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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 26, 2015
Atlanta, Georgia

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30333
February 26, 2015

AGENDA ITEM		PURPOSE	PRESIDER/PRESENTER(s)
Thursday, February 26th			
10:30	**Welcome & Introductions**		Dr. Jonathan Temte (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
10:45	**Meningococcal Vaccines**		
	· Introduction	Information & Discussion	Dr. Lorry Rubin (ACIP, WG Chair)
	· Considerations for use of serogroup B meningococcal (MenB) vaccines in persons at increased risk · Public comment		Ms. Jessica MacNeil (CDC/NCIRD)
	· Proposed policy option	**Vote**	Ms. Jessica MacNeil (CDC/NCIRD)
	· VFC Vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
11:15	**Influenza**		
	· Introduction		Dr. Ruth Karron (ACIP, WG Chair)
	· Preliminary 2014-15 vaccine effectiveness estimates · Update on Live Attenuated Influenza Vaccine (LAIV)	Information & Discussion	Dr. Brendan Flannery (CDC/NCIRD) Dr. Kathleen Coelingh (MedImmune)
	· Proposed recommendations	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
11:45	**Human Papillomavirus (HPV) Vaccines**		
	· Introduction		Dr. Joseph Bocchini (ACIP, WG Chair)
	· Summary of 9vHPV clinical trial data and GRADE · Overview of cost effectiveness	Information & Discussion	Dr. Emiko Petrosky (CDC/NCHHSTP) Dr. Harrell Chesson (CDC/NCHHSTP)
	· Proposed recommendations for use of 9vHPV vaccine	**Vote**	Dr. Lauri Markowitz (CDC/NCHHSTP)
	· VFC vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
12:15	**Yellow Fever Vaccine**		
	· Introduction	Information	Dr. Joseph Bocchini (ACIP, WG

	& Discussion	Chair)
· Summary of GRADE for yellow fever vaccine booster doses · Consideration of booster doses in specific populations		Dr. Erin Staples (CDC/NCEZID)
· Proposed recommendations for yellow fever vaccine booster dose	**Vote**	

12:45 Public Comment

1:00 Adjourn

Acronyms

CDC	Centers for Disease Control & Prevention
GRADE	Grading of Recommendations Assessment, Development and Evaluation
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]
VFC	Vaccines for Children
WG	Work Group

Acronyms Used in This Document

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
AE	Adverse Events
AFP	American Family Physicians
AGS	American Geriatric Society
AHIP	America's Health Insurance Plans
aHUS	Atypical Hemolytic Uremic Syndrome
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraepithelial Neoplasia
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
DHS	Department of Homeland Security
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FLU VE	Influenza Vaccine Effectiveness Network
GRADE	Grading of Recommendation Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* Type b
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IDSA	Infectious Disease Society of America
IHR	International Health Regulations
IHS	Indian Health Service
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
ITSU	Immunization Technical Support Unit, Public Health Foundation of India
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
MCV4	Meningococcal Conjugate Vaccine
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACI	National Advisory Committee on Immunization, Canada
NTAGI	National Technical Advisory Group on Immunization, India
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NITAG	National Immunization Technical Advisory Group, Peru
NMA	National Meningitis Association
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PNH	Paroxysmal Nocturnal Hemoglobinuria
PHFI	Public Health Foundation of India
PIDS	Pediatric Infectious Diseases Society
QALYs	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SAHM	Society for Adolescent Health and Medicine
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VSD	Vaccine Safety Datalink
WG	Work Group
WHA	World Health Assembly
WHO	World Health Organization
WVU	West Virginia University
YF	Yellow Fever

Welcome and Introductions

Dr. Jonathan Temte
ACIP Chair

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Following Dr. Temte's greeting and call to order, Dr. Pickering welcomed everyone to the February 2015 Advisory Committee on Immunization Practices (ACIP) meeting. He expressed appreciation for everyone's understanding about the CDC closure and the necessary cancellation of the first day of the meeting due to the inclement weather. He indicated that the proceedings of this meeting would be available to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. He then recognized Stephanie Thomas and Natalie Greene who were to be present throughout the duration of the meeting to assist with various meeting functions.

Emphasizing that there would be a crowded agenda for the day, Dr. Pickering noted that handouts of presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within 90 days following this meeting. Meeting minutes are posted on the ACIP website generally within 90 days of ACIP meetings. Members of the press interested in conducting interviews with ACIP members were instructed to contact Michael Sennett, Joey Smith, or KD Hoskins for assistance in arranging interviews.

Dr. Pickering welcomed the following international guests in attendance:

- Nearly every meeting, a delegation attends from a member country of the World Health Organization's (WHO's) Pan-American Health Organization (PAHO). Members of Peru's National Immunization Technical Advisory Group (NITAG) attended this meeting, led by Dr. Robert Espinozo, NITAG Chair. With Dr. Espinozo were Dr. Washington Toledo, National Immunization Program Manager; and Dr. Abel Salinas and Ms. Lourdes Castillo, NITAG members.

- Seven members of India's National Technical Advisory Group on Immunization (NTAGI), led by Dr. Gangadeep Kang; and three members of the NTAGI secretariat, led by Dr. Inamdar were present. Dr. Kang is a Professor in the Department of Gastrointestinal Sciences at the Christian Medical College in Vellore, India and is a member of India's NTAGI. Dr. Inamdar is the Senior Advisor for Evidence to Policy at the Immunization Technical Support Unit (ITSU) in the Public Health Foundation of India (PHFI), and is a member of the NTAGI Secretariat.

- The following three long-time friends were in attendance from Japan:
  - → Dr. Mitsuaki Hosoya, Chair and Professor of Pediatrics at Fukushima Medical University in Fukushima, Japan
  - → Dr. Nobuhiko Okabe, Director General of Kawasaki City Institute for Public Health in Japan.
  - → Dr. Hajime Kamiya, Medical Officer, National Institutes of Infectious Diseases in Tokyo, Japan.

As a reminder for future international visitors to ACIP meetings, due to changes in Department of Homeland Security (DHS) Policy, additional forms will be required for each meeting at the time an international guest registers. It is critical that international visitors complete and submit these forms as soon as possible following registration. Stephanie Thomas, Committee Management Specialist, will be able to help with any questions and concerns about the process. The next ACIP meeting will convene at CDC on Wednesday and Thursday, June 24-25, 2015. Registration for all meeting attendees is required and will be open Friday, February 27. 2015. The registration deadline for United States (US) citizens is Wednesday, June 10th, and for non-US citizens is Wednesday, June 3rd. Registration is not required for webcast viewing.

Notes regarding members and liaison representatives included the following:

Ex Officio Members

- Jeff McCollum attended this meeting on behalf of Amy Groom, representing the Indian Health Service (IHS).

- Dr. Eric Sergienko is the new *ex officio* member representing the Department of Defense (DoD).

Liaisons

- Dr. Caroline Quach attended on behalf of Dr. Ian Gemmill, representing the Canadian National Advisory Committee on Immunization (NACI).

- Dr. Kimberly Martin attended on behalf of Dr. Terry Dwelle, representing the Association of State and Territorial Health Officials (ASTHO).

- ACIP welcomed the American College of Nurse Midwives (ACNM) as a new liaison organization, and Carol Hayes as their representative. ACNM is one of four professional organizations that works with CDC in preparation of the yearly adult immunization schedule.

- Dr. Carrie Byington, representative of the American Academy of Pediatrics (AAP) was appointed Chair of AAP's Committee on Infectious Diseases (COID) on July 1, 2014.

- Dr. Ken Schmader, American Geriatric Society (AGS), attended via teleconference.

To avoid disruptions during the meeting, Dr. Pickering requested that those present turn off all cell phones. He explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public

comment was scheduled following the afternoon sessions during both meeting days. Time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before any votes. Those who planned to make public comments were instructed to visit the registration desk in the rear of the auditorium to have Stephanie Thomas record their name and provide information about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

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

With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those specific vaccines. However, they are prohibited from participating in committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in a discussion with a proviso that he or she abstains on all votes related to the vaccines of that company. It is important to note that at each meeting, ACIP members state any conflicts of interest.

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

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

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

A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submitted as e-mail attachments to Stephanie Thomas at hkp4@cdc.gov

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. There have been two publications since October 2014: the Child Adolescent Immunization Schedule and the Adult Immunization Schedule. In addition, "ACIP Recommendations on the Use of Typhoid Vaccines" are projected to be published in the *MMWR* on March 27, 2015.

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.

The following resource information pertaining to ACIP is available on the CDC website:

Vaccine Safety:
www.cdc.gov/vaccinesafety/index.html

Immunization Schedules (2014):
http://www.cdc.gov/vaccines/schedules/index.html

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

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

You Are the Key to HPV Cancer Prevention:
http://www.cdc.gov/vaccines/youarethekey

Vaccines for Preteens and Teens:
http://www.cdc.gov/vaccines/who/teens/index.html

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

- Belongia: Receives research funding from MedImmune and has a conflict on influenza vaccines

- Bennett, Bocchini, Campos-Outcalt, Harrison, Harriman, Karron, Kempe, Pellegrini, Reingold, Riley, Romero, Rubin, Temte, and Vazquez: No conflicts

Dr. Temte then acknowledged Dr. Pickering's many years of service. He said that he had the pleasure of first meeting Dr. Pickering when they were both involved in the March 2000 CDC Measles Elimination Meeting convened in Atlanta. Over those years, he noticed the number of people who were in attendance at that meeting who have also been present at ACIP meetings. Dr. Temte noted that they also had the great pleasure of having Dr. Pickering's wife, Mimi, and daughter, Maggie, in attendance during this meeting. His son, Andrew, was unable to attend due to a scheduling conflict. Dr. Temte recounted that everyone sitting around the table had benefitted from the hospitality of the Pickerings, who have often hosted some of the ACIP members for a respite and wonderful home-cooked meal.

As the Executive Secretary of ACIP, Dr. Pickering has overseen more than 25 ACIP meetings. He has brought uniformity in presentations and enhanced the level of all of the work being done by the committee, including high quality products. He has conducted meetings through outbreaks, a pandemic, a government shutdown, and now during a Southern snowstorm. He has shepherded over 50 ACIP-related *MMWR* articles, including articles on universal influenza vaccination and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) administration during pregnancy. He was instrumental in the adoption of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) Methodology in 2010; has been an eloquent spokesperson for vaccines and CDC's immunization policies and recommendations; and has graced everyone with his expertise, experience level, sensibilities, sensitivities, wisdom, and leadership over the last 9 years.

In conclusion, Dr. Temte said, “It’s a magical world, Larry ol’ buddy. We just want to give you our thanks and appreciation for your many endeavors to keep it a magical world for millions of children and adults.”

Meningococcal Vaccines

Introduction

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

Dr. Rubin expressed his gratitude to Dr. Pickering for all of his contributions. He indicated that in the interest of time, this session would include a discussion of and vote on the meningococcal B vaccine for high-risk individuals. Discussion of the broader use of meningitis B vaccines for adolescents will be deferred until the June 2015 meeting.

Considerations for use of Serogroup B Meningococcal (MenB) Vaccines in Persons at Increased Risk

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

For use of serogroup B meningococcal (MenB) vaccines in persons at increased risk, Ms. MacNeil summarized current meningococcal vaccination recommendations for persons at increased risk, reviewed the groups at increased risk for serogroup B meningococcal disease, reviewed immunogenicity and safety data for the MenB vaccines, summarized the outcomes from the GRADE evaluation, and presented proposed policy option language for a vote.

Meningococcal conjugate vaccines are routinely recommended for persons ≥2 months of age at increased risk for meningococcal disease, including persons with persistent complement component deficiencies, persons with anatomic or functional asplenia, 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, and military recruits.

There are now two serogroup B meningococcal vaccines licensed in the US for use in persons 10 through 25 years of age. Trumenba® is a three-dose series and was licensed by the Food and Drug Administration (FDA) in October 2014. Bexsero® is a two-dose series and was licensed by the FDA in January 2015. Bexsero® was also licensed in several other countries for use in persons ≥2 months of age.

The work group (WG) has been discussing a number of different options for use of MenB vaccines. To address the immediate need of protecting groups at increased risk, the WG suggested language for vaccination of persons with persistent complement component deficiencies, persons with anatomic or functional asplenia, microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*, and persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak. The WG also has been reviewing available data and discussing options for broader use of MenB vaccines in adolescents and college students. Policy options for broader use of MenB vaccines will be discussed during a future meeting.

The WG has discussed a number of age-group options for recommendations for persons at increased risk, including the current licensed age indication for both MenB vaccines, which includes persons 10 through 25 years of age. Additionally, the WG considered language for persons aged ≥2 months at increased risk as Bexsero® is currently licensed for persons over age two months in other countries. However, data are not currently available for use of Trumenba® in children less than 10 years of age. The schedule and reactogenicity profile for MenB vaccines are quite different in young children compared to adolescents. The WG plans to review the data for persons aged 2 months through 10 years, and may propose extended policy options for persons at increased risk in the future. During this session, the WG suggested language for use of MenB vaccines in persons 10 years of age and older who are at increased risk for meningococcal disease. This extends beyond the licensed age indication, but the WG is comfortable that there are no theoretical differences in safety for those >25 years as compared to those 10 through 25 years of age.

Regarding the groups at increased risk for serogroup B meningococcal disease, persistent or genetic deficiencies in the complement pathway are well-known to increase risk for meningococcal disease. These deficiencies are rare and only affect about 0.03%[1] of the US population. Individuals with persistent complement component deficiencies are at up to a 10,000-fold[2] increased risk for developing meningococcal disease and often develop recurrent infection [[1]P Densen. Complement deficiencies and meningococcal disease. Clin Exp Immunol. Oct 1991; 86(Suppl 1): 57-62; [2]Cohn et al. Prevention and Control of Meningococcal Disease. MMWR. March 22, 2013; 62 (RR-2)].

Eculizumab (Soliris®) is a monoclonal antibody that is approved for treatment of atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH). It functionally creates a complement deficiency by binding to C5 and inhibiting the terminal portion of the complement cascade. Several individuals (n=5/326) in the clinical trials for eculizumab have reportedly developed meningococcal infections despite prior vaccination with conjugate vaccines. Persons being treated with eculizumab were not explicitly included in the conjugate vaccine recommendations; however, meningococcal vaccination is required for persons prior to treatment [http://soliris.net/sites/default/files/assets/soliris_pi.pdf].

Persons with functional or anatomic asplenia also appear to be at increased risk for meningococcal disease. However, the data are less compelling than for pneumococcal disease risk[1]. This group includes sickle cell disease, which affects approximately 90,000 to 100,000 persons of all ages[2] in the US. In asplenic persons, the case-fatality ratio is also elevated for meningococcal disease (40% to 70%)[3]. It has been demonstrated that people with asplenia have a significantly lower response to one dose of meningococcal C (MenC) vaccine[4] [[1]Cohn et al. Prevention and Control of Meningococcal Disease. MMWR. March 22, 2013; 62 (RR-2); [2]http://www.cdc.gov/ncbddd/sicklecell/data.html; [3]Updated recommendations for the use of

meningococcal conjugate vaccines. MMWR. January 28,2011; 60(3): 72-76; [4]Balmer, P et al. Infection and Immunity, Jan 2004, 332-337].

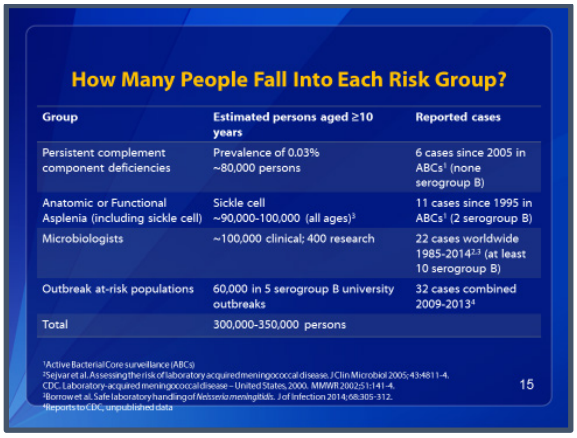
Microbiologists who work with *Neisseria meningitidis* are also at increased risk for meningococcal disease. In a review by Sejvar et al (2005), 16 cases were reported worldwide between 1985 and 2001. All occurred among clinical microbiologists in medical microbiology laboratories, with 7 cases due to serogroup C and 9 due to serogroup B. None of the cases in the review occurred in persons working in hematology, chemistry, or research laboratories. Of the 16 cases, 8 (50%) were fatal, and 15 occurred in microbiologists who had performed strain manipulation on an open laboratory bench. Since this review, 6 additional cases of meningococcal disease have been reported in microbiologists. Of these, 2 occurred in the US and 1 each occurred in New Zealand, France, Sweden, and Argentina. These cases included cases in industry and research microbiologists [Sejvar et al. Assessing the risk of laboratory acquired meningococcal disease. J Clin Microbiol 2005; 43:4811-4. CDC. Laboratory-acquired meningococcal disease – United States, 2000. MMWR 2002;51:141-4. Borrow et al. Safe laboratory handling of *Neisseria meningitidis.* J of Infection 2014; 68:305-312].

