and the WG was saying “no.”

Dr. Foster (APhA) assumed “equipment” was referring to epinephrine, which is what most guidelines require. Perhaps the wording would be better if the word *drugs* was used rather than *equipment*. Most places do not have equipment, but pharmacists are trained to handle these types of reactions as part of the pharmacist training program. He did not think that would exclude people from getting vaccines in pharmacies.

Dr. Riley noted that the WG did not ask the question about whether it was okay or not okay.

Dr. Karron clarified that the intent of the WG was that for those children who had a previous episode of anaphylaxis, that perhaps more of a medical environment would be appropriate. She wondered whether they were struggling over a problem that was truly a problem in the sense that a child who has had an anaphylactic response is not a child that is likely to be vaccinated in a pharmacy or a school setting. They would be more likely to be vaccinated in a healthcare setting.

Dr. Belongia wondered whether it would help to say *clinical practice setting* instead of *medical setting* to be clearer.

Dr. Savoy (AAFP) did not understand why a patient would think that a pharmacy-based or school-based clinic is not a healthcare, medical care, or provider-based setting. Aside from it not being inpatient, which is fairly obvious, it was not apparent how any of the words being suggested would clarify that.

Dr. Kempe thought this was a scope of practice issue. A well-equipped pharmacy clinic with a nurse practitioner who has handled anaphylaxis, that is probably within her scope of practice. She was not sure they could be more specific about the scope of practice for a provider in a given setting.

Dr. Bennett asked whether there was language in the General Recommendations that they could duplicate and place into this recommendation, or if they could refer back to the General Recommendations.

Dr. Messonnier thought that the problem was that this language was very similar to Item 1. It seemed that they were trying to say that additional precautions should be taken with these children with a history of anaphylaxis. One way to fix that might be instead of putting it here, to put the language with Item 1. The issue is not specific to this. Item 1 says everyone should get a vaccine in a place where they could have recognition and treatment of anaphylaxis. A sentence could be added there to say, "Patients with a history of anaphylaxis should take special care to make sure that this is available." That would be a more general statement than trying to attach it to an influenza vaccine.

An inquiry was posed regarding whether that would also remove the stratification. Dr. Messonnier clarified that she was not suggesting removing the stratification. She was just noting that there were two sentences, both of which recommended the setting in which vaccine should be given. It might make more sense to combine them, because they were trying to make the contrast between Item 1 and Item 4 in which they were trying to say that this should be a more stepped up setting.

Dr. Rubin asked for clarification regarding whether Dr. Messonnier was suggesting that they move the language in Item 4 and make it part of Item 1.

Dr. Messonnier said she felt that the WG was trying to contrast that in general, everybody should get a vaccine in a certain setting but that patients with a history of anaphylaxis to egg should have more precautions. She thought the language would work better if it was included in Item 1.

Dr. Karron amended her motion to move the language under Item 4 to become paragraph 2 in Item 1. Then there would only be 3 points: 1, 2, and 3.

Dr. Bennett clarified that there would still be 4 bullets, as only part of Item 4 would be moved.

Dr. Messonnier thought they were trying to achieve parallelism between a setting for everybody and setting for people with a history of egg allergies.

Dr. Belongia thought there appeared to be a contradiction. The last part of Item 4 seemed to imply that that was the situation for people who have reported having had bad reactions to eggs in the past. They can get any vaccine, but those people should receive vaccines in that setting. However, Item 1 says that everybody should receive a vaccine in that setting. That was discordant.

Dr. Bennett thought that if they could craft it in Item 1 it might be easier than trying to have it in two different places and be slightly different.

To clarify, Dr. Cohn suggested moving the paragraph in Item 4 that read, “The selected vaccine should be administered in a medical setting in which a healthcare provider with experience in the recognition and management of severe allergic conditions is immediately available” and move it to Item 1, but tailor/finalize the language slightly to reflect that same message in Item 1 after the vote and send it around to everyone for approval before it is published.

Dr. Grohskopf said she was somewhat confused, because if they moved the last sentence from Item 4 and placed it in Item 1, there would be no difference specified between the two classes of individuals. Basically, 3 and 4 would be the same after that.

Dr. Karron agreed, noting that there were some general statements in the bullets that apply to everybody. Everybody should receive vaccines in settings where appropriate expertise is available. Anyone who has a reaction to influenza vaccine should not get it again. Then there are two categories of people: A, people who have had mild reactions (Item 3) and Category B, people who have had more severe reactions (Item 4). She thought to move information from Item 4 would not follow that logical flow.

Dr. Messonnier thought where people were getting stuck was understanding the categories, but not understanding what they were trying to convey would be different about people in Item 4. Pharmacists might say that now there are clinics where there are providers with experience in recognition and management of severe allergic reactions. Therefore, if someone has had a severe allergy, she wondered what they were suggesting they do.

Dr. Karron clarified that Item 1 said “in a setting where” and Item 4 said “medical setting,” which was the WG’s attempt to say that this should be a clinical setting.

Dr. Bennett asked whether it would be possible in Item 1 to delineate these specific groups just outlined clearly and directly.

Dr. Karron did not think it flowed from Item 1.

Dr. Rubin pulled up a document from the AAP from *Pediatrics* 2007 titled “Preparations for Emergencies in the Offices of Pediatricians and Primary Care Providers.” In part, the paper stratifies how close an office is to a hospital (within 10 minutes, longer than 10 minutes). That stratification results in the type of equipment / expertise that is appropriate for the office, including airway management. He thought they were talking about the same thing. Airway management equipment was not as likely to be available in a pharmacy. That might change with more data.

Dr. Kempe thought they were getting two things confused. Item 1 pertained to generally being ready for anaphylaxis. This is about a belief on many people’s part in the past, which was probably false, that egg allergies specifically cause anaphylaxis with influenza vaccine. This is about people who have already had a severe allergic reaction. If they were known to have a reaction to influenza vaccine, it wouldn’t be given to them again. They were trying to uncouple the egg allergy issue from the influenza issue, and she thought it needed to be more explicit. Item 4 was not the same as Item 1.

Dr. Rubin was not clear that they were ready to make that step. If they were, the document would become a lot simpler.

Dr. Fryhofer (AMA/ACP) indicated that she was part of the WG and this was a long discussion during the WG meeting. Part of the reason they left *physician* was because that changed the context of the type of medical setting. The way the conversation was going, they might as well for Item 3 say “children with an egg allergy of any severity can get any of the vaccines.” However, she did not think that was the WG’s intent.

Dr. Riley’s understanding was exactly what Dr. Rubin said, which was that they were not ready to jump all the way to “don’t worry about it.” However, she thought she was hearing that the concern was that someone might still have anaphylaxis, so what they really wanted was availability of airway management. Why not just put that in? She would not try to lump that together with Item 1, because it would be confusing. The progression was general, mild allergy, then severe allergy.

Dr. Belongia thought that would address the ambiguity to a great degree if that term was used specifically.

Dr. Netoskie (AHIP) agreed with Dr. Riley. It seemed to him that under the topic of egg allergy, the most important message to begin with is that “you may administer vaccine to people who have had egg allergy issues.” He thought that should be first, followed by the conditions where there may be various levels of concern. From the physician education perspective, that is the key message that should come across first.

Dr. Schaffner (NFID) expressed concern that they were drifting into the ultimate management of anaphylaxis. From his point of view, the place where vaccines are administered need two pieces of equipment: an epi pen and a cell phone.

Dr. Rubin pointed out that the critical difference in Items 3 and 4 was that in 3 the vaccine *should* be administered and in 4 the vaccine *may* be administered.

Dr. Moore emphasized that the data from allergists suggest that there is not even a biological plausibility to this causing anaphylaxis because of the minutia. She said she understood the difference in injection versus ingestion, but that that is difficult to make a case for. Perhaps they could state “Out of an abundance of caution” and then say that there is no evidence at this point that there are a lot of people who are having anaphylactic reactions to influenza vaccines who have a history of egg allergy.

Dr. Grohskopf responded that that is discussed in the background section that precedes this recommendation, in addition to the literature, including all of the literature discussed by Dr. Kelso. Going back the last several years, one of the concerns has been that there is a recommendation from the allergy community as well as the ACIP recommendation, which is for everybody. One thing that has been voiced consistently over the last three or four years has been the venues and settings in which vaccination is occurring have expanded and are much more diverse. There was overall some concern that there may be some settings that, even though it is repeatedly recommended that certain equipment should be available, it might not be. Perhaps including some particular language would help.

Dr. Bennett said she thought they needed to go to vote, but that they needed to clarify what they would be voting on since they had gone back and forth. Her proposal was to vote on what they had at the moment, and then if there was a wording change the WG felt should be made, they trust them to make the changes and review them after the fact. She did not think that continuing the discussion was going to get them anywhere, as they seemed to be going around in circles. She said if anyone adamantly objected, she would be happy to listen, but she thought they needed to move forward.

Ms. Pellegrini emphasized that they wanted to get this right. It is important and is a big change that would take a long time for physicians, patients, and families to get used to. She did not understand exactly what they had to do during this meeting, and whether they were under pressure for something to be published.

Dr. Bennett responded that they must approve these recommendations so that the *MMWR* could be published in a timely manner. What they did not have to do was approve the exact wording. They merely had to approve it in spirit.

Dr. Fryhofer (AMA/ACP) noted that she is a practitioner who sees patients. When she saw the word “equipment” it meant to her that she needs to have an anesthesiologist there to intubate the patient. She thought this was creating a barrier that was an unintended consequence. Adding the airway management will make people think they have to be ready to intubate a patient. That is not a reality.

Dr. Bennett clarified that she was proposing that they vote without that, as it was added after the original language. She proposed they vote on the amended motion. She emphasized that there was no way this would be perfect by the end of the day, and that they should move forward with the sense that there would be an opportunity to see the specific wording and make comments on it after the WG has a chance to incorporate the comments. She said she had total trust in them that they understood the subtleties of what was said during the discussion.

Vote: Influenza Vaccine Recommendations for 2016-2017

Dr. Karron made a motion to approve the 2016-2017 Influenza Vaccine Recommendations for 2016-2017 with the changes as proposed. Dr. Walter seconded the motion. The motion carried with 11 affirmative votes, 0 negative votes, and 3 abstentions. The disposition of the vote was as follows:

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

Zika Virus**Update on CDC's Response to Zika Virus**

Toby L. Merlin, MD
Director, Division of Preparedness and Emerging Infections
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Merlin provided an update on CDC's response to Zika Virus. He summarized the current situation, CDC's response activities, and the challenges and opportunities for vaccine development.

The Zika virus outbreak has grown in size and reach and is attracting interest from public and the media abroad, as well as in the US. In response to this emerging public health threat, CDC activated its Emergency Operations Center (EOC) on January 22, 2016 to help coordinate the public health response. On February 1, 2016, the WHO declared a [Public Health Emergency of International Concern](#) (PHEIC) because of clusters of microcephaly and other neurological disorders in some areas affected by Zika.

On February 8, 2016, CDC elevated its EOC activation to a Level 1, the highest level. President Obama also announced a request for \$1.8 billion in emergency funds for several agencies to accelerate research into a vaccine and educate populations at risk for disease [<https://www.whitehouse.gov/the-press-office/2016/02/08/fact-sheet-preparing-and-responding-zika-virus-home-and-abroad>].

The goals of the CDC Zika virus response are as follows:

- ❑ Characterize the effects of Zika Virus infection (Zika) in the current outbreak
 - Effects of Zika in pregnant women, including the risk of fetal loss and congenital malformations, including microcephaly
 - Determine the risk of GBS associated with Zika

- ❑ Promote and evaluate interventions to prevent Zika, particularly in at-risk populations (pregnant women)
 - Personal protective measures (insect repellent, contraception)
 - Vector control
 - Prevention of transmission via blood and transplantation
 - Travel advisories

- ❑ Enable detection of Zika by development and distribution of Zika laboratory diagnostics

Current CDC investigations and collaborations include the following:

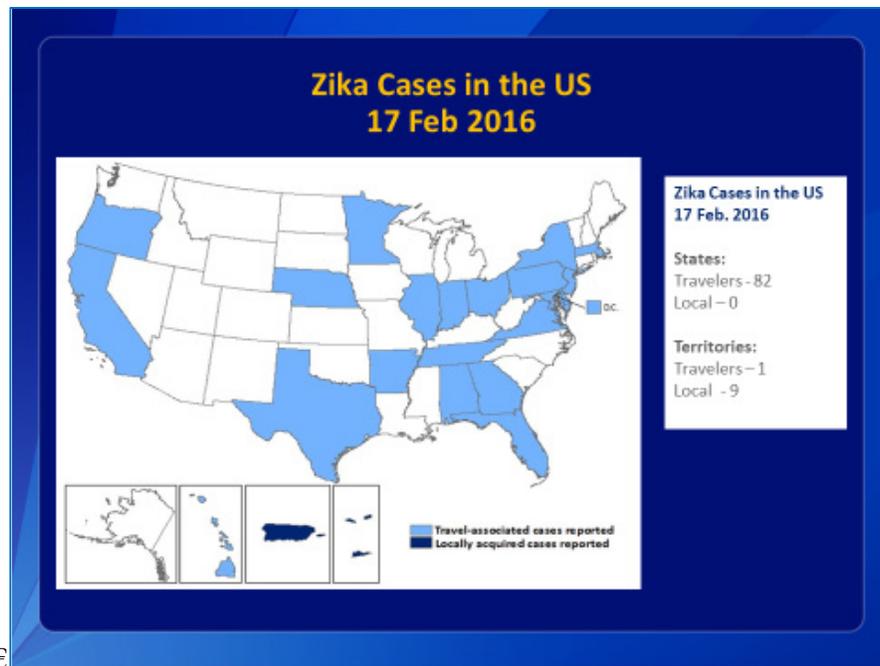
- ❑ Brazil
 - Retrospective case-control study for risk of fetal Zika infections, potential co-factors, and microcephaly
 - Retrospective case-control study for risk of GBS

- ❑ Columbia (protocols pending approval)
 - Prospective pregnancy cohort study to define spectrum of fetal outcomes associated with Zika infection
 - Virus persistence in semen, urine

- ❑ Domestic (particularly Puerto Rico)
 - Pregnancy registry and follow-up of cases

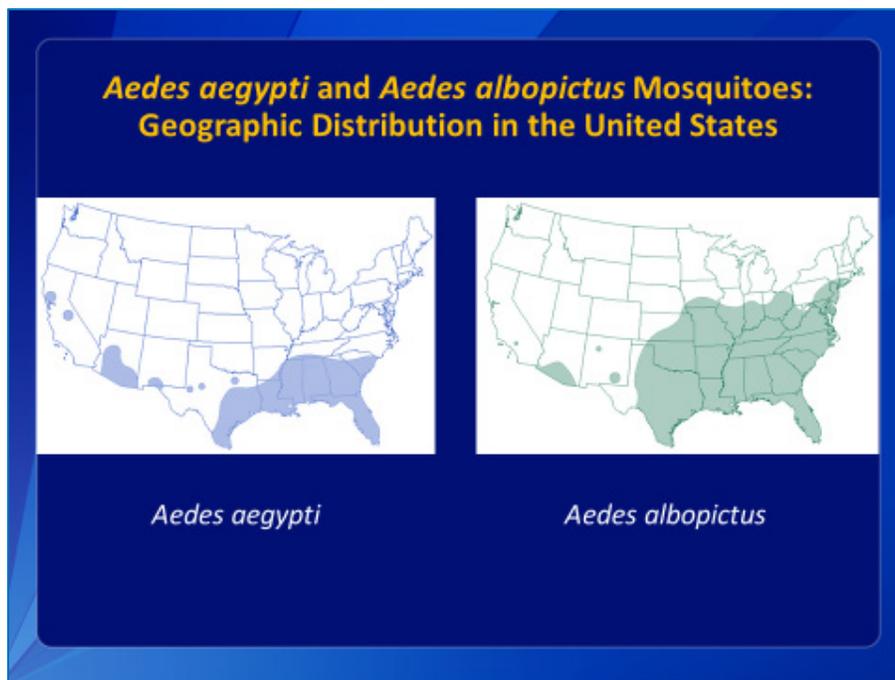
- ❑ Other studies
 - Histopathologic examination of tissues from affected pregnancies

Prior to 2015, Zika outbreaks occurred in Africa, Southeast Asia, and the Pacific Islands. In May 2015, the first locally-acquired cases in the Americas were reported in Brazil. Currently, outbreaks are occurring in many countries in the Americas and US territories, including Puerto Rico, American Samoa, and the US Virgin Islands. Thus far, local mosquito-borne transmission of Zika has not been reported in the continental US. Since 2011, there have been laboratory-confirmed Zika virus disease cases identified in travelers returning to the US from areas with local transmission. With current outbreaks in the Americas, cases among US travelers will most likely increase. The following map depicts Zika cases in the US as of February 17, 2016:



Imported cases may result in virus introduction and local spread in some areas of the US where *Aedes* mosquitoes are present. CDC is not able to predict how much Zika virus will spread in the continental US. However, recent chikungunya and dengue outbreaks in the continental US suggest that Zika outbreaks may be limited to small, geographic clusters.

The following maps depict the approximate distribution of *Aedes aegypti* and *Aedes albopictus* mosquitoes in the US:



Aedes aegypti mosquitoes have been identified across the southern half of the US from California to Florida, while *Aedes albopictus* has been identified throughout much of the Southern and Eastern US. Imported cases may result in virus introduction and local spread in some areas of the US where *Aedes* mosquitos are present.

CDC is not able to predict how much Zika virus would spread in the continental US. The spread of Zika is most likely due to the movement of people, not the movement of mosquito populations. For Zika to cause an outbreak in the continental US people infected with the virus need to enter the US. An *Aedes* mosquito must bite the infected person during the relatively short time that the virus can be found in the person's blood. The infected mosquito must live long enough for the virus to multiply and for the mosquito to bite another person.

The best way to prevent diseases spread by mosquitoes is to protect against mosquito bites through the following efforts:

- Wear long-sleeved shirts and long pants
- Stay in places with air conditioning or that use window and door screens to keep mosquitoes outside
- Use Environmental Protection Agency (EPA)-registered insect repellents:
 - When used as directed, these insect repellents are proven safe and effective even for pregnant and breastfeeding women
 - Insect repellents should not be used in babies younger than 2 months of age
 - Products containing higher than 30% N,N-diethyl-meta-toluamide (DEET) should not be used in children, and products containing para-menthane-diol (PMD) should not be used in children younger than 3 years of age
- Use mosquito netting to cover babies younger than 2 months of age in carriers, strollers, or cribs to protect them from mosquito bites
- Do not use oil of lemon eucalyptus in children younger than 3 years of age
- Sleep under a mosquito bed net if air conditioned or screened rooms are not available or if sleeping outdoors

Recent chikungunya and dengue outbreaks in the continental US suggest that Zika outbreaks in the US mainland may be limited to small, geographic clusters. Better housing construction, less crowding, regular use of air conditioning, use of window screens and door screens, and state and local mosquito-control efforts have helped to limit transmission of these mosquito-borne viruses.