The Sejvar paper estimated an attack rate of 13/100,000 among microbiologists who work with *Neisseria meningitidis*[1]. The high case fatality ratio observed among microbiologists who have developed meningococcal infection is likely due to exposure to high concentrations of organisms and highly virulent strains. The majority of cases have occurred among clinical microbiologists who were not using respiratory tract protection at the time of exposure.

The final group includes persons at risk because of a serogroup B meningococcal disease outbreak. Fortunately, meningococcal outbreaks are rare, historically causing only about 2% to 3% of US cases[1]. However, five serogroup B clusters/outbreaks have been reported on college campuses during 2009 through 2013. In two of these recent outbreaks, students were estimated to be at a 200- to 1400-fold increased risk for meningococcal disease during the outbreak period. In the recently published guidance for serogroup B meningococcal outbreaks in institutional settings, the thresholds for considering vaccination were defined as 2 cases in institutions with populations less than <5,000 persons and 3 cases in institutions with populations of ≥5,000 persons[2] [[1] National Notifiable Diseases Surveillance System[2]http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf].

During the first two months of 2015, two outbreaks of serogroup B meningococcal disease were reported on college campuses in the US. Two cases occurred among students at a Rhode Island college, which has 4500 students. A vaccination campaign was conducted in response to the cases using Trumenba®, and approximately 98% of the target population received Dose 1. Four cases of serogroup B meningococcal disease have been reported at an Oregon university with 25,000 students, including one death. Two of the four cases were epidemiologically linked, but were not close contacts with one another. Planning is currently underway for a MenB mass vaccination campaign scheduled to begin on March 2, 2015. Additional sporadic cases of serogroup B meningococcal disease in college students have also been reported to the CDC this winter.

The following table summarizes the risk groups and includes the available data on cases that have occurred in each of the risk groups:



How Many People Fall Into Each Risk Group?

Group	Estimated persons aged ≥10 years	Reported cases
Persistent complement component deficiencies	Prevalence of 0.03% ~80,000 persons	6 cases since 2005 in ABCs[1] (none serogroup B)
Anatomic or Functional Asplenia (including sickle cell)	Sickle cell ~90,000-100,000 (all ages)[3]	11 cases since 1995 in ABCs[1] (2 serogroup B)
Microbiologists	~100,000 clinical; 400 research	22 cases worldwide 1985-2014[2,3] (at least 10 serogroup B)
Outbreak at-risk populations	60,000 in 5 serogroup B university outbreaks	32 cases combined 2009-2013[4]
Total	300,000-350,000 persons	

[1]Active Bacterial Core surveillance (ABCs)
[2]Sejvar et al. Assessing the risk of laboratory acquired meningococcal disease. J Clin Microbiol 2005;43:4811-4.
CDC. Laboratory-acquired meningococcal disease – United States, 2000. MMWR 2002;51:141-4.
[3]Borrow et al. Safe laboratory handling of *Neisseria meningitidis*. J of Infection 2014;68:305-312.
[4]Reports to CDC, unpublished data

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Approximately 300,000 to 350,000 individuals fall into these groups. Although only a handful of cases have been documented in Active Bacterial Core surveillance (ABC) or the published literature, these groups are well-known to be at increased risk for meningococcal infection and are currently recommended to be vaccinated with meningococcal conjugate vaccine, but remain at risk for serogroup B meningococcal disease.

Three groups are included in the current conjugate vaccine recommendations but are not proposed to be included for MenB. First-year college students living in residence halls are not included because they are being considered in the broader adolescent and college student policy options. Travelers are also not being considered because their risk is primarily due to serogroups other than B. Military recruits are not being considered because the current MenB epidemiology in the military is similar to the US population[1] and the Department of Defense (DoD) sets its own vaccination policies [[1]Broderick M, et al. Incidence of Meningococcal Disease in the United States Military Before and After Adoption of the Conjugate Vaccine (MCV-4). EID. Feb 2015].

In summary of the available immunogenicity and safety data, both of the MenB vaccines have a demonstrated immune response in the general adolescent population. Nearly all adolescents in clinical trials achieved protective antibody titers after either three doses of Trumenba® or two doses of Bexsero®. For Bexsero®, response rates were somewhat lower in a small study conducted among US and Polish adolescents. However, it is important to remember that immunogenicity data are not directly comparable for Trumenba® and Bexsero® in part because the primary endpoints differed for each of the vaccines. Immunogenicity data are not currently available from persons in most of the groups at increased risk, although limited data are available for use in laboratory workers. Only limited short-term (18 through 23 months) antibody persistence data are available for Bexsero®. Persistence data for Trumenba® should be forthcoming shortly, which will be important for informing booster recommendations for these groups at increased risk in the future.

Several pieces of additional data are needed for both vaccines to inform policy decisions, including immunogenicity against additional strains to evaluate breadth of coverage, antibody persistence data, safety and immunogenicity data (concomitant vaccination, groups at increased risk, other age groups), and additional safety data. A number of these studies are ongoing, and data will be reviewed by the WG when available.

New data on the safety and immunogenicity of concomitant administration and the safety and tolerability of Trumenba® have become available since the October 2014 ACIP meeting. A detailed description of the newly available data for Trumenba® was provided to the voting members of ACIP. The safety and immunogenicity of concomitant administration of Trumenba® with Menactra® and Adacel® were evaluated. The local and systemic reactogenicity profiles were demonstrated to be similar when Trumenba® was administered alone or concomitantly with the other vaccines. In addition, non-inferior immune responses to all Tdap and MenACWY antigens and the MenB test strains were observed.

In a large-scale safety study which evaluated the safety and tolerability of Trumenba®, the safety profile observed was consistent with studies that supported licensure. There are limited plans for both manufacturers to collect immunogenicity data from persons in the groups at increased risk. A small immunogenicity study is currently underway for 150 persons 2 through 17 years of age with complement component deficiencies and asplenia receiving two doses of Bexsero®. Data from this study are anticipated to be available in 2016. In addition, small studies are currently ongoing for both Trumenba® and Bexsero® in laboratory workers.

In summary of safety, MenB vaccines are more reactogenic than other vaccines given during adolescence. However, the majority of local and systemic reactions to the MenB vaccines are mild to moderate in severity and are transient, with the most common adverse event (AE) reported being pain at the injection site. Serious adverse reactions (SAEs) are rare, and rates are similar between vaccine recipients and controls in the clinical trials. Safety data specific to the groups at increased risk are not currently available, but are anticipated to be similar to the general population.

In terms of other sources of safety data for MenB vaccines, there is limited experience outside of clinical trials. Most of this experience is with Bexsero®, which has been administered to approximately 17,000 persons vaccinated under an expanded access Investigational New Drug (IND) program for outbreak response at two US universities and in over 40,000 persons vaccinated in a regional public health program in Québec. No concerning patterns were observed among AEs following any of the vaccination programs. For Trumenba®, no post-licensure safety data are currently available, but it is CDC's understanding that safety data are being collected for Trumenba® in conjunction with the two current outbreak responses in Rhode Island and Oregon.

The WG also reviewed data on theoretical concerns from mouse models about the potential for development of autoimmune disorders following MenB vaccination. The FDA also reviewed these data, and did not observe any differences in the rate of autoimmune disorders between vaccine recipients and controls in the safety studies that supported licensure. Post-licensure safety surveillance will be conducted to detect potential safety signals. However, a large number of doses must be administered to detect any potential safety signals in the Vaccine Safety Datalink (VSD). In the meantime, passive reports to the Vaccine Adverse Event Reporting System (VAERS) will be monitored.

In summary of the GRADE evaluation outcomes, as a reminder, the first step in the GRADE process is to formulate the study questions. The following initial study questions were agreed upon by the Meningococcal WG, although Ms. MacNeil focused only on the last two during this session:

Questions	Population
1. Should MenB vaccine be administered routinely to all adolescents and young adults?	Adolescents and young adults 10 through 25 years of age
2. Should MenB vaccine be administered to college students to prevent outbreaks?	College students 15 through 25 years of age
3. Should MenB vaccine be administered to persons at increased risk for serogroup B meningococcal disease?	Microbiologists, persons with persistent complement component deficiencies or functional or anatomic asplenia (including sickle cell anemia)
4. Should MenB vaccine be administered during outbreaks?	Individuals at increased risk for serogroup B disease because of an outbreak

The outcomes that were ranked as critical for each question by the Meningococcal WG included the following:

- ❑ Burden of disease
- ❑ Mortality of disease
- ❑ Long-term sequelae
- ❑ Serogroup B strain coverage
- ❑ Short-term immunogenicity
- ❑ Persistence of immunogenicity (1 to 2 years after vaccination)
- ❑ Serious adverse events

The first four outcomes cannot be assessed in GRADE because they are surveillance data. These outcomes were evaluated using a modified assessment, and the last three outcomes were assessed using GRADE. In GRADE, all of the available data for each outcome are evaluated on the following six criteria to determine whether the overall evidence type is moved up or down and a final evidence type is assigned:

- ❑ Risk of bias (methodological limitations)
- ❑ Inconsistency
- ❑ Indirectness
- ❑ Imprecision
- ❑ Publication bias
- ❑ Other considerations (strength of association, dose gradient, direction of all plausible residual confounding)

Given the time constraints during this meeting, Ms. MacNeil reviewed only the available data that were used to assess the benefits and harms for each vaccine, and the final evidence type assigned to each MenB vaccine for use in persons at increased risk and in outbreak settings. A copy of the full presentation for the GRADE evaluation was provided in the ACIP members' binders.

For Bexsero®, a total of six studies were reviewed, including two open-label studies and four randomized-control trials. The majority of the studies assessed several outcomes. Four of the studies have been published. However, data were also used from additional unpublished

studies. In addition, safety data from three vaccination campaigns were reviewed for SAEs. For Trumenba®, a total of eight studies were reviewed, including three open-label studies and six randomized-control trials. The majority of the studies assessed several outcomes. Results of three of the studies have been published. However, additional unpublished data were also used. Antibody persistence data are not yet available for Trumenba®, so they were not assessed in this evaluation.

The overall evidence type for use of Bexsero® among persons at increased risk for serogroup B meningococcal disease was graded as Type 3, and among outbreak at risk populations as Type 2. The overall evidence type for use of Trumenba® among persons at increased risk for serogroup B meningococcal disease was graded as Type 3, and among outbreak at risk populations as Type 2. Based on the available data and evidence reviewed, the WG supports routine vaccination of persons at increased risk for meningococcal disease for several reasons, including the demonstrated disease risk in the specific risk groups and that these groups are currently recommended to be vaccinated with MenACWY conjugate vaccines. Additionally, there is a demonstrated immune response to MenB vaccines in the general adolescent population and there are no theoretical safety concerns for persons >25 years of age from vaccination as compared to persons aged 10 through 25 years.

The WG also supports harmonization of the current MenACWY conjugate vaccine recommendations with the proposed MenB language in two areas where the language differs. First, use of eculizumab (Soliris®) will be explicitly included as an indication for vaccination with MenACWY conjugate vaccine. Secondly, the wording for the use in outbreaks will be aligned with the proposed wording for MenB vaccines to read, “Persons identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroups A, C, W, or Y.” The two sets of recommendations would still differ for certain special populations (e.g., travelers, first-year students living in residence halls, and military recruits) who are not included in the proposed MenB language.

The WG’s proposed language for use of MenB vaccines for persons at increased risk was as follows:

> A serogroup B meningococcal (MenB) vaccine series should be administered to persons aged ≥10 years at increased risk for meningococcal disease. (Category A) This includes:
>
> - ❑ Persons with persistent complement component deficiencies[1]
> - ❑ Persons with anatomic or functional asplenia[2]
> - ❑ Microbiologists routinely exposed to isolates of *Neisseria meningitides*
> - ❑ Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak
>
> [1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)
> [2]Including sickle cell disease

In addition, the following guidance for use was proposed:

- Depending on the MenB product used, a complete two- or three-dose series of vaccine is required for protection from serogroup B meningococcal disease.
- The same vaccine product should be used for all doses.
- No product preference is to be stated.

In conclusion, Ms. MacNeil thanked the members of the ACIP Meningococcal WG for the dedication and thoughtful discussions over the last several months as they quickly worked through a review of the available evidence for these new MenB vaccines.

Discussion Points

Regarding the differences between the quadrivalent MenACWY and the B vaccine and recognizing that the military sets its own vaccination policy, Dr. Reingold asked whether it was generally envisioned that differences between use of the B vaccine and use of the quadrivalent in terms of travelers and college students would remain differences in terms of how the two vaccines are used.

Ms. MacNeil responded that the differences would remain. The plan is to consider adolescents and college students in June 2015 as part of the broader recommendations. But, the differences for travelers and the military would remain.

Dr. Harriman asked whether the WG would also consider the use of B and MenACWY meningococcal vaccines for infants, noting that the Affordable Care Act (ACA) requires that Category A and B recommendations be covered.

Dr. Rubin replied that the WG intends to consider MenACWY use in infants during future deliberations.

Dr. Sawyer (PIDS) requested clarification regarding why the use for high risk begins at age 10 as opposed to a younger age, given that one of the vaccines is licensed for use in children younger than 10 years of age.

Ms. MacNeil indicated that currently in the US, the minimum licensure age is 10. Bexsero® is licensed down to two months of age in other countries. The WG will eventually review this issue. For this vote, they only wanted to propose the recommendation for 10 years of age and older.

Dr. Harrison asked what is being done specifically to monitor safety in the context of these vaccines during outbreaks, and what the DoD's protocol is in terms of using these two vaccines.

Ms. MacNeil replied that when the vaccine was used under an IND, as part of the IND, a specific safety follow-up was done. Her understanding is that this is also being done for Trumenba® in the two current outbreaks, although CDC is not involved in those investigations.

Dr. Sergienko (DoD) responded that MenACWY vaccine is currently being administered. The Joint Preventive Medicine Working Group met last month to discuss MenB vaccine, and they do not think there is an indication for administering that in the recruit population at this point.

Dr. Duchin (NACCHO) asked whether the threshold for vaccination for use of the MenB vaccine as currently stated for the IND would remain the same for the vaccine if a vote was taken to approve the use of that vaccine in outbreak settings. He also inquired about what is known regarding the impact of the vaccine on carriage.

Ms. MacNeil responded that the thresholds for the use of MenB vaccines in institutional settings under an IND are being used for the current outbreak, which will likely continue in the near-term. There are plans to review the entire outbreak guidelines and present results during the October 2015 or February 2016 ACIP meeting. While little is known about carriage, carriage studies will begin at the universities currently experiencing outbreaks. Hopefully, there will be more data regarding carriage available by the June or October 2015 ACIP meeting.

In the spirit of full disclosure, Dr. Temte emphasized that recommendations for a universal vaccination would be discussed during the June 2015 ACIP meeting.

Public Comments: High Risk MenB Recommendations

Dr. Mary Ferris
Student Health Director
University of California Santa Barbara

We have a campus of 30,000 students, faculty, and staff. In November 2013, our campus community was devastated by an outbreak of four cases of meningococcal serogroup B disease within a 10-day period. It resulted in life-threatening complications to our first case of a 19 year old lacrosse team member who suffered amputations to both legs and has extensive skin grafts and scarring, but did survive. So, I know you're aware of the devastating consequences of this terrible disease. But, you may not know the impact it has on a university when an outbreak occurs. National news outlets camped out on the campus. There was widespread fear and even panic among the students, faculty, staff, and the surrounding city. The local school district initially prohibited our student teachers from their sites. Parents drove in to take their children back home. Our campus childcare center refused to have the student volunteers there. Parents demanded we close the campus, but did not want their students to come home for the Thanksgiving holiday. It was really terrible for all of us, as you can imagine.

Our local public health department and the CDC helped us and established special phone lines to handle the high volume of increasing distress calls. We greatly appreciate all the help they gave us. And as you know, we were able to obtain the MenB vaccine through a special FDA approval with the assistance of the CDC. But, we would have preferred to avoid this disaster completely by protecting our students in advance with a vaccine that covers MenB. So, we're glad to have your approval of the vaccine for outbreak settings, but we think that we would benefit even more if our students came to campus already protected by the vaccine. Outbreaks will happen again, and as you are hearing, it's currently going on at the University of Oregon, and they're struggling to find a source to pay for those vaccines. Even one case in a college setting has major repercussions on the institution, and most colleges will not have the resources to pay for vaccines when these outbreaks occur.