Currently, there is no vaccine or medication to prevent infection or disease. Developing safe and effective vaccines for the prevention of emerging infectious diseases, such as Zika, is a priority for the US government. Preliminary evidence indicates that a vaccine could be effective in preventing Zika virus infection. Natural infection elicits neutralizing antibodies, and the virus

appears to show minimal antigenic and genetic variation across strains. Moreover, there are limited data revealing neutralization across viral strains.

Plans are under development to leverage existing infrastructure to provide a coordinated and collaborative framework to support the accelerated development of Zika vaccines. Ongoing partnerships between National Institutes of Health / National Institute of Allergy and Infectious Diseases (NIH / NIAID), the Biomedical Advanced Research and Development Authority (BARDA), CDC, FDA, and the DoD's Walter Reed Army Institute of Research (WRAIR), and industry partners will provide a coordinated and collaborative framework to support the accelerated development of Zika vaccines. There are many approaches and technologies being put forth, including recombinant, live-attenuated, live-chimeric with other flavivirus components, nucleic acid, whole-inactivated virions, and other virus-vectored platforms. These vaccine candidates are all in exploratory stages of development.

The President's emergency funding request includes support for vaccine research and diagnostic development and procurement. The request includes funding for research, rapid advanced development, and commercialization of new vaccines and diagnostic tests for Zika virus. There is also some funding for the US Agency for International Development (USAID) to create new incentives for the development of vaccines and diagnostics.

Vaccine Development Update

Bruce Gellin, MD, MPH
Director, National Vaccine Program Office
Department of HHS, Public Health and Science

Dr. Gellin further described the vaccine development process and development pertaining to Zika virus. He first explained that the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) coordinates federal efforts to enhance chemical, biological, radiological, and nuclear threats (CBRN) and emerging infectious diseases (EID) preparedness from a medical countermeasure (MCM) perspective. He explained that he wanted to put Zika virus vaccine development in the context of the PHEMCE, given that it is "all hands on deck" regarding who has equities they can provide.

The PHEMCE is led by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and includes three primary HHS internal agency partners: CDC, FDA, and NIH. Also included are several interagency partners: DoD, VA, the Department of Homeland Security (DHS), and the US Department of Agriculture (USDA). PHEMCE Agency Lead roles are depicted in Figure 2 below:

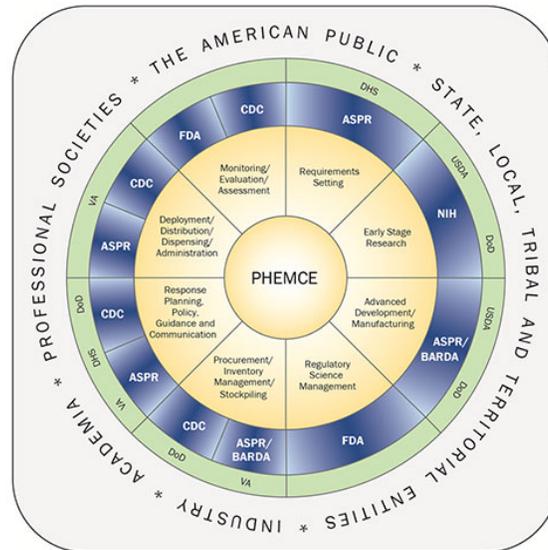


Figure 2: PHEMCE Agency Lead Roles



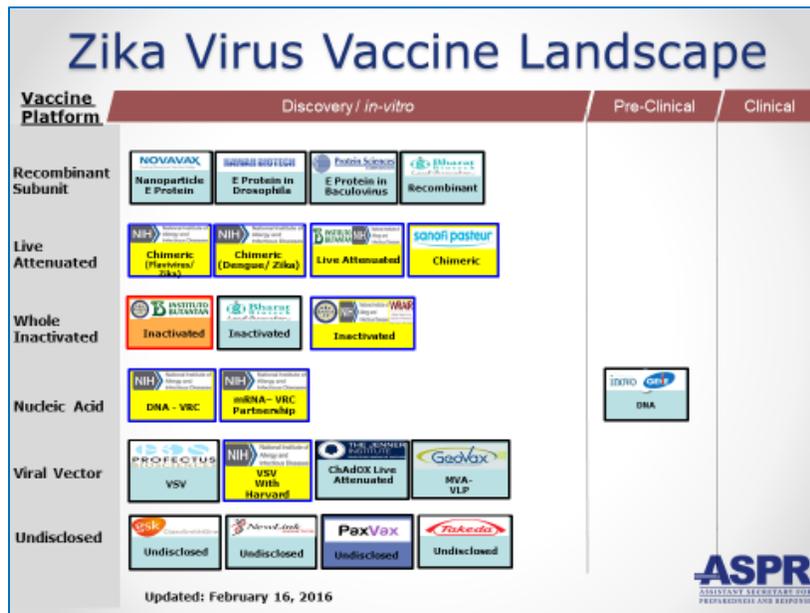
The PHEMCE strategic goals are to:

- Identify, create, develop, manufacture, and procure critical MCM
- Establish and communicate clear regulatory pathways to facilitate MCM development and use
- Develop logistics and operational plans for optimized use of MCM at all levels of response
- Address MCM gaps for all sectors of the American civilian population

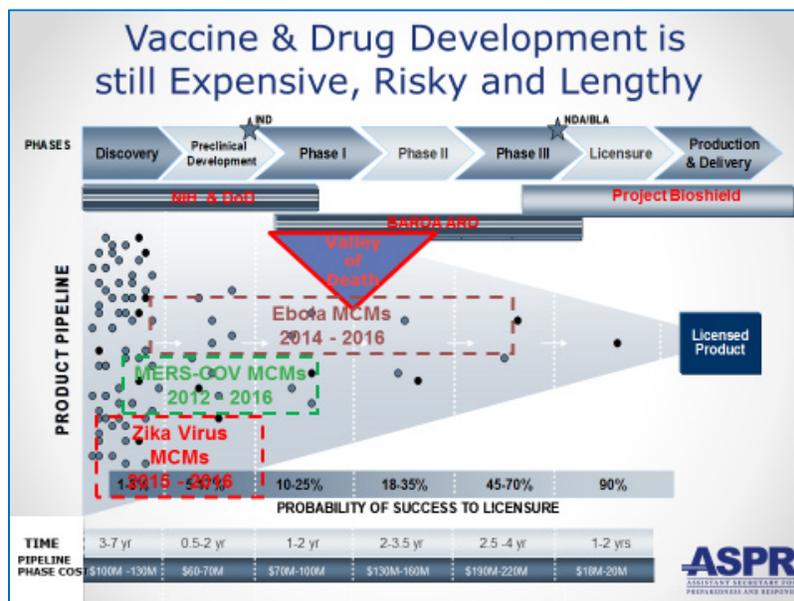
The HHS priorities on MCM for Zika virus include the following:

- Detect Zika Infection*
 - Support advanced development of rapid serological diagnostics, including point of care, for the detection of antibodies in persons previously infected with Zika virus
- Prevent Zika Infection*
 - NIH/DOD/BARDA collaboration for USG-developed, manufactured, and evaluated Zika virus vaccine
 - NIH and BARDA to support private sector development of vaccine through federal funding opportunities
 - HHS to support international collaborations, including vaccine production at the Butantan Institute in Brazil
- Secure and Protect Blood Supply*
 - Support advanced development of high throughput molecular diagnostics for screening blood supply
 - Support late stage pathogen reduction systems

The current Zika virus vaccine development landscape as of February 16, 2016 is depicted in the following graphic showing the various platforms and stages of clinical development:



It is important to understand that the vaccine and drug development pipeline is expensive, risky, and lengthy. This is illustrated by the following graphic that highlights the progress with Zika virus vaccine development relative to Ebola and Middle East Respiratory Syndrome (MERS) vaccine development:



It is clear that there is a significant amount of interest in Zika virus vaccine development, and there are numerous technologies that could be utilized. There are a number of key questions and concerns related to Zika virus vaccine research and development, including the following:

- ❑ *Safety Concerns*
 - Pre-existing immunity to Zika, YF, dengue, and vaccine platforms
 - Is there a potential for antibody dependent enhancement?
- ❑ *Intended Usage*
 - General usage (GUP) and post-exposure (PEP) prophylaxis
 - Special populations: pregnant women, women of child bearing age (WOCBA), infants, children
- ❑ *Vaccine Properties*
 - Vaccine components (e.g., E protein, whole virus, adjuvants, other viruses)
 - Level and type of elicited immunity
 - Kinetics of vaccine immunity
 - Duration of immunity (Heterologous Prime/Boost Approach)
 - Routes of administration
 - Platform technology maturity
 - Manufacturing process maturity (potency assays, vaccine stability)
- ❑ *Zika Virus Natural and Adaptive Immunity in Animals and Humans*
 - Correlates of protective immunity
 - Immunogenicity and protection study design
 - Assays and reagents

There have been several workshops since early February 2016, and there are additional upcoming workshops of interest:

- ❑ March 1-2, 2016 in Washington, DC
PAHO Meeting on the Zika virus research agenda and its public health implications in the Americas
- ❑ March 28-29, 2016 in Washington, DC
HHS Stakeholders meeting on Zika virus and Medical Countermeasures

Contact information of interest pertaining to Zika virus vaccine development includes the following:

- ❑ Request a Tech Watch Meeting Through www.medicalcountermeasures.gov
 - Contact Jonathan Seals, Director Strategic Science and Technology Division, jonathan.seals@hhs.gov

- ❑ BARDA Broad Agency Announcement
 - [BAA-16-100-SOL-00003](#) will support innovation through development of platform technologies that enhance capabilities for development and manufacturing of MCMs.
 - Technical Point of Contact: Mark Craven: mark.craven@hhs.gov
- ❑ NIH Federal Funding Opportunity
 - [NOT-AI-16-026](#) will support high-priority Zika virus research areas detailed in the solicitation

Cholera Vaccine

Introduction

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

Dr. Reingold reminded everyone that the Cholera Vaccine WG was formed in August 2015. During the October 2015 ACIP meeting, the WG presented an overview of cholera background and epidemiology. PaxVax filed a BLA with the FDA in October 2015 with a request for priority review for the use of its vaccine CVD 103-HgR. The vaccine is currently undergoing a fast-track review, which the FDA is anticipated to complete by June 2016. The plan is to call for an ACIP vote on recommendations for use of CVD 103-HgR in June 2016 for use in adults.

Since October 2015, the ACIP Cholera Vaccine WG has drafted policy questions, identified important and critical outcomes for review, conducted a systematic literature review, completed an initial GRADE evaluation of the evidence, and discussed considerations for recommendations for use. This is a somewhat unusual vaccine in that some of the studies are actually challenge studies in which the organism is intentionally introduced.

Dr. Reingold indicated that during this session, Dr. Danzig from PaxVax would present clinical data on CVD 103-HgR, Dr. Wong from CDC would summarize the GRADE evaluation and WG plans, and that presentations would include the information and background needed for discussion about cholera vaccine to inform ACIP decisions during upcoming meetings.

Vaxchora™ Clinical Data

Lisa Danzig, MD
VP Clinical Development and Medical Affairs
PaxVax

Dr. Danzig presented pivotal data that have been filed in support of the BLA for PaxVax CVD-103-HgR vaccine called Vaxchora™. She briefly reviewed the background on CVD-103-HgR and the clinical re-development program that included human challenge studies in which efficacy, lot consistency, immunogenicity, and bridging to older adults were determined.

PaxVax is a privately held global specialty vaccines company with a mission to develop, manufacture, and commercialize innovative vaccines against infectious diseases in a socially responsible manner. PaxVax has approximately 180 dedicated employees who work across locations in the US and Europe. The PaxVax headquarters is in Redwood City, California. Its research and development site is in San Diego, California. The Thörishaus, Switzerland site includes multiple manufacturing, office, and laboratory spaces for Vivotif[®] production, quality testing, product release, and supply chain.

PaxVax is initially focused on delivering vaccines for the travelers' markets, with the following products: Vivotif[®], which is a typhoid vaccine live oral Ty21a; Vaxchora[™], which is the oral cholera vaccine that is under FDA review; an Ad4 vector program that has included programs in HIV, influenza, anthrax, and Ad4/7; and new research and development that focuses on travel and specialties, including Zika virus vaccine.

Vibrio cholerae (*V. cholera*) O1 biotypes are the most common (Classical, El Tor). Each biotype has two distinct serotypes. The transmission route is via contaminated water and food. It causes a toxin-mediated secretory diarrhea, which if severe can be rapidly fatal if untreated. This is known as cholera gravis. It is endemic in over 50 countries and is found primarily in Asia and Africa. In addition, there has recently been extensive disease burden in the Caribbean. Approximately 3 to 5 million cases are estimated to occur per year, with more than 100,000 deaths. It is estimated that the majority (80%) of mild to moderate diarrhea cases do not come to medical attention, and therefore go unreported. Everyone is susceptible, but there is an even greater risk with blood group O and probably hypochlorhydria, but the reasons are unknown [Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis 2015;9(6):e0003832].

There is no licensed cholera vaccine in the US. Because cholera causes explosive diarrhea, infection can be rapidly fatal. If untreated, in its severest form cholera makes headlines. CVD 103-HgR is not a new vaccine. It is a live, attenuated *V. cholerae* serogroup O1, serotype Inaba, classical biotype strain in which the toxigenic A1 ADP-ribosylating subunit of cholera toxin was deleted and only the non-toxic immunogenic B binding subunit of cholera toxin is synthesized. The first lots were tested in volunteers in 1988. It was available in 1994 through Berna commercially as Orochol[®], Mutacol[®], and Orochol[®] E (the higher dose). It was licensed in Switzerland, Canada, Argentina, Australia, and New Zealand in the 1990s. In 1997, Berna submitted a BLA to the FDA. There was a VRBPAC in 1998 that included a discussion of the design of the challenge studies that would be needed to support licensure in the US. The endpoints were discussed at that time, and a challenge study was redesigned that would be able to support the demonstration of an efficacy claim in a non-endemic population such as US travelers.

For unrelated business reasons in 2004, the production at Berna ceased. Subsequently, when Crucell bought Dukoral[®] in 2006, they returned the rights of the cholera vaccine to the Center for Vaccine Development (CVD) from which PaxVax acquired the right to re-develop CVD-103-HgR in 2010. The PaxVax BLA for an adult indication was submitted on October 16, 2015 and was accepted for filing on December 15, 2015 with a review classification of "Priority." The review goal date June 15, 2016 and this is on track. Proposed labeling feedback is anticipated by mid-May 2016. No Advisory Committee is planned.

The commercial experience is more than 500,000 doses distributed over 10 years. The vaccine was well-tolerated, with an excellent safety profile. There have been more than 35 scientific publications between 1988 and 2010, which have been provided to the WG. Summarized briefly, efficacy in non-endemic populations was demonstrated in healthy volunteer cholera challenge studies with a number of cholera strains. The challenges ranged from 8 days to 6 months following vaccination¹. There were field efficacy studies in endemic populations². Safety, immunogenicity, and dose-finding studies were conducted in developed and developing countries³. Orochol E is a 1 log higher dose, which is not included in the current vaccine formulation or application. Special populations include pediatric and HIV⁴, and concomitant yellow fever (YF), malaria prophylaxis, and oral polio vaccination (OPV)⁵ were also studied. Safety and immunogenicity of re-immunization at 2.5 and 3.5 years⁶ following vaccination were also studied and published. Interestingly, since there are no data on persistence, the seroconversion by serum vibriocidal antibody (SVA) following primary immunization was 81%.

Following re-immunization, SVA was 57% at 2.5 years and 65% at 3.5 years. Fecal antibodies also decreased at 2.5 versus 3.5 years. This suggests that primary immunization elicited long-term local immunologic memory [¹Orochol Historical Studies: Table 1. North America Challenge Studies – (El Tor Inaba, El Tor Ogawa, Classical Inaba strains tested); ²Orochol Historical Studies: Table 5. Studies in Cholera Endemic Areas; ³Orochol Historical Studies: Table 2. RCT N. America or European Adults, Table 6: Non-pivotal Safety/Immunogenicity Studies; ⁴Orochol Historical Studies: Table 3: Pediatric Studies, Table 4: Special Populations; ⁵Orochol Historical Studies: Table 6: Non-Pivotal Safety/Immunogenicity Studies and Other Studies of Relevance; and ⁶Kollaritsch et. al. Vaccine 18 (2000) 3031-3039; Levine *BMC Biology* 2010, 8:129].

The following table offers an overview of the current clinical program:

Study	Objective(s)	Design & Type of Control	Test Product; Route of Administration
Phase 1 Safety 002	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	4 x 10 ⁸ CFU/dose; oral
Phase 3 Challenge 003	Demonstrate protection from live cholera challenge	Randomized, double-blind, placebo-controlled	5 x 10 ⁸ CFU/dose; oral
Phase 3 Lot Consistency 004	Demonstrate clinical lot consistency	Randomized, double-blind, placebo-controlled	1 x 10 ⁹ CFU/dose; oral
Phase 3 Older Adult 005	Demonstrate equivalence in immune response of older and younger adults	Randomized, double-blind, placebo-controlled	1 x 10 ⁹ CFU/dose; oral

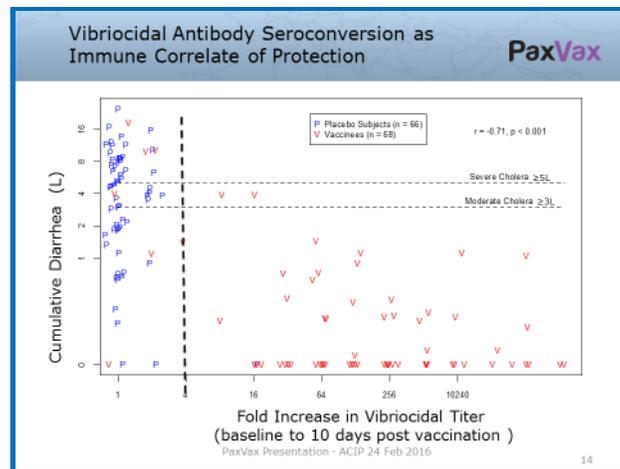
The Phase 1 study has been published. It confirmed the safety and immunogenicity of the earlier formulation. There was limited shedding and there was no transmission to household contacts. The household contacts of the study recipients received fecal swab stool culture and antibody tests to determine whether they were exposed to the organism when the vaccinee brought it home [Clinical and Vaccine Immunology; p. 66 –73; January 2014; Volume 21; Number 1].