We need the ACIP to establish MenB vaccine as part of routine adolescent immunizations so that our entering students can be protected before they arrive on campus and are exposed to meningococcus, not just after an outbreak occurs. We also can benefit from your recommendation for pre-entry vaccination so that we can enforce that in our entry immunization requirement before students even get to campus. The majority of our students are first-generation college students, coming from low-income families, and do not have the ability to afford this vaccine unless it's covered by health insurance, which, as you know, follows your recommendations. Thank you for allowing me to speak. I sincerely hope you'll consider the impact of this disease on both the individuals and our colleges and universities when you make your decision.

Seth Ginsberg
Co-Founder / President
Global Healthy Living Foundation (GHLF)

I have no disclosures to make today. GHLF receives funding through grants and partnerships with industry, private foundations, as well as the government. I'm here today on behalf of Dr. Neal Raisman, who was here down from Columbus yesterday and, unfortunately, needed to return to an urgent issue back at home. So, instead I'll read his brief comments here, and I will not attempt his Boston accent.

> *My name is Neal Raisman. In 2005, I was the father of two. Today, I am the father of one. On the morning of September 27th, my youngest son, Isaac, woke with a headache and was dead of meningococcal by 4:30 the same day. I found his body. He had less than 12 hours from the time he told us he had a headache until he died, and a vaccine would have prevented his death. It's an epidemiological story you all know too well, but it's a personal story I never wanted to know. Today I'm here as a spokesperson for the Global Healthy Living Foundation, and together we are asking this committee to endorse the FDA labeling recommendation, which is for immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B for individuals 10 through 25 years of age.*
>
> *My words here today and your committee meeting could not come at a more immediate time. As you know, eight days ago, Lauren Jones, a student at the University of Oregon, added her name to the list of those who have died of meningitis. Just three days ago, a UC Davis student was diagnosed with meningitis. At the University of Oregon, students who have the money will be able to get the vaccine for meningitis B and those who do not will remain exposed to its ravages.*
>
> *Since the FDA approved vaccine for meningococcal strain B in November of 2014, people have died. Did they die because the ACIP didn't act? Perhaps. Although the vaccine was available to those who could afford to pay for it, without your recommendation, as you know, insurance companies and Medicaid won't cover the cost. It's not difficult to conclude that informed people with the money to pay for the vaccine have lived and those who can't afford it or don't know about it have died. This is counter to everything the ACIP, the CDC, the FDA, and, of course, the NIH stand for. Your endorsement vote for the FDA recommendation would realign this committee with its mission and with the values and expectations of parents with college-aged children. We expect the government to tell us when the health of our children is in danger and then help us decide what to do about it.*

Because meningitis is nearly always fatal, the low numbers of people affected mask the toll these cases take on families, such as mine, and on our communities. My job today is to help you understand the depth of the emptiness that we parents feel every day and the heartache we feel for those parents who are about to join our ranks—the ranks of families minus one. Please act so other young people and their families are not so violently affected by meningitis. Please act so there are no more Isaacs and Laurens. Thank you very much.

Dr. Susan Even
ACIP Liaison
American College Health Association

I just wanted to speak on behalf of the American College Health Association (ACHA), which is very aware of the devastating physical and emotional impact of meningococcal disease on the individual college student and their families, and the campus communities in sporadic cases and outbreaks, as have been eloquently described. The American College Health Association is committed to promoting implementation of CDC's immunization recommendations on college campuses, including pre-matriculation meningococcal conjugate vaccine (MCV4). Now that MenB vaccines are licensed and these cases continue to arise, ACHA appreciates being involved in the ongoing discussion regarding use in outbreaks, appreciates the impact that this guidance will have in promptly responding to this challenging situation, and also supports prompt deliberations and an expeditious decision regarding the general recommendations for MenB vaccine so information will be available to parents, families, students, and campuses for the students entering in the fall of 2015. Thanks.

Vote: MenB Vaccines for Persons Aged ≥10 Years at Increased Risk for Meningococcal Disease

Dr. Romero made a motion to approve the MenB vaccines recommendation for persons aged ≥10 years at increased risk for meningococcal disease. Dr. Kempe seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Vaccines for Children

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

Dr. Santoli explained that the purpose of this revision was to update the resolution to: (1) clarify eligible groups for meningococcal conjugate vaccines; (2) streamline the schedule and interval information for meningococcal conjugate vaccines by incorporating links to published documents; and (3) add meningococcal serogroup B vaccines recently licensed for use. The following minor clarifications in language were proposed (changes were shown in yellow in the presentation, but are underlined in this document):

Meningococcal Conjugate Vaccines (MenACWY and HibMenCY)

Eligible Groups:

- Children aged 2 months through 10 years who are at increased risk for meningococcal disease attributable to serogroups A, C, W, and Y, including:
  - Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D or taking eculizumab [Soliris®])
  - Children who have anatomic or functional asplenia, including sickle cell disease
  - Children traveling to or residing in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with local population will be prolonged
  - Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroups A, C, W, or Y
- All children aged 11 through 18 years

Recommended Vaccination Schedule and Intervals:

> Recommended schedules and intervals for meningococcal conjugate vaccines can be found at the following links:
> http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf
> http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6324a2.htm

Recommended Dosage:

> Refer to product package inserts.

Contraindications and Precautions

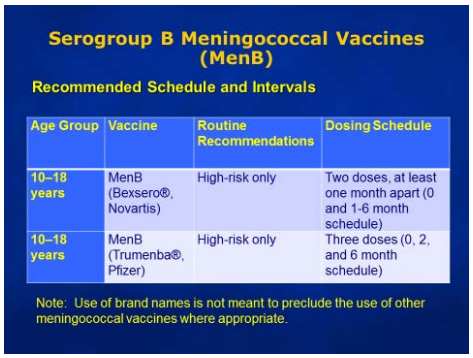
> Contraindications and Precautions can be found in the package inserts available at
> http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

Serogroup B Meningococcal Vaccines (MenB)

Eligible Groups:

- Children aged 10 through 18 years at increased risk for meningococcal disease attributable to serogroup B, including:
  - Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D or taking eculizumab [Soliris®])
  - Children who have anatomic or functional asplenia, including sickle cell disease
  - Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroup B

Recommended Schedule and Intervals:



Serogroup B Meningococcal Vaccines (MenB)

Recommended Schedule and Intervals

Age Group	Vaccine	Routine Recommendations	Dosing Schedule
10–18 years	MenB (Bexsero®, Novartis)	High-risk only	Two doses, at least one month apart (0 and 1-6 month schedule)
10–18 years	MenB (Trumenba®, Pfizer)	High-risk only	Three doses (0, 2, and 6 month schedule)

Note: Use of brand names is not meant to preclude the use of other meningococcal vaccines where appropriate.

Recommended Dosage:

Refer to product package inserts.

Contraindications and Precautions:

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

The following language would appear at the end of the recommendation:

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

Discussion Points

In terms of eligible groups, Dr. Bocchini requested clarification regarding HibMenCY vaccine, which is not a travel vaccine and would not be recommended for children who are traveling because it does not include A.

Dr. Santoli replied that the eligible groups section could be amended to make that more clear.

Vote: VFC Resolution for MenB Vaccines for Persons Aged ≥10 Years at Increased Risk for Meningococcal Disease

Dr. Harrison made a motion to approve the VFC MenB vaccines recommendation for persons aged ≥10 years at increased risk for meningococcal disease. Ms. Pellegrini seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Additional Meningococcal Vaccine Public Comments

Frankie Milley
Founder / National Director
Meningitis Angels

At the time my son, Ryan, got meningitis, there was a vaccine but there was no marketing, there was no recommendation, and there was no accessibility, so he died. With permissive recommendations, he still would have died because we still wouldn't have known about it. You know, to me, this is like if you have a ship with 100 passengers on board, you have 100 life vests and that ship is sinking, you'd hand out 50 of those life vests and the other people watch theirs hanging in the closet as they drown. You've done a great job in protecting these kids so far from this disease. We've got half of the puzzle there. We need to finish the puzzle. I am really encouraging you, as you move forward, to work fast on this because I really believe a permissive recommendation in an outbreak—somebody's going to die before that happens or be left debilitated. That's wrong. We shouldn't have to have a sacrificial lamb. I would encourage you to move away from those living in dorms. We've been fighting this 10 years and we still argue with physicians every day that they don't have to live in a dorm to get this. Five of our kids were told, "You don't live in the dorm. You don't get the vaccine." All five of them died. So, I just want to encourage you to really think about moving fast on this issue so other kids don't die. Thanks again.

Scott Parkhurst
Meningitis Angels

My son Jake is the youngest of two of my boys. He was an A student Junior in high school. He loved golf. He skied, snowboarded, and rode motorcycles. He was into baseball. I got a call Saturday night about a year ago to the day that he wasn't feeling well. He was with his mom and I said, "Drink your fluids and we'll see how you feel in the morning." The next morning, I texted him to follow up on how he was feeling, and he said his mom was taking him to urgent care. At 10:30 Monday morning, I texted his mom and she said was being put in an ambulance to take him to the hospital. I drove to the hospital. I was in the ER and the doctor pulled me and his mom aside and said, "He may not make it." I said, "Fight for your life" and he nodded his head. They took him to ICU and he was in a medically-induced coma. They had to help him

fight with antibiotics. Later that evening, they noticed that one of his pupil's was dilated and they thought there might be some brain issues, and so they started to wean him off of the medication. He wasn't showing any responsiveness, so they did an EEG and determined that he was brain-dead. Jake was dead in 36 hours—cause of death, Meningitis B. I took my oldest boy to Canada to get him vaccinated for Meningitis B. I believe a permissive recommendation would be the death of Jake all over again. Thank you.

Andy Marso
Meningitis Angels

I prepared some remarks, but obviously, I just kept paring them down and paring them down. In the interest of time, I wrote a 270-page book about my experience, so if you want it, Dr. Pickering has a copy. Really, the time element here doesn't necessarily matter because no matter how much time I had, I wouldn't have been able to convey to all of you the horror of going from a completely healthy college student to within 24 hours being life-flighted on a helicopter to a Level 1 trauma center with my lungs failing and struggling to breathe. I wouldn't be able to convey to you what my parents felt when they arrived that night, and I was already unconscious, and the doctors told them I might not survive. I wouldn't be able to convey to you the deep distress of waking up from that coma three weeks later and realizing I couldn't move my hands and feet, and having doctors remove the bandages to show me that my arms and legs were rotting while still attached to my body. I would not be able to convey to you the pain of the next three months, both physical and emotional, that I spent in a burn unit at KU Medical center having my arms and legs debrided daily. I would not be able to convey to you the post-surgical pain of amputations that were still necessary to my feet and hands. I would not be able to convey to you the frustration of the year of physical and occupational therapy that I needed to be able to wipe myself and feed myself as a 23-year old man.

No matter how much time you could give me, it would not repay my father's insurance company for the $2 million in medical bills that we billed them that first year. It would not compensate me for all of the thousands in out-of-pocket costs I have paid every year since for my medical needs, including my prosthetics to walk and to stand. Those costs will be with me for the rest of my life. When you consider these recommendations, please consider not just the costs, but the cost burden. Mass vaccination spreads that cost burden equitably among a large population. Neglecting to vaccinate large populations concentrates the cost burden for this disease on families like mine, and it is enormous. The recommendation that you all made today is a start, but it's barely a start. What it basically says is that if you go to a school like the University of Missouri where they just had a confirmed MenB case, you've got to wait for two more people to get sick because that's a big school. So, they're not going to bring in the vaccine until at least two more people critically ill. That's not acceptable. That's not preventative medicine. That's crisis management, and it's not even very effective crisis management. I would much rather see us prevent this before it happens. So, what I encourage you all do is be bold and consider your legacy. We have a chance to wipe out a disease that causes incalculable human suffering. One of the most important pieces of that puzzle is your recommendation. Thank you.

Lynn Bozof
National Meningitis Association (NMA)

I have no disclosures to make. As many of you know, NMA is comprised of survivors and families who have all suffered tremendously from meningococcal disease. In January, NMA hosted a round table of survivors, their family members, infectious disease specialists, college health officials, and others who could all offer a unique perspective and knowledge about meningococcal disease. We would like to share the outcome from that meeting, which is in your packet and also is available on the back table. It gives voice to the concerns and worries of the participants. The report points out the long-term impact on survivors, the life-altering changes for all of their families, and the effects on an entire community long after the immediate impact. So, as others have said, as you consider serogroup B recommendations in light of all of the cases and outbreaks that have occurred recently, please consider these life-altering and life-changing perspectives. I've heard from so many families who have lost children to the B serogroup who thought their children had been protected because they had been vaccinated according to CDC recommendations. We now have the tools to protect against the most common strains of this disease. We need to do the right thing and routinely recommend vaccination for adolescents and teens. It's the only way that parents who rely on physician recommendations can have the opportunity to fully protect their children. Thank you. We have a short PSA to show.

Patty Wukovits
National Meningitis Association (NMA)

In 2012, my beautiful daughter, 17 year old Kimberly, a healthy high school senior in New York, died of serogroup B meningococcal disease just one week before graduating. We buried her in her prom dress just two days before she would have been able to wear it at her prom. I'm a nurse, and when Kim got sick, I was sure it wasn't meningitis because she'd been vaccinated. I assumed that the recommended vaccine covered it all and I thought she was safe. After losing Kim, I dedicated myself to learning more. There were no approved serogroup B options then, but there are now. Please try to think about the message that parents will hear, "The CDC recommended that your child be vaccinated against meningococcal disease, but this vaccine won't protect against all strains of the disease. There is an additional vaccine that protects against the strain most common in adolescents. It is not recommended, but your child can get it if you want it and if you're able to obtain it." As a health care professional, this is an extremely complicated message to deliver and, more importantly, it's a hard message for a parent to hear and understand. We cannot expect parents to know that their children are not protected against serogroup B, and we cannot expect health care providers to act without strong guidance from this committee. That's why I'm asking you to consider broad recommendations for this vaccine. A recommendation would make it easy for parents to do the right thing to vaccinate their children. The bottom line is Kimberly would be alive today if she had had the opportunity to have been protected by the B vaccine. Instead, as her mother, I am standing here literally in Kim's shoes, the very shoes she should be wearing right now in her third year of nursing school fulfilling her dreams to become a pediatric nurse. Please help ensure that all children get the protection they need so that what happened to my family and to Kimberly does not happen again. Thank you.

Carl Buher
National Meningitis Association (NMA)

Thank you guys. I'm so grateful to have the chance to speak here today representing the National Meningitis Association. I survived bacterial meningitis when I was 14, and just last year learned that it was serogroup B. I spent five months in the hospital, lost three of my fingers and both of my legs below the knee on Halloween. I had 11 surgeries. It took me almost four years to learn to walk again on my prosthetics. To date, my medical bills have far exceeded $2 million, but I still consider myself lucky. Eleven years later, I have a college degree, a great job, and a beautiful wife. Most survivors I know feel the same way. We have pretty good attitudes and have been able to find the positives in this disease. For example, my wife and I like to talk about my perks list, which includes things like my feet no longer fall asleep and the ability to know exactly what shoe size I need. However, there are also some cons. I can no longer enjoy fuzzy slippers and Ziploc® bags have become my worst enemy. But no matter how lucky we are, most of us will deal with the effects of this disease for the rest of our lives. My fellow survivor, Samantha, has had more than 37 surgeries in 30 year and still has pain on a daily basis. Kyla lost both legs and most of her fingers and has gone through a dozen surgeries in recent years to lengthen her thumb, because she says "opposition is everything." Blake learned so much as an outpatient before a transplant that he became a dialysis nurse. Some of us, Like Francesca, have invisible scars like the loss of cognitive function, or hearing, or vision. Many of us endured and some continue to endure anxiety, fear, and depression because of this terrible disease. When we get together, we talk about the challenges we deal with that most people don't even think about, like how to take a shower when you're traveling with no legs or how hard it is to count to 10 on your fingers when you're missing a few. For most of us, it will affect our finances for the rest of our lives. Our cost of living will always be higher, and we may need additional support and more obvious things, such as needing more time off work to deal with additional surgery or complications. Even with great insurance plans, we pay enormous co-pays and out-of-pocket expenses for other things no insurance will cover, such as retrofitting cars to fit our needs or renovating homes. We are all very different, but one thing we agree on—we don't want anyone to have to go through what we went through and still deal with it on a daily basis. When you look at the cost of prevention, I hope you'll calculate how high the cost of survival is as well. Thank you for your time.