That supported moving forward with the PXVX-VC-200-003 challenge study to demonstrate efficacy at two time points. This pivotal efficacy challenge study used a closely monitored human infection model involving the ingestion of virulent *V. cholerae* O1 El Tor Inaba strain N16961 strain at 1×10^5 colony forming units (CFU). The primary objective was to determine whether a single dose of PXVX0200 provides significant protection against a challenge with virulent cholera. The challenge was given at 10 days and 3 months after vaccination. The primary endpoint was the development of moderate to severe diarrhea or moderate to severe cholera, which was equal to or greater than 3.0 liter purge for the illness. “Severe” was defined as a 5.0 liter purge, and “moderate” was defined as 3.0 liter purge. Without rehydration therapy, this endpoint would be potentially life-threatening because the plasma volume for an average person is 2.5 liters. The success criterion was that the lower two-sided 95% confidence bound on protective efficacy must be greater than or equal to 30%. The secondary objectives were to: 1) evaluate the impact of vaccination on disease severity, total stool volume by weight, incidence of diarrhea of any severity, incidence of fever, incidence of fecal shedding of wild type *V. cholerae*, peak concentration *V. cholerae* detected in stool; and 2) evaluate the tolerability of the vaccine.

In terms of the data, the attack rate for moderate cholera for 3.0 liter liquid stool was 6% in the vaccine group challenged after 10 days. Relative to the placebo group at 59%, that is a significant reduction. Vaccine efficacy was 90%, with a lower bound of 63%. At the 3-month challenge, the attack rate was 12%. Vaccine efficacy was 80%. This study met the primary endpoints, with the lower bound over 30%. The subgroup analyses on the primary endpoints did not show major differences between blood groups O or non-O, males or females, or black or white. Not everyone was selected to be challenged, so there was a group who was followed for safety.

Protection was demonstrated for secondary endpoints including diarrhea of any severity (defined as >4 loose stools within a 24 hour period), volume of diarrhea, number of loose stools, number of days passing loose stools, and a 99% reduction in shedding of the challenge strain in the vaccine versus placebo groups during the 11 days following challenge.

Vibriocidal antibodies are a measure of immunity and have been inversely correlated with infection with cholera¹. In terms of the SVA against classical Inaba prior to challenge for the placebo and challenge groups, peak titers reached about 100-fold greater than baseline at 10 days after study. While they subsequently declined, there is persistence of the antibody level above the placebo or the baseline level [M. Pasetti and M. Levine, Clinical and Vaccine Immunology, 19(2012) N11 p.1707–1711]. Here are these data following the 10-day post-vaccination titers:



These are the peak antibody titers, this time expressed as the fold increase from baseline on the x-axis against cumulative diarrhea by volume on the y-axis. Each subject is marked with a P in blue or a V in red, which represents the challenged subjects who received a placebo or vaccine. The vaccine recipients had high fold increases on the right and low stool volumes, in contrast to placebo recipients whose fold increases did not exceed 4-fold and who had high stool volumes.

The serum vibriocidal fold-increase measured on Day 11 was a predictor of protection against development of moderate to severe cholera following challenge in Study 003. As expected, since the vibriocidal response is thought to be mediated by the LPS, similar results were attained when vibriocidal assays were performed with strains representing the other major biotypes and serotypes. The GMT percent 4-fold rise for vaccinees and placebos were similar to those with the Classical Inaba strain as shown in the following table:

Challenge Study 003 Post-immunization Vibriocidal GMT and Percent 4-Fold Rise				
Cholera Strain used in Serum Vibriocidal Assay	Vibriocidal GMT Day 11 (95% CI)		Percent With 4-fold Vibriocidal Rise at Day 11	
	PXVX0200 N = 94	Placebo N=102	PXVX0200 N = 94	Placebo N=102
Classical Inaba	4313*	65	89%*	2%
El Tor Inaba	6898*	63	90%*	4%
Classical Ogawa	2324*	94	86%*	3%
El Tor Ogawa	2239*	72	88%*	5%

Equivalence was demonstrated in lot consistency for three lots with approximately 900 subjects per group, given that the geometric mean ratios for each pair of lots was 0.78-1.20 which was within the pre-specified interval of 0.67-1.5. Safety was also assessed in this 3000 subject study (004 Safety Profile). The single dose of cholera vaccine was well-tolerated in this study. Reactogenicity signs and symptoms after vaccine administration were reported by 51.90% of vaccine and 43.15% of placebo recipients ($p=0.0024$). There was slightly more reactogenicity in the vaccine group, but there were no meaningful differences in reactogenicity across lots.

There were no significant differences between vaccine and placebo recipients with exception of: 1) headache reported in 28.93% (791 of 2734) vaccine recipients and 23.62% of (81 of 343) placebo recipients ($p=0.0419$); most were mild (516 vaccine, 50 placebo) or moderate (261 vaccine, 30 placebo); and 2) diarrhea, which although rare in both vaccine and placebo groups was reported 3 times more frequently in vaccine (3.88%) versus placebo (1.17%) ($p=0.0079$) recipients.

Most diarrhea was mild or moderate (defined as ≥ 4 or ≥ 5 loose stools/24h respectively); severe diarrhea was defined as ≥ 6 loose stools/24h and was reported in 0.8% (22 of 2789) vaccine recipients and 0.0% (0 of 350) placebo recipients. The median duration of diarrhea was 1 day and resolved in all subjects within 2 days of onset. The median day of onset was 2 days after vaccination (range 1-7 days). There was one death during the study, which was a suicide that was considered to be unrelated, and 20 subjects reported at least one SAE (17 Vaccine, 3 Placebo) which were all considered to be unrelated to the study.

Since a 4-fold rise in serum vibriocidal titer was correlated with protection, this was used to bridge the immune response from an older population to a younger population in which efficacy was demonstrated in study PXVX-VC-200-005. This study met the primary endpoints by demonstrating with 95% confidence that the seroconversion rate in older adults was within 10% of the rate in younger adults, and that the seroconversion rate in older adults was at least 70%, which was the pre-specified endpoint.

In terms of the overall reactogenicity across all of the Phase 3 studies combined, 3325 vaccine and 563 placebo recipients participated in one of the Phase 3 studies. "Any" reactogenicity was reported in 50% of vaccinees and 46% of placebo subjects ($p=0.06$). Most reactogenicity was mild or moderate. The breakdown of the solicited post-immunization reactions within 7 days in the combined analysis for Studies 003, 004, 005 is shown in the following table:

Symptom	Vaxchora n=3325	Placebo n=562	<i>p-value</i>
Malaise	30.0%	29.4%	0.8
Headache	27.8%	26.0%	0.4
Abdominal Pain	18.3%	17.0%	0.5
Nausea	17.4%	15.6%	0.3
Anorexia	15.6%	16.8%	0.4
Diarrhea (≥ 4 loose stools/24h)	3.8%	1.6%	0.008
Fever	0.7%	1.1%	0.3

The vaccine was well-tolerated and there were no significant differences between groups, with the exception of an approximately 2% increase in diarrhea more frequently in the vaccine group. However, that was mostly mild or moderate and was presented because a contributing element of that was from the consistency trial.

Adverse events were collected through Day 29 for most studies, with a follow-up period of up to 181 days in subsets of all of the studies. The most common AEs described are show in the following table, and are listed by decreasing order of frequency in the vaccine group:

Symptom	Vaxchora n=3235	Placebo n=562
Headache	2.5%	2.7%
Fatigue	2.2%	3.2%
URI	2.1%	2.1%
Back pain	1.4%	1.1%
Flatulence	1.1%	1.8%
Abdominal pain	1.1%	0.9%
Diarrhea (≥4 loose stools/24h hr)	0.5%	1.1%

No meaningful differences were observed between the rates of vaccine and placebo recipients reporting unsolicited AEs during study. No SAEs were considered to be related to vaccine. The efficacy demonstrated in the human challenge correlates with the vibriocidal immune response at 11 days following vaccination. Vibriocidal titers were plotted for the subset of subjects from whom blood was taken at Days 29, 91, and 181. At all time points, titers remained well above the placebo and respective baseline.

Primed antigen-specific B cells also become memory B cells, which differentiate into antigen antibody secreting cells upon antigen re-exposure. Immunoglobulin G (IgG) and Immunoglobulin A (IgA) memory B cells from LPB toxin b-subunit (CTb) and toxin co-regulated pilus subunit (TcpA) have previously been found in cholera-infected patients for up to a year following disease [Harris, J. Infection and Immunity 2009]. The percent of anti-LPS IgA memory B cells measured in peripheral blood pre-challenge correlated with protection in the vaccinated subjects who were immunized over a challenge on Day 91. For comparison, there were some unchallenged vaccinees also in whom memory B cells appear to be induced. For reference, in the placebo group who was followed for safety and was not challenged at 170 days post-challenge, there was also a strong induction of memory B cells. So anti-LPS memory B cells increase and remain elevated at Day 181, which likely demonstrates an anamnestic response at 6 months.

In summary, PaxVax redeveloped CVD 103-HgR (PXVX0200, Vaxchora[®]). It was well-tolerated, with no related SAEs; a slight (~2%) increase in diarrhea, most of which was mild to moderate; and a similar profile to Orochol[®]. Protective efficacy against challenge was 90% at 10 days following vaccination and 80% at 3 months following vaccination. The vaccine was found to be immunogenic in healthy adults 18 through 45 years of age and 46 through 65 years. There was 90% to 94% seroconversion by SVA to Classical Inaba. Seroconversion also was demonstrated by SVA with other biotypes and serotypes (Classical Ogawa, El Tor Inaba, El Tor

Ogawa). Vibriocidal seroconversion correlates with efficacy. Vibriocidal Ab levels remained well above baseline at Day 181. Anti-LPS memory B cells increase and remain elevated at Day 181.

Discussion Points

Dr. Stephens asked whether Dr. Danzig could comment further on shedding in terms of other family members.

Dr. Danzig replied that in the Phase 1 studied, two subsets were measured every other day for the first week and shedding was demonstrated in the vaccinees. All household contacts were measured with blood draws and fecal swabs or stool cultures, and no transmission of the shedding was demonstrated.

Cholera Vaccine GRADE Evaluation and Work Group Plans

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 the results of the cholera vaccine GRADE evaluation. She reiterated that no cholera vaccine is currently available in the US. Vaccines are available outside the US, but these require two doses. CVD 103-HgR, a live-attenuated, single dose oral cholera vaccine was previously licensed in other industrialized countries and marketed as Orochol[®] or Mutacol[®], before manufacture ceased for business reasons. The company PaxVax acquired the license to re-develop this vaccine as Vaxchora[™], which Dr. Wong referred to in this presentation as the newer formulation of the vaccine. As noted earlier, a BLA was filed in October 2015 for adults 18 years of age or older, with an FDA action date expected in mid-June 2016.

The WG examined the following policy question for the GRADE evaluation:

“Should live attenuated oral cholera vaccine CVD 103-HgR be recommended for use in adults 18 years of age or older who are at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?”

The population includes adults who live in the US and are traveling to cholera-affected areas. The intervention is CVD 103-HgR administered as a single oral dose. The current option is that no oral cholera vaccine is currently recommended or available to adults in the US.

Prior to reviewing the evidence, the WG selected outcome measures to be included in the evidence profile. Preventing cholera death, life-threatening cholera diarrhea, and severe cholera diarrhea were classified as critical outcomes. Preventing cholera diarrhea of any severity and inducing a vibriocidal antibody response were considered to be important outcomes. Serious and systemic adverse events and decrease in the effectiveness of co-administered vaccines or medications were considered to be critical outcomes.

The WG conducted a systematic review of PubMed and Embase papers in any language published between 1988, when the vaccine was first developed, and January 2016. Efforts were made to obtain available unpublished literature. The references of relevant papers were

reviewed for additional studies of interest. Articles were included if they presented data on CVD 103-HgR and involved human subjects, reported primary data, included data relevant to the outcome measures being assessed, and included data for a relevant dose.

In the initial review, 77 studies were identified. Of these, 49 were excluded (41 that either did not include CVD 103-HgR data or any primary data, 8 pediatric studies, and 1 cost-benefit analysis). This left 28 studies in the GRADE evaluation. Of the 28 studies, there were 3 studies of the newer formulation, all of which were RCTs. There were 25 studies of the older formulation, including 18 RCTs and 7 observational studies. Of the 28 studies, 5 were cholera challenge studies, including 3 RCTs (1 of which used the new formulation) and 2 observational studies. The following table summarizes the number of studies, by type, that were available to examine the outcomes of interest:

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Evidence related to GRADE outcomes

OUTCOME	No. RCTs	No. observational	Data available
Benefits			
Prevent cholera death	4*	1	Yes, limited
Prevent life-threatening (>5L) cholera diarrhea	1*	0	Yes, limited
Prevent severe (>3L) cholera diarrhea	3*	0	Yes
Prevent cholera diarrhea of any severity	4*	3	Yes
Induce vibriocidal antibody response	19*	3	Yes
Harms			
Serious adverse events	20*	4	Yes
Systemic adverse events	20*	4	Yes
Decrease effectiveness of co-administered vaccines or medications	3	1	Yes, limited

* Includes ≥1 RCT with the new formulation of CVD 103-HgR vaccine

Outcomes for which limited data were available included preventing cholera death, preventing life-threatening cholera diarrhea, and decreasing the effectiveness of co-administered vaccines or medications.

The GRADE evidence scoring method begins with an initial evidence type of 1 for RCTs and 3 for observational studies. Criteria for moving the evidence type down by 1 or 2 points include: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Criteria for moving up by 1 or 2 points include: strength of association, dose response gradient, and opposing plausible residual confounding. This leads to a final evidence type for each outcome of 1 through 4:

- 1 corresponds to evidence from RCTs or overwhelming evidence from observational studies
- 2 corresponds to RCTs with important limitations, or exceptionally strong evidence from observational studies
- 3 corresponds to observational studies, or RCTs with notable limitations
- 4 corresponds to clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

The WG attempted to assess prevention of cholera death as an outcome of vaccination. However, cholera challenge studies are not designed to assess this outcome. There was one large field study that showed no difference in deaths from diarrhea of any etiology between vaccinated and comparison populations. Cause of death was assessed by verbal autopsy in an Indonesian population monitored over 4 years. The following table summarizes the challenge and field studies, with no differences in deaths detected:

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Evidence of benefits: prevention of cholera death

- Challenge studies not designed to assess this outcome
- One large field study showed no difference in deaths from diarrhea of any etiology between vaccinated and comparison populations
 - Cause of death assessed by verbal autopsy

	Study	Site	Type	Population	Time post-vaccination	Deaths, vaccinated persons	Deaths, comparison persons
CHALLENGE	Levine 1988	U.S.	RCT	Adults	1 month	0/6	0/8
	Tacket 1992	U.S.	Obs	Adults	4-6 months 8 days	0/14 0/11	0/15 0/11
	Tacket 1999	U.S.	RCT	Adults	3 months	0/28	0/23
	Chen, Cohen 2014*	U.S.	RCT	Adults	10 days 3 months	0/35 0/33	0/66
FIELD	Richie 2000	Indonesia	RCT	Adults and children (2-41y)	Up to 4 years surveillance	6/33696 [diarrhea, any etiology]	8/33812 [diarrhea, any etiology]

* New formulation of CVD 103-HgR vaccine

The WG felt that there was insufficient evidence to assess prevention of cholera death by the vaccine. There was insufficient evidence to assess prevention of cholera death. Most criteria were unable to be assessed.

One RCT addressed the outcome of prevention of life-threatening cholera diarrhea [Chen, Cohen *et al*, 2014]. This study was with the new formulation of the vaccine. Challenge with toxigenic *V. cholerae* O1 in vaccinated and comparison groups was performed at 10 days or 3 months after vaccination. The risk ratio was less than 1, which suggests a protective effect of the vaccine. There was strong evidence from 1 RCT with the newer formulation of vaccine that CVD 103-HgR prevents life-threatening cholera diarrhea. The overall evidence type was 1.

There were 3 RCTs that addressed prevention of severe cholera diarrhea [Chen, Cohen *et al*, 2014; Tacket *et al*, 1999; and Richie *et al*, 2000]. There were 2 challenge RCTs, one of which assessed the outcome at multiple time points, that showed a strong consistent reduction in severe cholera diarrhea among vaccinated versus comparison individuals. There was one field RCT that found no significant difference in severe cholera diarrhea in vaccinated versus unvaccinated individuals. This study was conducted in Indonesia among children and adults. In this study, individuals rather than clusters were randomized. Cholera outcomes were assessed by sentinel surveillance over 4 years. Incidence of cholera was low during the study period, making detection of an effect difficult. The evidence type for prevention of severe cholera diarrhea was downgraded for inconsistency, given that the 1 large field trial showed no effect. However, there was strong evidence from other studies with old and new vaccine formulations

vaccine formulation were downgraded for indirectness. However, there was strong evidence from studies with old and new formulations that the vaccine induces a vibriocidal antibody response. The overall evidence type was 1.

There were 20 RCTs, 4 observational studies, and post-marketing surveillance data that examined AEs from the vaccine. For SAEs, there was 1 field RCT that found no difference in overall mortality in the vaccinated versus comparison population over 4 years. Overall, there were no differences detected between vaccinated and comparison populations for any SAEs. For systemic adverse events, there was 1 unpublished RCT with the new vaccine formulation that found a slightly higher proportion with diarrhea in vaccinated versus comparison persons. Overall, the evidence indicates that systemic adverse events occur at similar rates in vaccinated and comparison populations.

Post-marketing, spontaneously reported, serious unexpected adverse events were rare for Orochol[®], the older formulation of this vaccine. Of more than 500,000 Orochol[®] doses distributed, events included hospitalization with fever, gastroenteritis, vomiting, hemorrhagic cerebrospinal fluid in an 11-month old infant; 1 report of Guillain-Barre Syndrome (GBS) in a person who received multiple travel vaccines; 1 report of Angioedema; and 1 report of loss of hair. Of more than 200,000 Orochol[®] E doses distributed, there were no spontaneously reported adverse reactions.

Most evidence for serious and systemic adverse events came from studies of an older formulation of the vaccine; thus, the evidence type was downgraded for indirectness. There have been relatively few recipients of the newer formulation of the vaccine. The evidence type for these RCTs was downgraded for imprecision. Overall, SAEs were uncommon, and studies with old and new formulations of the vaccine suggest that AEs occur at similar rates in vaccinated and comparison populations. The final evidence type was 3 for RCTs and 4 for observational studies, and the overall evidence type was 3.