Sally Greenberg
Executive Director
National Consumers League

I'm here to support the routine schedule of Meningitis B. My organization has been around since 1899. We are the oldest consumer organization, and we also survey consumers on their attitudes about vaccines. What we found in our latest survey was that 87% of parents support getting their children vaccinated. The disease they fear most that vaccinating can prevent is meningitis. So, I'm here also to support the many parents and families who came out at their own expense. I come to this as a consumer advocate and wearing several other hats. One is that I had an uncle who had polio. He got it the year before the polio vaccine came out, and I watched my family suffer while he clung to life in an iron lung for two years and then went on to be a quadriplegic. One year later, this tragic condition could have been prevented. I'm also the parent of a college-aged kid who is a baseball player and lives in the dorms. As I meet with a lot of the meningitis victims, we take a very strong stand in favor and in support of safe and effective vaccines. I'm finding it very difficult to access that vaccine for him. It would be wonderful if this vaccine became part of the routine schedule. They have to order it. They're

not sure which one they want to order. There's a wealth of confusion. I've had maybe 10 phone calls and we still haven't figured out how to get this vaccine. So, it really isn't fair for my son to be the only guy to get it on his campus, which he probably will be. But, you know, I really feel so strongly that when you have something that's safe and effective, and thanks to all of you for the critically important work that you do, but there's just no reason why this shouldn't be part of the routine schedule. So, I'm really here with lots of hats on, but I think most importantly to support all of these families—the parents who came forward with these devastating conditions as a result of contracting Meningitis B and something that's totally preventable. Thank you for giving me the chance to speak. I appreciate it.

Additional Comments

Dr. Temte indicated that four letters pertaining to meningococcal infection and disease were submitted, and would be subsumed into the official minutes of the meeting. Those letters follow:

Leslie Maier
National Meningitis Association
Via Letter to Dr. Temte Date 2-24-15

Dear Mr. Temte:

My name is Leslie Maier and I am on the Board of Directors for the National Meningitis Association. I live in Tucson, Arizona. My son Chris was 17 and a senior in high school when he contracted meningococcal disease and died in less than 24 hours. The new meningitis vaccine was not available at that time for his age group. I believe he would be alive today had it been recommended.

I'm contacting you to request you write a letter to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices asking them to routinely recommend vaccines to protect adolescents against serogroup B meningococcal disease.
The FDA recently approved the first vaccines to protect against serogroup B in the United States. Since 2005, the CDC has recommended a vaccine to protect against strains A, C, W and Y, at age 11-12 with a booster dose at age 16. Many parents with children who suffered from serogroup B did not know that the vaccine their child received did not protect them against it.

Serogroup B meningococcal disease was also the cause of recent college outbreaks at Princeton University and UCSB. In the last 5 months, at least 2 other college students, in cases unrelated to these outbreaks, died from serogroup B. In the past month there were at least 5 more cases reported on college campuses across the United States.

I am one of the people affected by this horrible disease. My son's death devastated our family and community. Chris' high school classmates had difficulty finishing their final year of high school. His sister became an only child and is saddened that her new son will never have nieces or nephews to grow up with. His father and I have experienced the greatest loss possible, that of our child. Our goal is that no one else has to experience this terrible disease. We share our story to educate others about meningococcal disease, stressing the importance of vaccination.

A routine recommendation of serogroup B vaccines for adolescents would be a significant step forward in protecting them from this devastating disease. As someone whose life was profoundly affected by this disease, I encourage you to write a letter to the ACIP committee prior to their Feb. 25 meeting to help protect our children.

Sincerely,

Leslie Maier
National Meningitis Association

ACI
The American for Consumer Institute
Center for Citizen Research

February 3, 2015

Dr. Tom Frieden
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329-4027

Dear Director Frieden:

On behalf of The American Consumer Institute (ACI), a nonprofit educational and research organization, I am requesting that new vaccines for the serogroup B meningococcal (MenB) disease, which has infiltrated college campuses from coast to coast, be given a "permissive" recommendation at the next Advisory Committee on Immunization Practices (ACIP) meeting on February 25, 2015.

ACI respectfully requests that the ACIP avoid restricting the vaccine to high-risk groups or when there is an outbreak. Such an overly restrictive recommendation would make the vaccine only available to a select number of students with certain pre-existing conditions or to students whose families can afford to pay out of pocket, as well as after there is an outbreak. Further, under such a designation, two students would have to be stricken with potentially fatal MenB before other students on campus would be vaccinated. Worse yet, it would mean doctors would not likely stock the vaccines or educate parents about the MenB vaccination. This overly restrictive route would take the decision-making power regarding children's health away from parents and would ultimately continue a policy of responding to, rather than preventing, future MenB outbreaks.

The number of college students that have been stricken with MenB in the last several years is alarming. Last fall, two 19-year-old students at schools on opposite coasts died from the highly contagious bacterial infection. Sara Stelzer was a freshman at San Diego State University and Andrea Jaime was a nursing student at Georgetown University. Before these deaths, we saw outbreaks at Princeton and Drexel universities, which were related, and outbreaks at the University of California Santa Barbara (UCSB) and Kalamazoo College. A freshman lacrosse player at UCSB survived but had both feet amputated. I actually have personal experience with meningitis, having been afflicted with it as a child. I am one of the fortunate ones that recovered.

Currently, many parents have a false sense of security that their children are protected from MenB because they were immunized against other meningitis strains, as the Centers for Disease Control and Prevention (CDC) recommended in 2005. I had assumed my own daughter was protected because she was required to have a meningitis vaccine before entering college. But I was troubled to learn that unless the two MenB vaccines that were recently approved by the

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www.theamericanconsumer.org

Food & Drug Administration, Bexsero and Trumenba, are granted a permissive designation, she and other college students remain vulnerable.

The Affordable Care Act took an important step to ensure that families of all socioeconomic backgrounds have access to lifesaving vaccines. The law requires that any vaccine that receives a permissive recommendation from ACIP and is prescribed by a health care provider be covered under private insurance and the Vaccines for Children program. Without a permissive designation from ACIP for the MenB vaccines, this provision of the law would be undermined. Given that the lives of children and college students are at stake, ACIP and CDC should be promoting policies that help ensure all Americans are protected.

The key to preventing more avoidable student deaths and disabilities is granting a permissive designation so every child – not just those with parents wealthy enough to pay out of pocket – will have access to this lifesaving vaccine.

I thank you for your attention to this critical matter. I respectfully ask that a copy of this letter be distributed to each of the ACIP members prior to the February 25th meeting.

Sincerely,

Stephen B. Pociask
President and CEO
The American Consumer Institute
Center for Citizen Research
1701 Pennsylvania Ave., NW, Suite 300
Washington, DC 20006

CC: Dr. Larry K. Pickering
Executive Secretary
Advisory Committee on Immunization Practices

Congress of the United States
Washington, DC 20515

February 24, 2015

Thomas R. Frieden, M.D., MPH
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329

Dear Dr. Frieden:

We are writing in support of giving fair and due consideration to a broad recommendation for the use of vaccines preventing serogroup B Meningococcal disease (MenB), guaranteeing that students and their families will be able to protect themselves against this harmful disease.

As many as 1,500 cases of meningococcal disease occur annually in the United States each year. MenB now makes up about 40 percent of those cases and 10-15 percent of those with MenB die. Among those who survive, approximately one in five live with permanent disabilities, such as brain damage, hearing loss, loss of kidney function, and limb amputations.

In the last two years, students have been infected with the disease at Kalamazoo College, Princeton University, the University of California Santa Barbara, Georgetown University, University of Oregon, Providence College, San Diego State University, Yale University and Drexel University. There are other suspected cases at numerous high schools and colleges across the country. Making matters worse, approximately 25 percent of college freshmen are carriers for the disease, increasing the likelihood that these infections can spread.

We are pleased the Food and Drug Administration (FDA) recently approved two vaccines for this deadly disease. Both of these vaccines are approved for all individuals from 10 through 25 years of age. The Centers for Disease Control and Prevention and its Advisory Committee on Immunization Practices (ACIP) now has to recommend how accessible the vaccines will be.

The recent deaths and infections throughout the country are preventable. ACIP should consider at least a permissive recommendation, and ideally a routine recommendation, so that adolescents will have preventative access to the vaccines prior to an outbreak of disease.

A recommendation limited to high risk individuals and outbreaks only would create a significant barrier to access the vaccine. In this scenario, parents and adolescents are unlikely to be made aware that they are only protected against 4 of the 5 major disease causing strains and the option of protecting themselves against the fifth disease causing strain exists. Further, without a broad recommendation private insurance companies and public health initiatives like the Vaccines for Children program will not cover the costs of the vaccine limiting its access to only those who have the means to pay out-of-pocket.

Parents should be able to give their children the vaccine prior to an outbreak with no financial or other barrier. Ultimately, a restrictive recommendation from ACIP would deny access to the vaccines and leave nearly everyone in the United States, and our college students in particular, vulnerable to infection.

Vaccines have successfully reduced or eliminated cases of many horrific and preventable diseases, including other forms of meningitis. We hope CDC will expedite the deliberation process for recommending the newly approved MenB vaccines and ensure they are available to any parent who wants to protect their children. We look forward to your response.

Sincerely,

Erik Paulsen
Member of Congress

Marsha Blackburn
Member of Congress

Lynn Jenkins, CPA
Member of Congress

Tim Murphy
Member of Congress

Cc: Larry K. Pickering, M.D., Senior Advisor, National Center for Immunization & Respiratory Diseases, CDC

Anne Schuchat, M.D., Director, National Center for Immunization and Respiratory Diseases, CDC

February 20, 2015
Dr. Tom Frieden
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329-4027

Dear Director Fieden:

Our organizations, which together represent low-income and minority communities frequently disadvantaged in access to quality medical care, are writing as members of the Health Disparities Working Group. We urge you to give the two vaccines for bacterial meningitis (MenB) currently under consideration by the Advisory Committee on Immunization Practices (ACIP) a permissive recommendation at the Feb. 25, 2015 meeting.

The Affordable Care Act contained important provisions intended to address the vaccine gap in our country. Before passage of the law, this disparity meant vaccines were readily accessible to affluent communities, while low-income and minority communities lacked equivalent access. The National Institutes of Health (NIH) has identified access to vaccines as a major factor in curbing health disparities. Studies have found that minorities are less likely to receive immunizations because of limited access to preventative healthcare and lack of education on the importance of regular vaccinations. A recent Centers for Disease Control and Prevention (CDC) report found large racial, ethnic and income disparities in preventable hospitalizations, where blacks experience a rate more than double that of whites. Preventable incidents account for more than 1 million hospitalizations each year, at a cost of more than $6.7 billion annually.

The Affordable Care Act attempts to equalize vaccine access by requiring that the Vaccines for Children Program – which provides approximately 82 million vaccines to 40 million low-income children each year – cover vaccines to which ACIP has given a permissive recommendation. Private insurance must follow suit. But if ACIP only approves the vaccines for certain groups deemed high-risk or following an outbreak, vulnerable populations simply won't have access to the vaccines.

This deadly bacterial strain accounts for about 40 percent of meningitis cases in the United States. While rare, there have been some 50 adolescents that have been struck with it each year in recent years. Outbreaks on college campuses have been widely covered in the media given the deaths and amputations that have resulted. But in addition to college students, minority communities are also at great risk. Many low-income black families face key risk factors for bacterial meningitis, including over-crowding, underlying illnesses and tobacco use.

Victims of this disease are all too aware of its severity and devastating implications, and no more families should be put at risk by limiting the recommendation. The United States owes its most vulnerable citizens a long-term, proactive prevention strategy for MenB, rather than a reactive one that waits for tragedy before taking action.

Our organizations have sought to raise awareness about the growing disparity in health for low-income and minority families in the United States, which NIH recently labeled as one of the nation's greatest challenges. We strongly support efforts by ACIP to address the current vaccine gap and the devastating impact it has had on at-risk communities around the country, and we urge its members to grant a permissive designation to the MenB vaccines.

Sincerely,

MINORITY VACCINE DISPARITIES ALLIANCE

Dr. Christopher J. Metzler, CEO, Fitness, Wellness & Health

Georgia Buggs, M.P.H, RN, Former member, U.S., Department of HHS, The National Vaccine Advisory Committee (NVAC)

Cc: Dr. Larry K. Pickering
Executive Secretary
Advisory Committee on Immunization Practices

Influenza

Introduction

Ruth Karron, MD
Chair, Influenza Work Group

Dr. Karron thanked the WG for a tremendous effort, particularly over the last couple of months as they considered a lot of very late-breaking data. Since October 2014, the WG has engaged in continued discussion of the effectiveness of live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for both the 2013-2014 and the 2014-2015 influenza seasons. The WG has also reviewed data pertaining to the recently approved quadrivalent intradermal influenza vaccine. In the interest of time, some of the presentations were truncated. Included during this influenza session were updates on the interim vaccine effectiveness estimates for

the 2014-2015 season, an update on LAIV, and proposed recommendations for the 2015-2016 influenza season. Additional information that was not presented was included in ACIP member's packets, including an update on influenza surveillance and the new Fluzone® intradermal quadrivalent influenza vaccine.

Preliminary 2014-2015 Vaccine Effectiveness Estimates

Brendan Flannery, PhD
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Flannery presented brief updates on influenza vaccine effectiveness (VE) during the current season, and LAIV and IIV among children and adolescents from the US Flu VE network. The updated interim VE estimates were based on 4,913 patients with acute respiratory illness with cough of 7 or fewer days duration enrolled from November 10, 2014 through January 30, 2015. The study used a test-negative case-control design. All patients were tested for influenza and vaccination among influenza positive cases which was contrasted with that of influenza-negative patients. Of the enrollees, 67% were influenza negative and 33% were influenza positive. Of the influenza positive cases, 94% were type A and all subtyped A viruses were H3N2. More than half (n=764) of the H3N2 viruses were genetically characterized at CDC using a novel pyrosequencing assay that determines genetic group, from which antigenic properties can be inferred. Of the H3N2 viruses from US Flu VE network participants, 85% belonged to genetic groups that are generally low reactors with A/Texas/50/2012, while only 15% of H3N2 viruses were genetically more vaccine-like. Among influenza B cases from the Flu VE network, most were B Yamagata lineage, the B lineage included in both the trivalent and quadrivalent 2014-2015 vaccines.

In terms of the early interim VE results from the January 16, 2015 *MMWR* report, adjusted VE against A(H3N2) illness was 18% with a 95% confidence interval from 6% to 29%. None of the age-specific estimates for A(H3N2) were statistically significant and all confidence intervals overlapped. There was evidence of higher VE against influenza B viruses. Adjusted VE against influenza B for patients of all ages was 45%, with a 95% confidence interval from 14% to 65%.

For the 2014-2015 season, numbers of genetically characterized H3N2 viruses from patients enrolled in the US Flu VE network were sufficient to provide interim estimates of VE against predominant genetic groups of H3N2 viruses. Regarding adjusted VE against H3N2 illness for patients aged 6 months and older, 115 H3N2 viruses were genetically characterized as vaccine-like groups 3C.3 or 3C.3b, and 39% of these patients were vaccinated this season compared to 57% of influenza-negative patients. Adjusted VE against vaccine-like H3N2 viruses was 49%, with a confidence interval from 18% to 69%, suggesting that the vaccines perform better against vaccine-like viruses. Of the cases, 624 were due to group 3C.2a and 25 were due to group 3C.3a. This indicates no or low VE against viruses in these antigenically drifted or low-reactor groups, albeit with wide confidence intervals. Of note, the reference virus from the 3C.3a group, the Switzerland virus, was selected for the 2015-2016 influenza vaccines. There is cross-reactivity from the more common viruses from the 3C.2a group.

Regarding interim 2014-2015 VE, subjects aged 2 through 17 years of age were included in the VE analysis for LAIV and IIV among children and adolescents. Children who had received at least 1 dose of current season vaccine at least 14 days prior to illness onset were considered vaccinated for this analysis. Vaccine type was determined from the medical record if available, but parent report of vaccine type was used if no medical record documentation was available. Twelve children with unknown or unreported vaccine type were excluded. Vaccine effectiveness was calculated separately for LAIV and IIV, where patients unvaccinated this season were the referent group.

With respect to the interim adjusted VE estimates against H3N2-positive cases for one or more dose of 2014-2015 influenza vaccine by vaccine type, adjusted VE for one or more dose of any vaccine among 2 through 17 year olds was 7% with confidence intervals overlapping zero, or no effectiveness. Estimates for younger and older children were similar. Analyses for LAIV excluded children who received IIV. Similar proportions of influenza-positive and influenza-negative children received LAIV this season. Adjusted VE ranged from -20% to -24% with confidence intervals overlapping zero, suggesting no effectiveness for LAIV against H3N2 viruses so far this season. Analyses for inactivated vaccine excluded children who received LAIV. Adjusted VE estimates ranged from 15% to 19%, again with confidence limits including no effect and overlapping with confidence intervals for VE estimates for LAIV.

MedImmune is also conducting an observational study of vaccine effectiveness at four sites in the US. Interim 2014-2015 results from this study were prepared by MedImmune and shared with CDC for comparison with results from the US Flu VE Network. The study enrolls patients aged 2 through 17 years presenting with febrile respiratory tract illness of less than 5 days duration. Vaccination status is determined by medical record or registries and subjects vaccinated fewer than 14 days before onset are excluded. Influenza is confirmed by polymerase chain reaction (PCR) and influenza PCR-negative subjects are the comparison group. This analysis included 988 enrollees.

Regarding the number of influenza-positive cases and influenza-negative controls in each group of children and adolescents according to receipt of 2014-2015 influenza vaccine, adjusted VE for any vaccine against any influenza was 27% with 95% confidence intervals from -1% to 47%. Adjusted VE for LAIV was 19% and for IIV was 31%, with confidence intervals that included zero and that overlapped. Adjusted VE against H3N2 was 16% for LAIV and 33% for IIV, which reached statistical significance. There were too few influenza B cases to produce reliable estimates of VE by vaccine type for influenza B in children and adolescents.

In conclusion, low interim VE estimates are consistent with predominance of antigenically drifted H3N2 viruses. H3N2 accounted for 95% of influenza-positive cases at US Flu VE network sites, and more than 80% of genetically characterized H3N2 cases were substantially drifted from the H3N2 vaccine virus. In analyses by a viral genetic group, low or no VE was observed against drifted H3N2 viruses. There was limited circulation of vaccine-like H3N2 and influenza B viruses against which VE was higher. Interim VE estimates from the two studies provide no evidence of better protection for LAIV in the 2014-2015 season with the predominance of drifted H3N2 viruses. For final season VE estimates from the US Flu VE Network, the plan is to complete the genetic characterization of influenza viruses and update VE estimates for LAIV and IIV with verification of vaccine type and prior vaccination, comorbidities, and further analysis of differences in circulating viruses by site.

Dr. Flannery acknowledged the many contributors to the US Flu VE Network at the five participating sites, his CDC colleagues, and the investigators from MedImmune who shared their preliminary data for this presentation.

Update: Live Attenuated Influenza Vaccine (LAIV)

Kathleen Coelingh, PhD
MedImmune

Dr. Coelingh expressed appreciation for the opportunity to present an update on the effectiveness of LAIV. The results presented were from an investigation into the observed low effectiveness of LAIV against the H1N1 strain in 2013-2014 and the actions MedImmune is going to take to ensure the high effectiveness of LAIV in future seasons. MedImmune has discussed its findings in detail with the Influenza WG and, at their request, shared an abbreviated summary during this session.

In summary, moderate to high effectiveness of LAIV was observed for A/H3N2 and B stains in children in 2010-2011, 2011-2012, 2012-2013, and 2013-2014 and for all matched strains in prior studies. However, low effectiveness was observed for A/California H1N1pdm09 strain in US in 2010-2011 (trivalent formulation) and 2013-2014 (quadrivalent formulation). MedImmune has concluded that this issue is specific for A/California H1N1pdm09 LAIV and may be US-specific as LAIV appeared effective in Canada in 2013-2014.

The low effectiveness of A/California LAIV is not explained by manufacturing, poor stability under recommended storage (36-46°F), antigenic mismatch, prior vaccination, pre-existing immunity, or vaccine strain interference. MedImmune's best explanation is that the A/California H1N1pdm09 strain has a unique HA stalk sequence that compromises the stability of its hemagglutinin, making the strain less fit and more vulnerable to heat degradation. HA heat stability appears linked to the effectiveness of that California strain because detailed analysis of the available effectiveness data shows that vaccine shipping when outdoor temperatures are >80°F correlates with reduced effectiveness for A/California LAIV, but not other LAIV strains. To remedy this in the future, MedImmune will replace the A/California LAIV strain with an antigenically matched strain with a more stable HA.

With regard to recent VE data from recent studies in the US and Canada, in terms of VE against H3N2 and B strains in children 2 through 8 years of age in the CDC and MedImmune studies conducted during four recent seasons, LAIV effectiveness was consistently moderate to high against H3N2 and B strains in every season. In terms of effectiveness against the H1N1pdm09 strains, the strain contained in the LAIV was always the A/California strain in all of the studies. LAIV was effective against H1N1 in the 2009-2010 season, but not in the 2010-2011 or 2013-2014 seasons. To summarize, in the US, LAIV was consistently effective against H3N2 and B strains, but had variable effectiveness against the H1N1pdm09 strains.

A different picture was seen in the Canadian studies conducted in 2013-2014 by Dr. Danuta Skowronski, who kindly shared them with MedImmune. LAIV was highly effective in Canada against any influenza strain in individuals under 20 years of age and in children 2 to 8 years of age, which was statistically significant. As noted, 59% of the strains in the study were H1N1. The results were similar when looking at H1N1pdm09 strains only. However, due to fewer cases, these estimates had wide confidence intervals and were not statistically significant.

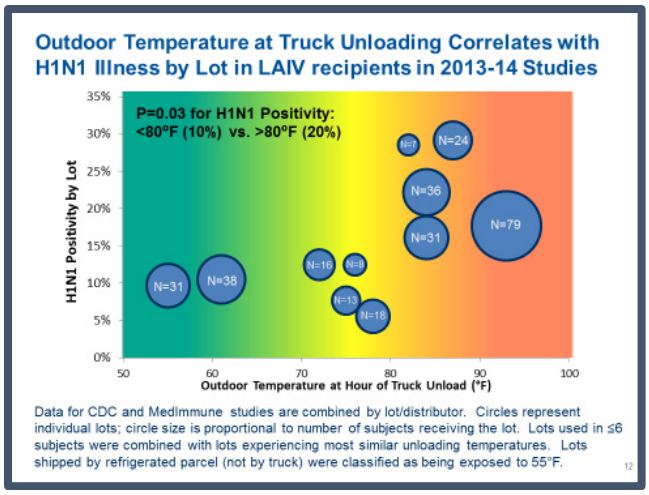
These results are supported by the results of a second Canadian study conducted by Jeffrey Kwong, which he presented during the Canadian Immunization Conference in December 2014. This was a cluster-randomized trial with LAIV and IIV in elementary school children in Ontario in 2013-2014. The incidence of influenza in the children was significantly lower among LAIV recipients compared to IIV recipients, indicating that LAIV did protect against the H1N1pdm09 strain in Canada in the 2013-2014 season. These results support the conclusion that the low effectiveness of LAIV against the H1N1 strain may have been US-specific.

Dr. Coelingh next focused on the hypothesis that is consistent with all of the data she showed and is the most biologically plausible explanation for the low effectiveness of the A/California LAIV strain in two recent influenza seasons in the US. It is believed that the unique A/California HA stalk sequence explains the low LAIV effectiveness against H1N1 in some of the US studies. The A/California wild-type and LAIV have a glutamic acid at Position 47, which is abbreviated E47, in the HA stalk that reduces the HA trimer stability and viral fitness. E47 is not present in seasonal viruses and is not prevalent in the current H1N1pdm09 strains. When the A/California strain is replaced in the upcoming season with a more recent H1N1 strain, that strain will not possess the E47 and will have enhanced HA stability and viral fitness.

MedImmune has shown that the E47 sequence significantly reduces infectivity in ferrets and increases vulnerability to heat degradation with temperatures between 120 □ and 160□F. T way to think about these experiments is that it takes more heat to pull apart a stable HA than it does to pull apart an unstable HA. The A/California LAIV strain with E47 in its stalk is readily differentiated from other seasonal Type A and B LAIV strains, including LAIV strains with known efficacy. Given the A/California strain's increased vulnerability to heat degradation, MedImmune hypothesized that even relatively minor and routine exposures to temperatures above the recommended storage temperature of 36° to 46°F could lead to potency loss, which in turn could lower the real-world effectiveness.

In the normal US distribution process, exposures to temperatures over 70° can occur at multiple points after leaving the MedImmune chain of control. Standard processes permit vaccine exposure to room temperature up to 79° for up to two hours after unloading from refrigerated trucks at distributors and also while packing out shipments to customers. In fact, MedImmune has documented that one of the lots most frequently used in both the MedImmune and CDC studies in 2013-2014 was outside the refrigerated warehouse for 1 hour and 15 minutes at the distributor. MedImmune has recently shown that a 1-log decline in A/California potency occurs after 24 hours at 91°, and is now studying the impact of shorter term exposures on strain potency and infectivity.

In the following graphic, the proportion of MedImmune recipients in the MedImmune and CDC studies who had H1N1 illness is on the vertical axis. On the horizontal axis is the temperature at the distributor sites on the date and time of truck unloading. Each circle on this graph represents a separate lot, and the size of the circle corresponds to the number of subjects receiving the lots in the studies. The actual number of recipients in each lot is given inside the circles:



As illustrated in this graphic, there is a strong and significant correlation between lot effectiveness and the outdoor temperature when the truck was unloaded at the distributor, with a cut point to around 80°. This suggests that the temperature exposure at the distributors during unloading may have adversely affected the performance of the A/California LAIV strain, which is consistent with this strain's increased vulnerability to heat degradation.

A similar association was shown between reduced A/California effectiveness and shipping during hotter weather, before mid-September. LAIV effectiveness against H1N1 was low in 2010-2011 and 2013-2014 in the US when most of the doses were shipped during warmer weeks before mid-September. In contrast, LAIV effectiveness against H1N1 was high in 2009-2010 in the US and 2013-2014 in Canada when doses were shipped in the cooler weeks after mid-September. This analysis is consistent with the hypothesis that the lower fitness of the California strain, its vulnerability to high temperature, and its potential exposure to temperatures above 36° to 46° during distribution reduced the effectiveness of the A/California LAIV strain in two influenza seasons.

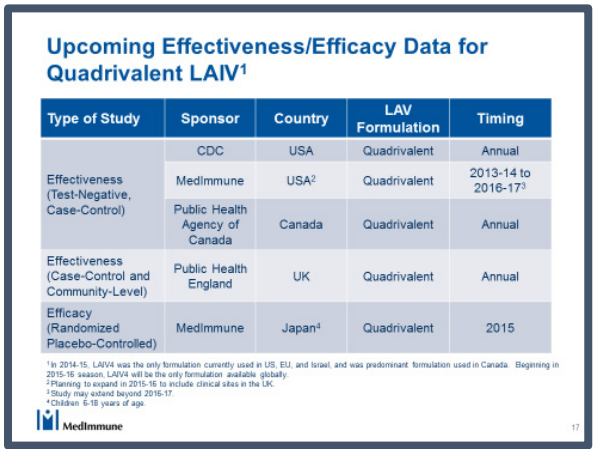
All of this brought MedImmune to its leading hypothesis that the reduced fitness and increased vulnerability of the A/California LAIV to heat degradation could explain the variable effectiveness of LAIV against H1N1 strains. Critical to this hypothesis is that it is known, from previous randomized control trials (RCTs), that LAIV efficacy can be significantly reduced at 1-log lower potency. The key point is that the primary deficiency is the unique characteristics of the A/California HA. The recent H3N2 and B strains, which do not have the unique vulnerability of the California strain, have been effective in all recent seasons. This is consistent with MedImmune's multiple previous RCTs.

Regarding MedImmune's plans for the 2015-2016 and future influenza seasons, the primary remedy is to replace the A/California strain in the 2015-2016 vaccine with an antigenically similar strain with a more stable HA. This strain will not contain the E47 residue, and will have a heat tolerance similar to strains with demonstrated effectiveness.

As mentioned earlier, none of the other LAIV strains have been ineffective, even though all of them were subject to the same distribution process and potential temperature exposures. This highlights that the normal LAIV strains are really quite resilient, and that A/California is the outlier in this respect. Nevertheless, MedImmune is working with its US distributors to eliminate

any significant exposures above the recommended storage temperature of 36 □ to 46□F durir
shipping and handling.

Going forward, additional effectiveness data are expected for quadrivalent LAIV from several studies as shown in the following table:



Upcoming Effectiveness/Efficacy Data for Quadrivalent LAIV[1]

Type of Study	Sponsor	Country	LAV Formulation	Timing
Effectiveness (Test-Negative, Case-Control)	CDC	USA	Quadrivalent	Annual
	MedImmune	USA[2]	Quadrivalent	2013-14 to 2016-17[3]
	Public Health Agency of Canada	Canada	Quadrivalent	Annual
Effectiveness (Case-Control and Community-Level)	Public Health England	UK	Quadrivalent	Annual
Efficacy (Randomized Placebo-Controlled)	MedImmune	Japan[4]	Quadrivalent	2015

[1] In 2014-15, LAIV4 was the only formulation currently used in US, EU, and Israel, and was predominant formulation used in Canada. Beginning in 2015-16 season, LAIV4 will be the only formulation available globally.
[2] Planning to expand in 2015-16 to include clinical sites in the UK.
[3] Study may extend beyond 2016-17.
[4] Children 6-18 years of age.

MedImmune

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In closing, MedImmune is confident that the replacement of the A/California H1N1pdm09 strain with a more robust strain with a more stable HA will result in future effectiveness that is consistent with what has been observed previously in LAIV in RCTs, and with what has been observed for other strains in the recent observational study.

Discussion Points

Dr. Karron requested clarity regarding whether it was correct that during the 2013–2014 season, the US was using quadrivalent vaccine and Canada, where effectiveness of H1N1 was demonstrated, was using trivalent vaccine. However, moving forward, it will be possible to compare quadrivalent to quadrivalent because all countries are now using quadrivalent.

Dr. Coelingh confirmed that this is correct. To make it easy for everybody, starting with the upcoming 2015-2016 season, everything will be quadrivalent globally. There will be data from the 2014-2015 season from other countries using quadrivalent.

Dr. Romero asked what measures are in place to check the stability of future strains, given that this is probably not just an anomaly and happens more frequently than realized.

Dr. Coelingh replied that MedImmune routinely makes its own strains, so they are responsible for ensuring that they choose the absolute best, most optimal strain. While screening for HA stability was not part of MedImmune's routine screening as this phenomenon had not been observed in the past, incoming strains being considered for inclusion in the vaccine are now being screened. She referred members to the backup slides in their handouts that showed that in the laboratory, it is possible to discriminate reliably between strains that have this unique characteristic and do not have heat stability. Though screening is done by sequence, it is more important to screen by actual function—to actually pressure-test it in the laboratory to determine which strains might be more optimal than others in terms of having better HA stability.

Dr. Reingold asked what is known about vaccine handling where it is being administered in terms of how long it might be left out. This is particularly important, given that vaccine is being administered increasingly in pharmacies and a variety of other places.

Dr. Coelingh responded that LAIV is quite stable even at 25° or what would be called "room temperature." In the clinic setting, vaccine is very resilient to being left out for a day. While she did not have specific knowledge about how vaccine is actually handled by providers, she surmised that there is probably an entire range. The goal in MedImmune's stability program is always to monitor vaccine at the recommended storage temperature of 2° to 8°, or refrigeration temperature, or 35° to 46° F. While MedImmune's stability program monitors the recommended storage temperature, they also go outside because it is known that some people like to prepare for a large clinic and they do not thaw one-by-one. MedImmune is very careful to ensure stability under those types of conditions as well.

Dr. Kimberlin (AAP) requested a reminder regarding VE during the 2013-2014 season for 9 through 17 year olds and whether it was statistically significant.

Dr. Coelingh replied that VE trended higher in 9 through 17 year olds than in the 2 through 8 year olds, which was a surprising finding. The finding was not statistically significant.

Dr. Loehr (AAFP) recalled that Dr. Coelingh mentioned that MedImmune's hypothesis is that it is a stalk on the H1N1. Dr. Flannery's presentation on VE for this year showed that the LAIV was not working particularly well this year and that it is an H3N2 season. He requested that Dr. Coelingh comment on that.

Dr. Coelingh indicated that what she presented during this session showed the occurrence in 2013–2014 that was related to the stalk sequence. The situation in the current season is entirely different, wherein the mismatch is significant. For H3N2 strains, Medimmune has shown good protection in the past against some of the mismatched strains. For example, in 1997, there was Sydney/Wuhan and in the comparative Belshe study in 2004-2005, there was also an H3 mismatch and the efficacy was really high in the eighties. Her own thought is that the kind of protection against a drifted strain that will be seen from any vaccine is dependent upon the degree of the match and mismatch. There are limits for every vaccine in terms of what degree of mismatch it is still going to work against. After all, the vaccine is changed every year to try to match it, and there is a reason why that is done.