There were 3 RCTs and 1 observational study that evaluated evidence for decrease in the effectiveness of co-administered vaccines and medications. No effect was identified on antibody response to live attenuated oral typhoid vaccine when co-administered with CVD 103-HgR. Of people given both vaccines, 62% to 83% developed anti-Typhi antibodies versus 66% of people given typhoid vaccine alone. No effect was identified on antibody response to YF vaccine when co-administered with CVD 103-HgR. Of people given both vaccines, 100% developed anti-YF antibodies. There was 1 additional study that evaluated CVD 103-HgR in combination with typhoid, YF, and OPV vaccines, as well as mefloquine, chloroquine, and proguanil. There was lower vibriocidal seroconversion in response to the cholera vaccine when chloroquine was co-administered with CVD 103-HgR versus CVD 103-HgR alone.

For typhoid or YF vaccine, the evidence type was downgraded for indirectness, as these studies used the older formulation of the vaccine. There was no suggestion that CVD 103-HgR decreases the effectiveness of typhoid or YF fever vaccines. There was insufficient evidence to determine the effect on other co-administered vaccines or medications. The RCTs received a final evidence type of 2, and one observational study received a final evidence type of 4. The overall evidence type was determined to be 2.

The following table reflects the full GRADE summary:

Outcome	Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	Final evidence	Overall evidence type
Prevent cholera death	4 RCTs	1	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	Insufficient evidence to evaluate outcome
	1 Obs	3	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	
Prevent life-threatening cholera diarrhea	1 RCT	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent severe cholera diarrhea	3 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent cholera diarrhea of any severity	4 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
	3 Obs	3	Serious (-1)	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	3	
Induce vibriocidal antibody response	19 RCTs	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
	3 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	2	
Serious/systemic adverse events	20 RCTs	1	No serious	No serious	Serious (-1)	Serious (-1)	No serious	None	3	3
	4 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	
Decrease effectiveness of co-administered vaccines and medications	3 RCTs	1	No serious	No serious	Serious (-1)	No serious	No serious	None	2	2
	1 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	

Overall, there was insufficient evidence to determine whether the vaccine prevents cholera death. The evidence suggests that the vaccine prevents life-threatening and severe cholera diarrhea, as well as cholera diarrhea of any severity, with an overall evidence type of 1. The evidence suggests that the vaccine induces a vibriocidal antibody response, with an overall evidence type of 1. The evidence did not suggest an association between the vaccine and any serious or systemic adverse events, with an overall evidence type of 3. The evidence, which was available with respect to oral live-attenuated typhoid vaccine and YF vaccine, did not suggest that CVD 103-HgR decreases the effectiveness of co-administered vaccines or medications. The overall evidence type for this outcome was 2.

In terms of considerations for formulating recommendations for use, cholera is rare in the US. Fewer than 25 cases per year have been reported since 2012; however, other years have had more cases. There were 42 cases reported in the US in 2011 during a cholera epidemic in Haiti, and there was a large outbreak on a flight from Argentina to Peru to the US in 1992. Cholera cases in the US are likely underreported. Infections that occur while traveling that

resolve before return to the US are not captured by US surveillance. Cholera has a short incubation period, and little information is available about cases that occur while traveling.

Cholera can be severe and rapidly life-threatening. The overall risk of cholera is very low for most US travelers, and it is treatable if medical services are readily available. However, certain populations may be at higher risk of exposure. These may include HCP, outbreak response workers, persons visiting friends or relatives, and persons traveling or living in cholera-affected areas for extended periods. Certain populations also may be at higher risk of poor outcomes, including those with low gastric acidity or blood type O, or persons without ready access to medical services. It is important to note that sanitation, hygiene, and safe water and food remain critical to preventing cholera and other enteric infections.

Overall, the evidence type is 1 for prevention of cholera diarrhea and induction of a vibriocidal antibody response. Overall, the evidence type is 3 for safety as assessed by serious and systemic adverse events and 2 for decreasing the effectiveness of co-administered vaccines and medications. There are insufficient data to evaluate whether CVD 103-HgR prevents death from cholera. Also, there are no data currently available on the safety and efficacy of this vaccine in pregnant women. In terms of the balance between benefits and harms, there is strong evidence that CVD 103-HgR prevents cholera diarrhea. SAEs were uncommon with the older formulation of vaccine. Limited evidence suggests that SAEs are also uncommon with the newer formulation. Systemic adverse events occur at similar rates in vaccinated and comparison groups.

High value is placed on the ability to prevent a severe, life-threatening illness in travelers at risk of cholera exposure or severe cholera illness, especially if medical care is not readily accessible. Cost-effectiveness was not evaluated in this review. Risk of cholera is very low for most travelers to cholera-affected areas. Travel vaccines are usually paid for by employers or by the travelers themselves, depending upon the circumstances.

The WG has discussed options for draft recommendations. One option is a broad recommendation: to recommend or consider the vaccine for adults planning to travel to a cholera-affected area. Another option is more targeted: to recommend or consider for adults who are at high risk of exposure (for example, cholera outbreak response workers) or at risk for severe illness.

Based upon review of the evidence for critical and important outcomes, the WG concluded that the vaccine is safe and effective. The WG is continuing to discuss a Category A versus Category B recommendation, and whether specific risk groups should be emphasized in the recommendations. The WG is evaluating evidence for duration of protection and for re-immunization. Evidence is being evaluated from selected subgroups, such as immunocompromised persons, separately from this GRADE review. The WG also is evaluating pediatric studies separately from this GRADE review, as a summary of these data may be helpful to clinicians considering off-label use in persons less than 18 years of age.

In conclusion, Dr. Wong reminded everyone that the original policy question assessed by this GRADE evaluation was, “Should CVD 103-HgR be recommended for use in adults at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?” As ACIP considers these questions, she asked the members also to consider whether within the policy option, specific risk groups should be emphasized, and whether there were additional data that would be helpful to ACIP to inform future discussions.

Discussion Points

Dr. Karron asked whether a lot of data would be available on duration of protection beyond 6 months.

Dr. Danzig replied that with the historical formulation, she presented re-immunization data from 2.5 to 3.5 years. PaxVax currently is negotiating final labeling with the FDA. They anticipate post-marketing commitments and will be designing them together with the FDA. However, no studies have been initiated to date so no data will be forthcoming soon.

Dr. Ezeanolue asked how soon data on pediatrics would be available. He thought she mentioned that these data were already available.

Dr. Danzig responded that PaxVax plans to submit the protocol to FDA by the end of 2016, so it will take a couple of years before the pediatric data with the new vaccine formulation are available.

Dr. Wong responded that historical data with the older formulation of the vaccine are available for pediatric populations, and these will be summarized while awaiting new pediatric data.



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 Pentacel[®] vaccine. In December 2015, Sanofi Pasteur announced a manufacturing delay with Pentacel[®] vaccine. As a result, Sanofi Pasteur is only able to meet approximately 70% of historical Pentacel[®] vaccine demand throughout the first half of 2016. At this time, sufficient supplies of the relevant individually administered vaccines DAPTACEL[®], ActHIB[®], and IPOL[®] are available to address the anticipated gap in Pentacel[®] supply.

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

Public Comment**Julie Lindberg, Pregnant Mother
Delivered in Person and by Letter Submitted to ACIP for the Record**

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Injury and Death by Vaccines February 24, 2016

First of all, I want to thank you for your expertise. Thank you for listening to these public comments. It is a privilege to be able to speak to you today.

I am here to talk about your recommendations in general, but first I want to share with you something new that affects me personally today. I am pregnant, and my health care provider follows your advice to recommend the inactivated flu vaccine and the Tdap. The CDC website tells me that the flu shot is safe for me and my child and that it has been shown to protect us from the flu. Unfortunately, the manufacturers for every single flu vaccine on the market today publicly state the exact opposite, in writing. Currently, Novartis, GlaxoSmithKline, Sanofi Pasteur, Protein Sciences Corporation, and bioCSL, state that safety and effectiveness of their flu vaccine have not been established for pregnant women. The same is true for Tdap, according to Sanofi Pasteur and GlaxoSmithKline. Both available Tdap vaccines, Adacel and Boostrix, contain high levels of aluminum. The World Health Organization states that one of the risk factors of heavy metal exposure is that it can cause microcephaly.

But I am not here to talk about the flu vaccine or Tdap. Or Brazil. I want to speak to you about all your recommendations. I am asking you today to slow down, maybe stop altogether, and reexamine the injury and death that all kinds of vaccines have caused.

Historically, this advisory committee has recommended vaccines that have not undergone safety testing with a true placebo, not another vaccine as a placebo, but a placebo that does nothing to the human body. You have recommended vaccines that are not tested for long-term effectiveness, vaccines that severely disable and kill. Your recommendations are being applied in deceptive, abusive, forceful ways, in our own country and across the globe. True informed consent is being sidestepped and ignored. This is wrong. I am asking you today to stop and challenge one another to look at these issues in the face.

The history of vaccines, from 1850 to today, particularly in the U.S., does not show that vaccines are responsible for the major decline of disease and death. Clean water, proper nutrition, effective sanitation, holistic medicine, and compassionate quarantine have saved millions of lives. I am asking you to stop and look at a broader view of history.