Proposed Recommendations 2015-2016 Influenza Season

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

Dr. Grohskopf acknowledged the Influenza WG members, as well as the many other people involved in the work that goes into compiling all of this information. For this meeting, there were two proposed recommendations for the next influenza season: 1) a reiteration of the core recommendations, and 2) proposed revisions for the upcoming season. The following language was proposed for a vote during this session:

Reiteration of Core Recommendations

Annual influenza vaccination is recommended for all 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

Use of LAIV for Children 2 Through 8 Years of Age Current Language (2014-2015)

- ❑ When immediately available, LAIV should be used for healthy children aged 2 through 8 years who have no contraindications or precautions.

Proposed revision (2015-2016)

- ❑ For healthy children aged 2 through 8 years who have no contraindications or precautions, either LAIV or IIV is an appropriate option. No preference is expressed for LAIV or IIV for any person aged 2 through 49 years for whom either vaccine is appropriate.

LAIV Recommendations (Proposed)—1

- ❑ All persons aged ≥6 months should receive influenza vaccine annually. Influenza vaccination should not be delayed to procure a specific vaccine preparation if an appropriate one is already available.

- ❑ (Proposed revision) For healthy children aged 2 through 8 years who have no contraindications or precautions, either LAIV or IIV is an appropriate option. No preference is expressed for LAIV or IIV for any person aged 2 through 49 years for whom either vaccine is appropriate. An age-appropriate formulation of vaccine should be used.

LAIV Should Not Be Used for the Following Persons (Proposed)—2

- ❑ Persons aged <2 years or >49 years
- ❑ Children aged 2 through 17 years who are receiving aspirin or aspirin-containing products
- ❑ Persons who have experienced severe allergic reactions to the vaccine or any of its components, or to a previous dose of any influenza vaccine
- ❑ Pregnant women
- ❑ Immunosuppressed persons
- ❑ Persons with a history of egg allergy
- ❑ Children aged 2 through 4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months
- ❑ Persons who have taken influenza antiviral medications within the previous 48 hours

LAIV Recommendations (Proposed)—3

- In addition to the groups for whom LAIV is not recommended above, the "Warnings and Precautions" section of the LAIV package insert indicates that persons of any age with asthma might be at increased risk for wheezing after administration of LAIV, and notes that the safety of LAIV in persons with other underlying medical conditions that might predispose them to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus]) has not been established. These conditions, in addition to asthma in persons aged ≥5 years, should be considered precautions for the use of LAIV.

LAIV Recommendations (Proposed)—4

- Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt, given the theoretical risk for transmission of the live attenuated vaccine virus.

Vote: Recommendations 2015-2016 Influenza Season

Dr. Bocchini made a motion to approve the recommendations for the 2015-2016 influenza season. Dr. Bennett seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

14 Favored: Bennett, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
1 Abstained: Belongia

Dr. Temte pointed out that despite the fact that ACIP made a strong recommendation in June 2014 using the GRADE process with moderate evidence, ACIP can change as evidence changes. He saw this as the real power of both transparency and having a formal process by which ACIP considers all of the evidence and makes changes as appropriate.

Human Papillomavirus (HPV) Vaccines

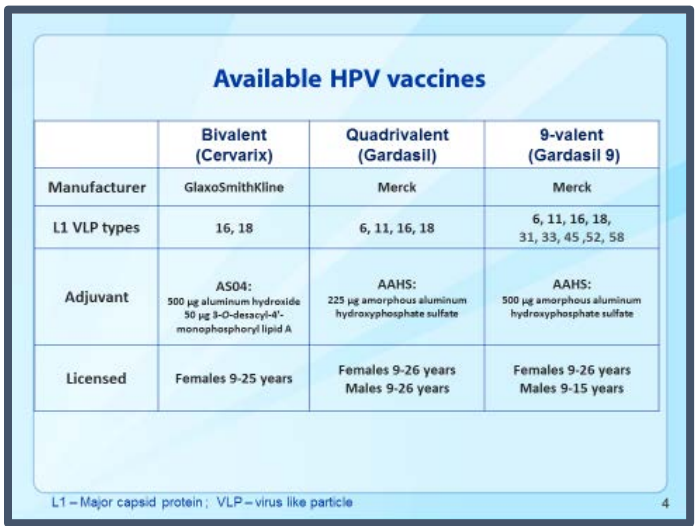
Introduction

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

Dr. Bocchini added his thanks to Dr. Pickering for his many years of leadership and his accomplishments as the ACIP Secretary. Due to the time constraints, the presentations for the HPV session were shortened to provide the members with the essential information that would lead to a vote.

As a reminder, the 9-valent HPV (9vHPV) vaccine was licensed by the FDA on December 10, 2014 for females 9 through 26 years of age and males 9 through 15 years of age. Trials were conducted with a 3-dose schedule. This is an L1 VLP vaccine similar to quadrivalent HPV vaccine, which targets 5 additional high risk oncogenic types (31, 33, 45, 52, and 58). In the US, these types are estimated to cause 14% of HPV-related cancers in women and approximately 5% of HPV-related cancers in males. Males 16 through 26 years of age were not part of the initial Biologics License Application (BLA) submitted to the FDA in 2013. Vaccine safety and seroconversion data from the trial in 16 through 26 year old males were presented to ACIP in October 2014. A supplemental BLA (sBLA) has been submitted to the FDA for this age group.

The current recommendation for HPV vaccination in the US is for routine vaccination at age 11 or 12 years. The vaccine series can be started as early as age 9. Vaccination is recommended through age 26 for females and through age 21 for males who have not previously been vaccinated or who have not completed the series. Vaccination is recommended for immunocompromised persons, including persons who are HIV-infected, and for men who have sex with men (MSM) through age 26. The current recommendation is for a 3-dose schedule given at 0,1-2, and 6 months. The following table shows the three licensed HPV vaccines that are currently available in the US:



Available HPV vaccines

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	9-valent (Gardasil 9)
Manufacturer	GlaxoSmithKline	Merck	Merck
L1 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
Licensed	Females 9-25 years	Females 9-26 years Males 9-26 years	Females 9-26 years Males 9-15 years

L1 – Major capsid protein ; VLP – virus like particle 4

In preparation for the vote during this session, a number of presentations have been provided to ACIP over the past year:

- ❑ Epidemiology and burden of disease due to HPV types
  - February 2014
- ❑ Clinical trial data
  - February 2014, June 2014, October 2014
- ❑ GRADE for 9vHPV
  - October 2014
- ❑ Health economic analysis
  - October 2014

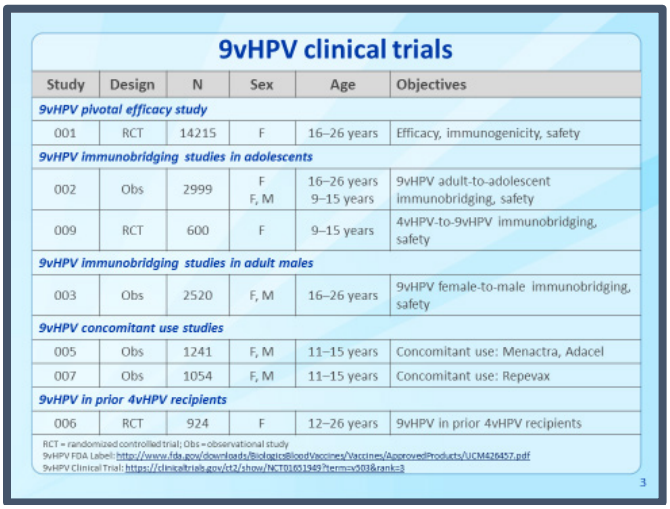
- ❑ Discussion of policy options
  - October 2014

Presentations during this session will focus on 9vHPV clinical trial data, vaccine impact and cost-effectiveness, considerations for recommendations, and a VFC resolution.

Summary of 9vHPV Clinical Trial Data and GRADE

Emiko Petrosky, MD, MPH
EIS Officer
Epidemiology and Statistics Branch
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

During this session, Dr. Petrosky presented a brief summary of 9vHPV clinical trial data, a review of GRADE for 9vHPV, and considerations for a 9vHPV recommendation. Listed in the following table are the 9-valent vaccine studies, which have all been previously presented to the ACIP:



9vHPV clinical trials

Study	Design	N	Sex	Age	Objectives
9vHPV pivotal efficacy study					
001	RCT	14215	F	16–26 years	Efficacy, immunogenicity, safety
9vHPV immunobridging studies in adolescents					
002	Obs	2999	F F, M	16–26 years 9–15 years	9vHPV adult-to-adolescent immunobridging, safety
009	RCT	600	F	9–15 years	4vHPV-to-9vHPV immunobridging, safety
9vHPV immunobridging studies in adult males					
003	Obs	2520	F, M	16–26 years	9vHPV female-to-male immunobridging, safety
9vHPV concomitant use studies					
005	Obs	1241	F, M	11–15 years	Concomitant use: Menactra, Adacel
007	Obs	1054	F, M	11–15 years	Concomitant use: Repevax
9vHPV in prior 4vHPV recipients					
006	RCT	924	F	12–26 years	9vHPV in prior 4vHPV recipients

RCT = randomized controlled trial; Obs = observational study
9vHPV FDA Label: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf
9vHPV Clinical Trial: https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3

As a reminder, protocol 001 is the pivotal efficacy study that compared the 9-valent vaccine to the quadrivalent vaccine in adult females. There were also immunobridging studies and concomitant use studies, and one study assessing the 9-valent vaccine in prior quadrivalent vaccine recipients. Dr. Petrosky presented only the results from Protocol 001, as this was the pivotal efficacy study, and summarized the results and safety findings from the other studies.

In Protocol 001, for the 5 additional types, the 9-valent vaccine demonstrated greater than 96% efficacy in preventing high grade cervical, vulvar, and vaginal disease, and 6-month persistent infection. For outcomes due to the 4 original types, the incidence of disease in either vaccine group was very low, and the 9-valent vaccine demonstrated comparable protection in preventing high grade cervical disease and anogenital warts. Both of the 9-valent and quadrivalent vaccines induced greater than 99% seroconversion for the 4 original types, and the geometric mean titers in the 9-valent vaccine group were non-inferior to the quadrivalent vaccine group.

In summary, the 9-valent vaccine trial demonstrated close to 97% protection against outcomes due to the 5 additional types and similar protection against disease due to the 4 original types. There was very little incidence of disease in either the 9-valent or quadrivalent vaccine groups. The 9-valent vaccine demonstrated non-inferior immunogenicity compared to the quadrivalent vaccine for the 4 original types. Although the data were not shown during this session, the vaccine also demonstrated non-inferior immunogenicity for all 9 HPV vaccine types in adolescent females and males compared to adult females, and in adult males compared to adult females—supporting the bridging of efficacy findings in adult females to these other groups. The concomitant use studies demonstrated no impact on immunogenicity and safety when the 9-valent vaccine was administered concomitantly with meningococcal vaccine (Menactra®), Tdap vaccine (Adacel®), and Tdap-IPV vaccine (Repevax®).

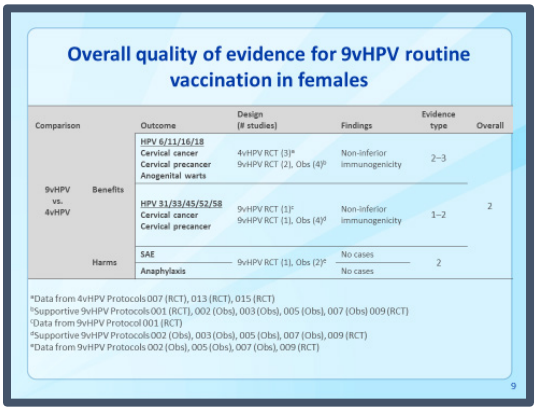
Regarding safety, the 9-valent vaccine was generally well-tolerated in over 15,000 recipients and had an AE profile similar to the quadrivalent vaccine across age, gender, race, and ethnicity, with the exception of a higher frequency of injection-site swelling and erythema in females of all age groups. Males had a lower frequency of adverse events compared to females, which is similar to what was observed in the quadrivalent vaccine program.

As a reminder, GRADE for the 9-valent vaccine was presented to the ACIP in October 2014. The 9-valent vaccine policy questions developed by the workgroup were:

- ❑ Should the 9-valent vaccine be recommended routinely for 11 or 12 year olds?

- ❑ Should the 9-valent vaccine be recommended for females aged 13 through 26 years and males aged 13 through 21 years who have not been previously vaccinated? (also referred to as catch-up vaccination)

The WG gave the overall evidence type for routine vaccination in females a ranking of 2, indicating that the data reflected a moderate level of evidence. The WG also gave the overall evidence for catch-up vaccination in females a ranking of 2. The following are the summary tables for routine and catch-up 9-valent vaccination in females:

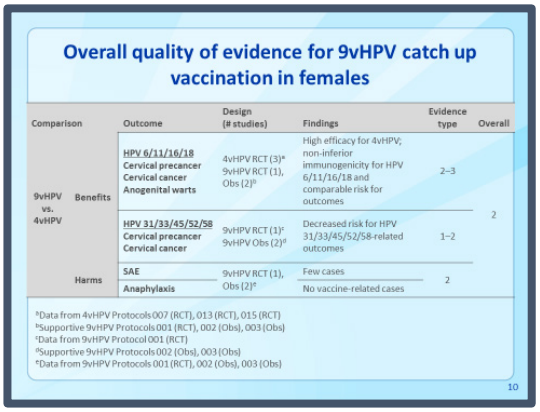


Overall quality of evidence for 9vHPV routine vaccination in females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	HPV 6/11/16/18 Cervical cancer Cervical precancer Anogenital warts	4vHPV RCT (3)[a] 9vHPV RCT (2), Obs (4)[b]	Non-inferior immunogenicity	2–3	2
		HPV 31/33/45/52/58 Cervical cancer Cervical precancer	9vHPV RCT (1)[c] 9vHPV RCT (1), Obs (4)[d]	Non-inferior immunogenicity	1–2	
	Harms	SAE	9vHPV RCT (1), Obs (2)[e]	No cases	2	
		Anaphylaxis		No cases		

[a]Data from 4vHPV Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs) 009 (RCT)
[c]Data from 9vHPV Protocol 001 (RCT)
[d]Supportive 9vHPV Protocols 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)
[e]Data from 9vHPV Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)

9



Overall quality of evidence for 9vHPV catch up vaccination in females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	HPV 6/11/16/18 Cervical precancer Cervical cancer Anogenital warts	4vHPV RCT (3)[a] 9vHPV RCT (1), Obs (2)[b]	High efficacy for 4vHPV; non-inferior immunogenicity for HPV 6/11/16/18 and comparable risk for outcomes	2–3	2
		HPV 31/33/45/52/58 Cervical precancer Cervical cancer	9vHPV RCT (1)[c] 9vHPV Obs (2)[d]	Decreased risk for HPV 31/33/45/52/58-related outcomes	1–2	
	Harms	SAE	9vHPV RCT (1), Obs (2)[e]	Few cases	2	
		Anaphylaxis		No vaccine-related cases		

[a]Data from 4vHPV Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive 9vHPV Protocols 003 (RCT), 002 (Obs), 003 (Obs)
[c]Data from 9vHPV Protocol 001 (RCT)
[d]Supportive 9vHPV Protocols 002 (Obs), 003 (Obs)
[e]Data from 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs)

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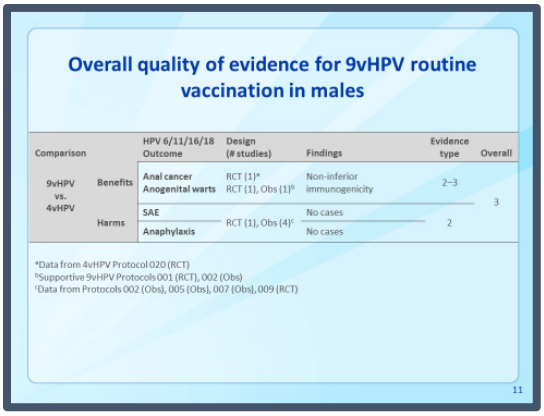
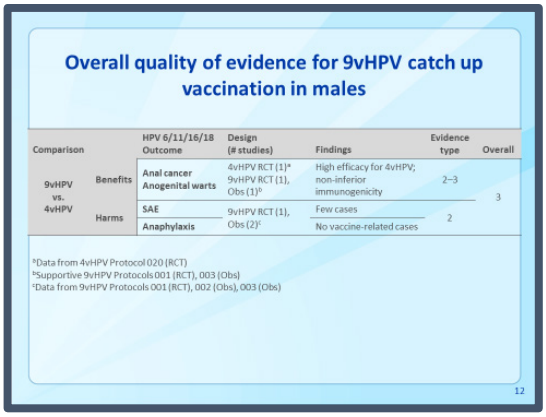
The WG gave the overall evidence type for routine and catch-up vaccination in males a ranking of 3, indicating a low level of evidence. The following are the summary tables for routine and catch-up 9-valent vaccination in males.





With regard to the considerations for formulating 9-valent vaccine recommendation, the data for the 9-valent vaccine are from randomized trials and immunobridging studies, and the WG gave an overall evidence type of 2 for females and 3 for males. The WG felt that the benefits of 9-valent vaccination outweigh the harms and placed a high value on the prevention of outcomes due to the 9 HPV vaccine types. The 9-valent vaccine is expected to be cost-saving compared to the quadrivalent vaccine. In conclusion, the WG proposed a Category A recommendation for the 9-valent vaccine.

Overview of Cost-Effectiveness

Harrell Chesson, PhD
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Chesson presented summaries of three models of 9vHPV in US, as well as the impact and cost-effectiveness of 9vHPV vaccination versus 4vHPV vaccination. The three US models of 9vHPV are as follows:

- US HPV-ADVISE model (Brisson et al.)
  - Based on published, 18-type Canadian model

- Merck Model (Weiss, Pillsbury, Dasbach)
  - Based on published 4vHPV model

- Simplified Model (Chesson et al.)
  - Based on published 4vHPV model

During the October 2014 ACIP meeting, there was a presentation of the US HPV-ADVISE model based on a published 18-HPV type Canadian model, which has been fitted to US data. The Merck Model and the Simplified Model are based on former models that have been expanded to include the additional types of the 9-valent vaccine. All three of the 9vHPV models are dynamic, meaning that herd effects were included in the results. A wide range of health outcomes were also included: Cervical pre-cancers and cancer; other HPV-associated cancers

(e.g., anal, vaginal, vulvar, penile, oropharyngeal); genital warts; and recurrent respiratory papillomatosis (RRP), with the exception that the HPV-ADVISE model does not include RRP.

In the interest of time, Dr. Chesson did not discuss all of these characteristics. In terms of the degree of complexity and comprehensiveness, the HPV-ADVISE Model ranks the highest. The Simplified Model ranks the lowest, and the Merck Model falls in between the two. All of the models assumed high efficacy for the 9vHPV and 4vHPV vaccines, a lifetime of protection, and the same cost assumptions (e.g., 9vHPV was assumed to cost $13 more per dose than the 4vHPV vaccine).

Based on data from Jemal and Saraiya, Dr. Brisson's October 2014 ACIP presentation regarding the potential for additional cancer prevention in the US, the greatest gain from the 9vHPV vaccine is in terms of cervical cancer prevention [Jemal JNCI 2013; Saraiya, JNCI (under review)]. Regarding the estimated effectiveness of the 4vHPV and 9vHPV vaccines in a scenario in which no cross-protection is assumed for vaccine administered to boys and girls, there is a 65% reduction in cervical cancer in the long-term with the 4vHPV vaccine. If both sexes were switched to 9vHPV vaccine, there would be an additional 14 percentage point decrease in cervical cancer. If cross-protection for the 4vHPV vaccine is assumed, the 4vHPV vaccine would have a greater impact and the marginal impact of the 9vHPV vaccine would be reduced. In terms of sex-specific 9vHPV vaccine strategies and the outcomes of cervical intraepithelial neoplasia (CIN) 2/3 and cervical cancer, the majority of the benefit is achieved through switching females to the 9vHPV vaccine.

Regarding the cost-effectiveness results from the HPV-ADVISE model, under the scenario of no cross-protection for 4vHPV vaccine, 9vHPV vaccination for females and 4vHPV vaccine for males compared to a strategy of 4vHPV vaccine for both sexes shows the incremental cost-effectiveness of switching females from the 4vHPV vaccine to the 9vHPV vaccine and indicates that this is cost-saving. This suggests that the additional costs of the 9vHPV vaccine are offset by the averted medical costs due to the additional benefits of the 9vHPV vaccine. The comparison of the strategy of 9vHPV vaccine for both sexes compared to the strategy of 9vHPV vaccine for females and 4vHPV vaccine for males shows that the incremental cost-effectiveness of switching males from 4vHPV to 9vHPV vaccine would be $31,000 per quality adjusted life year (QALY). In a scenario in which both sexes are switched from 4vHPV to 9vHPV vaccine, the cost per QALY would be less than zero or cost-saving. The WG believes that this is the most applicable scenario to the current decision facing ACIP, given that sex-specific vaccine strategies are not likely to be a viable policy alternative in the US.

In terms of the bottom line, all three models suggest that a scenario in which no cross-protection is assumed for the 4vHPV, switching from 4vHPV to 9vHPV likely would be cost-saving. When cross-protection is assumed for the 4vHPV vaccine, the results are similar across all models in that the cost per QALY gained by 9vHPV vaccination would be low. This strategy remains cost-saving in the HPV-ADVISE Model, and is only $8,000 per QALY in the Simplified Model. The results were consistent in a range of sensitivity analyses when 9vHPV vaccine was compared to 4vHPV vaccine for both sexes. The mean cost per QALY gained was less than $0 in most scenarios examined. The two exceptions were when 4vHPV cross-protection was assumed, in which the cost per QALY was $4,600 in the high coverage scenario and $6,600 in the low health care cost scenario. With respect to the uncertainty intervals generated in the analyses, the cost per QALY gained by the 9vHPV vaccine remained less than $10,000 when assuming no cross-protection for the 4vHPV vaccine and less than $25,000 when assuming cross protection for the 4vHPV vaccine.

In conclusion, the current 4vHPV program is expected to reduce HPV-related diseases substantially in the US. Switching to a 9vHPV program is expected to further reduce pre-cancerous lesions and cervical cancer. The HPV-ADVISE model suggested additional reductions of 19% and 14% reduction in CIN2/3 and cervical cancer, respectively, with perhaps more modest reductions in the other HPV-associated cancers. Providing 9vHPV vaccine for girls provides the great majority of benefits of providing 9vHPV vaccination to both sexes. Primary 9vHPV vaccine for both sexes is likely cost-saving compared to 4vHPV vaccine for both sexes. Again, these results are consistent not only across the three models, but also within each model as the assumptions are varied. The cost per QALY gained by 9vHPV did not exceed $25,000 in the sensitivity analyses, and was less than zero in most of the scenarios examined. Analyses of additional 9vHPV for prior 3-dose 4vHPV vaccine recipients is underway; however, preliminary results are highly variable because of the incremental health benefit in terms of the gain per person vaccinated is quite small.

Proposed Recommendations for Use of 9vHPV Vaccine

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

Dr. Markowitz mentioned with regard to Dr. Chesson's last point, that the provision of 9vHPV vaccine to individuals who have already received 4vHPV vaccine is an ongoing consideration for which additional modeling is being done. Given the time constraints due to the short ACIP meeting, it was not possible to address this issue adequately during this session.

For the 9vHPV vaccine recommendations, the plan is to publish an *MMWR* Policy Note. These are shorter than a full ACIP statement. There will be a link to the GRADE tables on the ACIP website. Specific sections Dr. Markowitz highlighted for discussion during this session included the following:

- Routine recommendations
- Administration/intervals
- Interchangeability
- Vaccine pregnancy registry
- Future policy issues

For each, she briefly reviewed some considerations discussed by the WG and then presented the draft wording to be included in the Policy Note.

For routine recommendations and age groups, the WG proposed the same age groups as in the current recommendations. 9vHPV use in males older than age 15 years would be off-label at present and was discussed previously with ACIP. Immunogenicity data in males 16 through 26 years were presented to ACIP in October 2014, included in GRADE, and were submitted to the FDA. Compared with 4vHPV, 9vHPV would provide little additional benefit for males. However, programmatic issues were considered for male recommendations, including the low likelihood that providers would stock two different HPV vaccines and the fact that there eventually will be a transition from 4vHPV to 9vHPV vaccine.

The proposed routine recommendation follows, with new wording underlined:

> "ACIP recommends routine HPV vaccination at age 11 or 12 years. The vaccination series can be started beginning at age 9 years. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated.* Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV. Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV."
>
> *Recommendation for men who have sex with men and for immunocompromised persons (including those with HIV infection) are also included in "Special Populations": "Vaccination is also recommended for men who have sex with men or for immunocompromised persons (including those with HIV infection) aged 22 through 26 years, if not vaccinated previously."
>
> "2vHPV, 4vHPV and 9vHPV all protect against HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States. 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers. 4vHPV and 9vHPV also protect against HPV 6 and 11, types that cause genital warts."

There will be a link to the GRADE tables in the recommendations. The proposed wording does not specifically state a preference for any vaccine, but outlines the differences between the vaccines and what they can protect against.

The current wording in the section on administration addressing intervals is, "The second dose should be administered 1–2 months after the first dose and the third dose 6 months after the first dose." Of note is that studies of 4vHPV and 2vHPV vaccine show that longer intervals between doses do not result in lower antibody titers, and some studies found higher titers after longer intervals. The WG discussed the value of mentioning flexibility in schedules. The pros and cons of this were discussed. Some WG members felt this was important to mention. Others were concerned about possible confusion for vaccination providers. The compromise was to allow flexibility by changing some of the wording. Also of note is that the intervals on the schedule will remain the same at 0, 1-2, and 6 months. The proposed wording for administration follows:

> "2vHPV, 4vHPV and 9vHPV are each administered in a 3-dose schedule. The second dose ~~should be~~ is administered at least 1 to 2 months after the first dose, and the third dose at least 6 months after the first dose. If the vaccine schedule is interrupted, ~~for either HPV4 or HPV2~~, the vaccination series does not need to be restarted."

There have been no studies of the interchangeability of HPV vaccines. However, there are some data on 9vHPV vaccine after three doses of 4vHPV vaccine from a study conducted as part of the 9vHPV vaccine clinical program. The WG discussed programmatic issues related to transition to the 9vHPV vaccine for consideration of wording. Again, the cross-outs and underlines show items to remove and add:

> ~~"ACIP recommends that the HPV vaccination series for females be completed with the same HPV vaccine product, whenever possible. However,~~ If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, for protection against HPV 16 and 18 ~~either~~ any HPV vaccine product may be used to continue or complete the series for females; ~~to provide protection against HPV 16 and HPV 18. Only HPV4 is licensed for use in males~~ 4vHPV or 9vHPV may be used to continue or complete the series for males."

No changes were proposed to the recommendations for vaccination during pregnancy. This section is being updated to reflect new information on vaccine in pregnancy registries. A pregnancy registry has been established for 9vHPV. Also of note is that the bivalent vaccine pregnancy registry was closed earlier this month with concurrence from FDA. Wording will be added about the 9vHPV vaccine and a note will be made that the quadrivalent and bivalent vaccine registries have been closed. The proposed pregnancy recommendation follows:

> "Patients and health care providers can report an exposure to HPV vaccine during pregnancy to Vaccine Adverse Event Reporting System (VAERS). A new registry has been established for 9vHPV. Pregnancy registries for 4vHPV and 2vHPV have been closed with concurrence from FDA. Exposure during pregnancy should be reported to the respective manufacturer."

The last issue for which there was discussion in the WG was Future Policy Issues, a short section proposed at the end of the Policy Note. The discussion centered on what should be included in the policy note specifically related to the ongoing trial of a 2-dose schedule with 9-valent HPV vaccine. Some WG members were concerned about confusion for providers, which could lead to delay in vaccination. However, the WG came to a compromise for the proposed wording for this section which follows:

> "A clinical trial is ongoing to assess alternate dosing schedules of 9vHPV. ACIP will formally review the results as data become available. HPV vaccination should not be delayed pending availability of 9vHPV or of future clinical trial data."

Though not under consideration during this session, the WG is discussing 9vHPV vaccine for persons who previously completed an HPV vaccination series. It is important to note that the manufacturer did not seek an indication for 9vHPV vaccine in persons who previously completed an HPV vaccination series. However, a study was conducted that evaluated 9vHPV vaccine in prior 4vHPV vaccinees (Protocol 006) and the data are included in the label. Due to the time constraints of this session, these data will be presented during the June 2015 ACIP meeting.

Discussion Points

Ms. Pellegrini thanked the WG for the revised language on administration. She thought it would be very helpful in parent education to be able to say that the series does not have to be completed within a very restrictive timeframe for teens. Regarding interchangeability, it seemed like there was an implicit recommendation not to use bivalent vaccine and that 4vHPV or 9vHPV vaccine should be used to complete a series.

Dr. Markowitz replied that for females, the goal was to convey that any vaccine could be used to continue or complete a series. Since only one vaccine was approved and recommended for males last time, there was not a separate statement for males. There are now separate statements.

Ms. Pellegrini indicated that she would communicate further with the WG offline.

Dr. Harriman said the same language indicated to him that if a provider has 4vHPV vaccine and that is what someone began with, it would be preferred.

Dr. Markowitz indicated that they tried to soften the language by removing the first sentence, because it suggested that ACIP recommends that the vaccination series for females should be completed with the same product whenever possible. They wanted to liberalize this, acknowledging what would eventually occur with the transition.

Dr. Harriman pointed out that if there was not a preference to use 4vHPV if that was already started, it seemed like the language used for males could be used.

Dr. Markowitz said the WG tried to make the language the same for males and females. The only difference is the vaccines that are recommended for males and females. She asked whether part of the language should address vaccine providers who do not know the previous vaccines given, do not have 4vHPV vaccine available, or are transitioning to 9vHPV.

Dr. Harrison suggested that it read, “If the vaccine series has already been started, either vaccine can be used to complete the series” rather than “if you do not have 4vHPV.”

Dr. Markowitz emphasized that the sentence was meant to apply to both males and females, and was not meant to read that way just for females.

Dr. Bennett pointed out that a provider could still be giving the bivalent vaccine for females; whereas, for males that would not be indicated.

Dr. Temte requested a reminder about the current percentage of 4vHPV vaccine being used in the US.

Dr. Markowitz replied that probably over 98% of vaccine being used is 4vHPV, so the recommendation is geared toward people who are giving quadrivalent vaccine.

Dr. Temte noted that in essence, the WG was being very inclusive but was also acknowledging reality, which he thought was nicely conveyed.

Dr. Sawyer pointed out that the statement that some studies have demonstrated higher titers with longer intervals will invite providers to ask how much longer. He asked how this would be addressed in the Policy Note.

Dr. Markowitz replied that some clarification could be added about this. There is limited room in the Policy Note, so it does not contain that level of detail. Perhaps some language could be added.

Dr. Sawyer thought that language should be added to put a boundary around the intervals in terms of what the data show. Then providers can decide.

Dr. Lett asked whether any language would appear in the Policy Note about the data pertaining to revaccination even though this information was not presented during this session.

Dr. Markowitz thought they could ask the ACIP members how they felt about this. The ACIP has not been able to discuss this, so they could be silent on that matter or could indicate some place in the Policy Note that this will be discussed in the future.

Dr. Schuchat indicated that this is an issue that ACIP has not been able to deliberate, so there are other ways that CDC can make some factual information available to clinicians pending ACIP deliberating on what they would like to say about the matter.

Dr. Temte stressed that because this will be addressed during the June 2015 meeting, he was not uncomfortable having a four-month window, especially in terms of an off-label use for a new product with which people are just becoming familiar .

Dr. Harrison requested clarity about whether there would be a vote in June or just an informal session about those previously vaccinated with quadrivalent vaccine.

Dr. Markowitz assumed they would be anticipating a vote on the wording if ACIP wanted that included in a Policy Note.

Dr. Harrison wondered whether consideration should be given to an informational session before the next meeting regarding this and the MenB issue. In the past, the members have had some difficulty being presented with a recommendation that addresses information that is not straightforward, or making decision on the spot and trying to take a vote during the same meeting.

Dr. Schuchat indicated that it would not be possible to convene an informational session prior to the June meeting.

Dr. Markowitz added that information could be provided to members as background materials before the June meeting, which would probably offer enough information for the members to be able to address this.

Dr. Middleman (SAHM) asked whether it might be helpful to add a statement about efficacy being known only if the series is completed in order to ensure that completion is the end game.

Dr. Markowitz suggested that one other way that might avoid confusion would be to eliminate the sentence entirely which states that "some studies have found" and just say that "the second dose should be administered at least one to two months later, and the third dose at least six months later." Others agreed that this would be a good idea. Dr. Markowitz pointed out that this does not differ from the current recommendations stating that if the vaccination schedule is interrupted, it does not need to be restarted. This was just to clarify by highlighting the intervals.