You have been given a position of authority and influence. You shape the beliefs and actions of people across the world. You influence the law and the economy. Take some time and turn your eyes away from the money and the power and the illusions. Both diseases and vaccines have ruined lives. Smallpox, polio, diphtheria, pertussis, and SIDS have not been reduced. They have been renamed. Prod one another to greater honesty. Take courage and walk away from that revolving door. Challenge each other to do what you can to end the harm and

heartbreak in the vaccine industry. We can wait for you. We have a multitude of safe options to prevent sickness while you take the time to “First Do No Harm.”

Disease exists in many forms. But it will not win in the end. Be courageous and ask for deeper wisdom in these matters. Thank you for your time.

Mara Berger
Parent of Adam Berger, Deceased
Letter Submitted to ACIP for the Record

February 8, 2016

From: Mara Berger, mother of Adam Berger, deceased
Address: 5801 N. Sheridan Road, Chicago, IL 60660
Email: maraberger@hotmail.com

Subject: To Recommend the Conjugate Vaccine to the Adult Population concerning Neisseria Meningitidis strain C

This is the third time I'm requesting that the ACIP recommends the conjugate vaccines Menactra and Menveo for routine usage in healthy adults 21-55 years old and to healthcare personnel for the purpose of protecting them from contracting meningococcal disease/Neisseria meningitidis bacterial strains A, C, Y and W135. The ACIP and CDC have never targeted or recommended the conjugate vaccines to them, which appears to be intentional and without explanation. The fact is that healthy adults and healthcare personnel do contract meningococcal disease and can suffer sequelae or die. The ACIP, CDC and HHS are aware that one of them who died two years ago was my son, Adam age 44, who was healthy and a nursing student. He had contracted Neisseria meningitidis strain C and died within hours. After he died, I did extensive research and learned that Neisseria meningitidis is a vaccine preventable disease, which would have prevented his untimely and needless death. The ACIP and CDC cannot continue to turn a blind eye and ignore the fact that healthy adults as well as those in the healthcare field are at risk for meningococcal disease. Unbeknownst to me, many health facilities such as the prestigious teaching hospital that Adam worked at in Chicago didn't mention meningococcal disease to Adam or recommend the conjugate vaccines for strains A, C, Y and W135 because they follow the CDC, which doesn't recommend the vaccines to adults over 21 years or healthcare personnel for routine use. Healthy adults without medical conditions are just as at risk to contract meningococcal disease. Does the ACIP and CDC want healthy adults to believe that because they're healthy, that they won't contract the disease? Anyone, anytime and anywhere can contract dangerous Neisseria meningitidis suddenly and even with proper care, can die within hours. That is why it's most important to prevent the disease before it starts with vaccination and adults should have that choice and know the risk of not getting vaccinated. I never heard of meningococcal disease or Neisseria meningitidis prior to Adam's death. I feel duped by the CDC. Since the government's top health agencies don't recommend the vaccine to protect us, why would they educate the public about the disease and vaccines to prevent it. They wouldn't. Therefore, healthy adults and healthcare personnel are at risk for the disease. The ACIP and CDC are supposed to make sound medical decisions and protect all people and save lives. The conjugate vaccine Menactra was approved by the FDA in 2005 for 9-month to 55 year olds for routine usage and Menveo was approved in 2010 for 9-month to 55 year olds for routine usage. The ACIP and CDC never recommended either one for healthy adults 21-55 and healthcare personnel for routine usage. I want to know

the scientific or medical reason that the ACIP and CDC have never recommended those conjugate vaccines to them. In my opinion, any other excuse or reason would be egregious and irresponsible. They refuse to recommend the vaccines, yet, the CDC's website states that *Neisseria meningitidis* is the leading cause of infectious disease in the United States; that the vaccine is safe, immunogenic and effective; that vaccination in adults is low and that there has been no decrease of incidence in adults. My research written by an expert in a reputable medical journal states that the average age to contract meningococcal disease is 45 years old and male although women contract it also. In terms of incidence of the disease resulting in mortality or morbidity, the greatest burden of disease is among adults 25-64 years old in which 60% of the cases and 70% of fatalities occur. The ACIP and CDC omitting that information on their website is very troubling because omission is a lie. The federal government appoints individuals to represent and protect the public and physicians take an oath to "Do No Harm." In my opinion, much harm has been done over the years. What I already knew, but Health Secretary Burwell confirmed in a letter to me stated that "Based on its comprehensive analysis of the available evidence, it is possible that ACIP might not recommend an FDA-licensed vaccine for routine use. However, physicians or other healthcare providers would still be able to administer the FDA-licensed vaccine according to the labeled indications." Therefore, it appears that physicians can act in their patients' best interests and bring up the subject of meningococcal disease and the vaccine to prevent it to their healthy patients and those persons entering the healthcare field. If physicians don't want to supply and store the vaccine, they can send their patients to the pharmacy for the inoculations. In my opinion, someone must be held accountable and responsible for the intentional and irrational decision to not recommend a life-saving vaccine to prevent maiming and death. In memory of Adam, I'm going to educate adults about the risks of meningococcal disease and the conjugate vaccines to prevent it. I say to the ACIP...It's time to recommend the meningococcal conjugate vaccines to healthy adults 21-55 and healthcare personnel for routine usage.

Frankie Milley
Founder / National Director
Meningitis Angels
Letter Submitted to ACIP for the Record



Meningitis Angels

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Address PO Box 448, Porter, Texas 77365
Phone 713-444-1074

Ref: Meningococcal B Vaccines

Dear Dr. Nancy Bennett and ACIP Committee:

First let me say thank you for your service to all of us for your most important work on vaccines. The work you all do insures our country and the world we will be protected from vaccine preventable diseases.

Today, I am writing to ask you to strongly consider full recommendations for the use of MenACWY vaccines in HIV-infected persons and among men who have sex with men (MSM). At the same time though not on the agenda. I am asking you to also reconsider stronger recommendations for the use of the meningococcal B vaccines among teens and young adults. The US, as you know, is still experiencing outbreaks with the most recent in California. Each time this happens another life is at risk. Another family may have to bury a child, as I did needlessly, or care for one severely disabled.

The current recommendation for this age group is not working as well as it should. It leaves health care providers confused and afraid of the liability of giving a vaccine not fully recommended by the ACIP Committee. The permissive recommendations do NOT allow for proper education on the disease and vaccines. Affordability and accessibility due to permissive recommendations as always are an issue.

I am asking the committee to please once and for all to do the right thing. Please give strong recommendations for all 3 of the high risk groups listed above. The decision to protect lives from disease and death are never the wrong ones.

Respectfully, Thank You, Frankie Milley, Mom to Ryan,
Meningitis Angels, National Executive Director

Hollie Smith and Laura Matrka
Letter Submitted to ACIP for the Record

NOTICE OF DENIAL
(To Hollie Smith)

Dear

Catamaran, an OptumRx company ("OptumRx"), on behalf of L Brands Inc, is responsible for reviewing pharmacy services provided to L Brands Inc members. OptumRx received a request on 2/1/2016 and reviewed it to provide the following medication, GARDASIL INJ, at a zero dollar cost to you.

Why was my request denied?

This request was denied because you did not meet the following clinical requirements: In order for the plan to cover a vaccine at zero copay, the requested vaccine must be listed as recommended per the Advisory Committee on Immunization Practices (ACIP) guidelines (see <http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html> for specific details).

The reason(s) OptumRx did not approve this medication can be found above. This denial is based on the GARDASIL drug coverage policy.

What if I need help understanding why my request was denied?

Contact OptumRx at 8776656609 for assistance with understanding this letter and the decision to deny you a service or coverage.

How can I obtain the material(s) used to review this request?

You may request, free of charge, a copy of the drug coverage policy, actual benefit provision, guideline, protocol or other similar criterion on which the denial decision is based, including the diagnosis code and the treatment code and their corresponding meanings, by calling OptumRx at 8776656609, or by writing to OptumRx at the address below:

OptumRx Prior Authorization
Department
P.O. Box 5252
Lisle, IL 60532-5252

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To Whom it May Concern:

I am writing to request coverage of the Gardasil vaccine for patient _____ for the condition of Recurrent Respiratory Papillomatosis, caused by HPV strains 6 and 11, for the following reasons.

1. Patients with RRP fail to clear the HPV virus, whereas normal people typically clear it within 9 months or so. They have an incompletely-understood susceptibility to HPV that may put them at increased risk of other HPV-mediated disease such as infection with HPV 16 or 18 leading to oropharyngeal or cervical malignancy.
2. Recent data indicates that RRP patients who receive the Gardasil vaccine have a decreased number of surgeries per year and a longer interval between surgeries. The average interval between procedures in the non-vaccinated group was 271.2 days; after vaccination, this increased to 537.4 days. The average number of surgeries per year prior to vaccination was 2.16; this dropped to 0.93 surgeries per year after vaccination. (Hocevar-Boltezar et al Eur Arch Otorhinolaryngol "Human papilloma virus vaccination in patients with an aggressive course of recurrent respiratory papillomatosis." 2014;271:3255–3262.)

Decreased number of procedures would lead both to better health for these patients and obvious financial benefit to the insurance companies who cover them.

Thank you for your consideration,
Laura Matrka, MD



Certification

Upon reviewing the foregoing version of the February 24, 2016 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

February 18, 2016
Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2015 – June 30, 2016

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

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National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
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Term: 07/01/2012 – 06/30/2016

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Centro Nacional Para la Salud de la Infancia Y La Adolescencia / National Center for Child and Adolescent Health

Ministry of Health / Secretaría de Salud
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