Vote: HPV Package

Dr. Rubin made a motion to approve the package of HPV vaccine recommendations, with deletion of the sentence pertaining to antibody levels being higher with longer intervals between doses. Dr. Vazquez seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

14 Favored:	Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Riley, Rubin, Temte, and Vazquez
0 Opposed:	N/A
1 Abstained:	Reingold

Dr. Fryhofer (ACP) acknowledged the time constraints of the current meeting, but emphasized that the question regarding revaccination with 9vHPV of patients who received 4vHPV is raised by many practitioners. ACP looks forward to guidance from ACIP and in getting the word out about what should be done.

Dr. Neuzil (IDSA) thought one of the most common questions following publication of the new recommendations would relate to the timeline of the availability of 9vHPV vaccine. Therefore, it would be helpful if someone could comment on that before the end of the session.

Julie McCafferty (Merck) indicated that Merck has 9vHPV vaccine currently available, as well as a continued supply of Gardasil®. They are also waiting for greater commercial coverage from an insurance perspective for 9vHPV vaccine to be more broadly available in the US.

Vaccines for Children

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

Dr. Santoli explained that the purpose of this presentation was to update the resolution to include use of a 9vHPV vaccine that was recently licensed for use and to clarify the schedule and timing of vaccine intervals. The recommendations proposed follow.

Eligible Groups:

Gender and Age	Bivalent HPV Vaccine	Quadrivalent HPV Vaccine	9-Valent HPV Vaccine
Females, 9 through 18 years	Eligible	Eligible	Eligible
Males, 9 through 18 years	Not eligible	Eligible	Eligible

Recommended Schedule and Interval:

- ACIP recommends routine HPV vaccination at age 11 or 12 years. Eligible females and males as young as 9 years old may be vaccinated. Vaccination is recommended for females and males 13 through 18 years of age who have not been previously vaccinated or who have not completed the full series.

- HPV2, HPV4 and HPV9 are each administered in a 3-dose schedule. The second dose is administered at least 1 to 2 months after the first dose and the third dose at least 6 months after the first dose.

- If vaccination providers do not know, or do not have available the HPV vaccine product previously administered, or are in clinical settings transitioning to HPV9, for protection against HPV 16 and 18, any available HPV vaccine product may be used to continue or complete the series for females; HPV9 or HPV4 may be used to continue or complete the series for males.

- If the vaccine schedule is interrupted, the vaccine series does not need to be restarted. The first and second doses should be separated by an interval of least four weeks. The second and third doses should be separated by an interval of at least 12 weeks, with a minimum interval of 24 weeks between the first and third doses.

Recommended Dosage and Contraindications/Precautions:

- Recommended dosage
  - Refer to product package inserts.

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

Statement Regarding Update Based on Published Documents

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

Discussion Points

Dr. Harriman suggested that it would be valuable to use the exact same language from the Policy Note in the VFC recommendation in terms of weeks and months.

Dr. Markowitz noted that some of the minimal intervals historically have been in weeks, which relates to registries and how they are used. The minimal intervals do mirror each other, which she did not show because these have not changed.

Dr. Temte pointed out that forecasting for systems needs a specific numbers of days, which cannot be done with months because the number of days in a month can vary. As long as it is consistent with other VFC resolutions, he thought they could let it stand.

Dr. Harriman emphasized that it would be nice for the language to be harmonized throughout. Perhaps it needs to go in the other direction—the Policy Note should mirror the VFC.

Dr. Schuchat indicated that the readers of the VFC are not the same. Obviously, there is strengthening of the quality when there is harmonization, so they will take this back.

Vote: VFC for HPV

Dr. Kempe made a motion to approve the VFC recommendations for HPV vaccination. Dr. Romero seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

14 Favored:	Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Riley, Rubin, Temte, and Vazquez
0 Opposed:	N/A
1 Abstained:	Reingold

Yellow Fever Vaccine

Introduction

Joseph A. Bocchini, Jr, MD
ACIP, Workgroup Chair
Japanese Encephalitis (JE) and YF (YF) Vaccines WG
Professor and Chairman, Department of Pediatrics
Louisiana State University Health Sciences Center

Dr. Bocchini indicated that during this session, the Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines WG would present follow-up information related to YF vaccine in anticipation of an ACIP vote. He thanked the members of the WG for their participation, especially Dr. Erin Staples for her work as the CDC lead for this WG.

As a reminder, WHO's Strategic Advisory Group of Experts (SAGE) concluded in April 2013 that a single dose of YF vaccine is sufficient to confer lifelong protection and that booster doses were no longer needed. Additional data, however, were indicated by the WHO for identifying specific risk groups who might benefit from a second dose or a booster dose. Since 1965, International Health Regulations (IHRs) have allowed countries to require a YF vaccine dose within the past 10 years for entry. In June 2014, the WHO's World Health Assembly (WHA) adopted an amendment to the IHR that extends YF vaccine protection to the life of the person vaccinated. That change will take effect in June 2016, so there will no longer be a requirement for countries to maintain that 10-year interval.

Because of those changes, the JE Vaccine WG was re-formed to include YF vaccine in October 2013. The WG met multiple times to discuss the booster doses. ACIP has heard three previous presentations on this topic, including a presentation of GRADE. In June 2014, the WG presented the initial set of recommendations. Subsequently, feedback was received from ACIP and the WG continued to meet to address the issues raised by the members. During the June meeting, there was general support to remove the booster dose requirement, but questions were raised about groups for whom additional doses would be considered. There was discussion regarding the immune response in children, the interval between doses in certain groups, and what constitutes high-risk settings for exposure to YF.

With respect to the issue related to children, the WG worked with AAP's COID. A presentation was made during COID's November 2014 meeting. An updated analysis on immune response for children and whether children's immune response to YF vaccine differed from adults were discussed. The WG also discussed the time interval for additional doses in pregnant women, hematopoietic stem cell transplant recipients, HIV-infected individuals, and high-risk settings for exposure to wild-type YF virus.

During this session, Dr. Staples presented a summary of the GRADE review, considerations for special populations, and proposed recommendations for consideration and a vote by ACIP.

GRADE Summary for YF Booster Doses, Consideration of Booster Doses in Specific Populations, and Proposed Recommendations

J. Erin Staples, MD, PhD
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention

Dr. Staples reminded everyone that the primary policy question the WG studied for GRADE was, "Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?" The intervention would be to remove the current recommendation for booster doses. The current option is to continue the current recommendation for booster doses of YF vaccine.

In terms of the outcome measures the WG assessed for YF vaccine booster doses in the GRADE evaluation, the benefits included vaccine efficacy, seroprotection, vaccine effectiveness, and seropositivity. However, there are no data on vaccine efficacy or seroprotection. The three harms the WG considered to be critical included SAEs, viscerotropic disease, and neurologic disease. Dr. Staples reviewed the main findings for each critical outcome.

Vaccine effectiveness was defined as a lack of vaccine failures. Among over 540 million doses of YF vaccine administered, 18 vaccine failures have been identified. Only 2 (11%) of the 18 vaccine failures occurred more than 10 years from the last dose of vaccine at 20 and 27 years. Regarding seropositivity data at ≥10 years following YF vaccination, there were 13 observational studies with immunogenicity data for 1137 persons. The estimate of seropositivity is 92% (95%CI 85%-96%) using a random effects model. There were three observational studies with immunogenicity data for 164 people ≥20 years post-vaccination. The estimate for seropositivity for this group is 80% (95% CI 74%-86%) random effects model.

Moving to the harms, there were nine observational studies that had data on 333 million doses of the vaccine distributed. There were 1255 subjects who reported SAEs following vaccination. Of the 201 subjects for whom the dose type was known, 7% occurred following a booster dose of YF vaccine. The data were similar for YF vaccine-associated viscerotropic and neurologic disease.

As a reminder, the initial evidence types used for GRADE are as follows (with 1 being the highest level of confidence in the estimated effects on the outcomes and 4 being the lowest):

1	Randomized control trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations or exceptionally strong evidence from observational studies
3	Observational studies or RCTs with notable limitations
4	Clinical experience, observational studies with important limitations, or RCTs with several major limitations

The quality of evidence for each of the five critical outcomes assessed for YF vaccine booster doses was 4, given that only observational studies were included. All of the observational studies had important limitations specifically related to bias and indirectness. The overall quality of evidence was 4.

An additional policy question was created to address persons who were considered by the WG not to belong to healthy travelers and laboratory workers, which was “Should booster doses of YF vaccine every 10 years continue to be recommended for travelers and laboratory workers who had a precaution to vaccination that might have negatively impacted their immune response to their primary dose of YF vaccine (e.g., pregnancy, asymptomatic HIV infection, or age 6 through 8 months)?

Two observational studies provided immunogenicity data for pregnant women following YF vaccination. In the first study, 39% (32/83) of pregnant women vaccinated during their third trimester seroconverted. This is in comparison to 94% (89/95) of the general population who received the vaccine at the same time in Nigeria as part of an outbreak response. In a second study conducted in Brazil, 98% (425/433) of pregnant women vaccinated primarily during their first trimester seroconverted and developed YF virus-specific antibodies. From these two studies, the conclusion can be drawn that the proportion of pregnant women who develop antibody titers following YF vaccination is variable, but data indicate a lack of initial seroconversion for some pregnant women. Given this, the WG suggests revaccinating women who receive their initial dose of YF vaccine while pregnant one time prior to their next at-risk travel.

There are no immunogenicity data for YF vaccine in hematopoietic stem cell (HSCT) recipients. However, the data suggests that most recipients become seronegative to live viral vaccine antigens post-transplantation. The Infectious Disease Society of America (IDSA) guidelines currently recommend re-administering live viral vaccines, specifically measles, mumps, rubella (MMR) and varicella vaccines post-transplant when the recipient is no longer immunosuppressed. Given this, the WG suggested revaccinating HSCT recipients one time prior to their next at-risk travel as long as they are immunocompetent.

Three studies compared the immunogenicity of YF vaccine in HIV-infected persons to uninfected persons. In the first study, 17% (3/18) of HIV-infected children had YF virus-specific antibodies on average 10 months post-vaccination. This is in comparison to 74% (42/57) in age and nutritionally matched children. In the second study, 83% (65/78) of HIV-infected travelers had YF virus-specific antibodies one year post-vaccination in comparison to 97% (64/66) of uninfected controls. In the third study, 77% (54/70) of HIV-infected travelers had YF virus-specific antibodies at 1 to 10 years post-vaccination in comparison to 88% (81/92) of uninfected controls. To summarize, the data indicate that HIV-infected persons are less likely to have sustained YF virus-specific antibody titers following vaccination. Given this, the WG suggested continuing doses of YF vaccine every 10 years for persons who received YF vaccine while infected with HIV.

A specific area of discussion following the June 2014 ACIP meeting was young children. There were 12 studies with immunogenicity data on 4675 children aged 4 months to 10 years in endemic areas at least 1 to 2 months post-vaccination. The estimated seroconversion rate is 93% (88%-96%) using a random effects model. Differences in seroconversion rates were compared among different pediatric age groups. Because the studies often aggregated their results by age, there were two age groups that could be readily explored. The seroconversion rates for children aged ≥9 months compared to children aged <9 months were 92% (95% CI 86%-96%) and 95% (95% CI 91%-98%), respectfully. The seroconversion rates for children aged ≥12 months compared to children aged <12 months were 89% (95% CI 78%-96%) and 93% (95% CI 87%-97%), respectfully. To summarize the pediatric data and note other considerations, the estimated pediatric seroconversion rate was 93% (95% CI 88-96%). The unadjusted seroconversion rate for adults at the same time point is 98% percent for all populations and 97% for endemic populations. As a reminder, the pediatric data were only from endemic areas. Based on available data, there are no clear age differences in seroconversion rates. When these data were presented and discussed with the AAP's COID, they concluded that young children were not immunologically different from adults in their response to YF vaccine.

The WG also considered persons thought to be at higher risk for YF virus exposure based on season, location, activities, and duration of their exposure. The situations in which persons are considered to be at risk for YF virus exposure include West Africa during peak transmission season, where the disease risk is estimated to be approximately 10 times higher than South America; areas with ongoing outbreaks; laboratory settings with regular exposure to wild-type YF virus; and travel for long periods of time (e.g., months to years).

To summarize YF vaccine booster dose data and considerations, very few vaccine failures were noted following YF vaccine. Most (92%) vaccine recipients are seropositive at ≥10 years post-vaccination. SAEs are uncommon following booster doses of YF vaccine. High value is placed on preventing a serious disease with no treatment and poor outcome. The current statement in the ACIP recommendations will no longer be relevant when the IHR is updated in June 2016.

Based on the available data, the WG concluded that a single dose of YF vaccine provides long-lasting protection in most travelers. Therefore, the WG would no longer recommend booster doses of YF vaccine for most travelers. YF vaccine booster doses should be recommended for persons whose immune response to a previous dose might have been compromised. Consideration should be given to YF vaccine booster doses for persons in higher-risk settings for exposure to YF virus. With this in mind, the WG proposed the following recommendations for ACIP's consideration and vote:

For Most Travelers

"A single dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers." (Recommendation category A)

Recommendations for Certain Populations

"Additional doses of yellow fever vaccine are recommended for certain travelers, including:

- Women pregnant when they received their initial dose of yellow fever vaccine should receive one additional dose of yellow fever vaccine prior to their next travel that puts them at risk for yellow fever virus infection.
- Individuals who received a hematopoietic stem cell transplant after receiving a dose of YF vaccine and who are sufficiently immunocompetent to be safely vaccinated should be revaccinated prior to their next travel that puts them at risk for yellow fever virus infection.
- Individuals who were HIV-infected when they received their last dose of yellow fever vaccine should receive a dose every 10 years if they continue to be at risk for yellow fever virus infection.

Persons being considered for additional doses of yellow fever vaccine should be assessed for contraindications or precautions." (Recommendation category A)

Recommendations for High-Risk Settings

"A booster dose may be considered for travelers who received their last dose of YF vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel. This would include travelers who plan to spend a prolonged period of time in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or areas with ongoing outbreaks." (Recommendation category B)

Recommendation for Laboratory Workers

"Laboratory workers who routinely handle wild-type yellow fever virus should have yellow fever virus-specific neutralizing antibody titers measured at least every 10 years to determine if they should receive additional doses of the vaccine. For laboratory workers who are unable to have neutralizing antibody titers measured, yellow fever vaccine should be given every 10 years as long as they remain at risk." (Recommendation category A).

Discussion Points

Dr. Reingold inquired as to whether the rationale for recommending vaccination for all pregnant women was because it is unlikely that women will know the trimester in which they were vaccinated.

Dr. Staples replied that the information was derived from only two studies, which is insufficient to conclude with certainty that the third trimester is the issue. The recommendation is more conservative in saying that if a woman is vaccinated during pregnancy, she should receive another dose if possible.

Dr. Campos-Outcalt asked whether the option of antibody titers had been considered for groups under consideration for revaccination other than laboratory workers, given that there was some seroconversion among all of the groups, and given that AEs can occur with the vaccine.

Dr. Staples indicated that the WG did discuss antibody titers. Currently, the only place that performs antibody titer testing is CDC's Fort Collins facility. This is done with a plaque neutralization test, and the results take about four weeks. The travel practitioners in the WG did not think this would be very practical from a time and logistics perspectives. CDC traditionally does antibody testing for many of the high-risk groups of concern. That is already being done and could be maintained. The number of laboratory workers who handle wild-type YF virus on a regular basis is quite small, and they will be aware of and should be able to obtain neutralization testing.

Ms. Pellegrini recalled that during the fall discussion regarding children, there was some question about whether travelers who were vaccinated as children would, indeed, have lifelong protection. She wondered whether the WG was able to find any data that would help clarify this.

Dr. Staples responded that the WG reviewed the pediatric data, and she showed all of the data available for the initial seroconversion. There is only one study available and the data do not deal primarily with YF. Instead, the study assessed children who received YF vaccine because they were going to receive their chimeric dengue vaccine. The children in this study were assessed based on age cohorts. Given that some of them had been revaccinated, the results are confusing and unhelpful. The AAP agreed that additional data would be beneficial, and this is one of the studies that the WG has highlighted for future work.

Dr. William Atkinson indicated that he was posing a question on behalf of Dr. Stanley Plotkin, who was unable to attend due to the Southern snowstorm. Dr. Plotkin's inquiry pertained to the study recently published in *Vaccine* showing 17% seronegative 5 to 9 years in normal individuals.

Dr. Staples replied that she would have to review the specific data to which Dr. Plotkin was referring, given that several YF vaccine studies had been published in *Vaccine* in the last six months. The WG has also been grappling with what actually constitutes "seroprotection," because different assays and different cutoffs are used to represent what would be detectable antibodies. Therefore, it would be difficult to comment on the results of a particular study without seeing those types of details.

Vote: YF Vaccine Booster Dose

Dr. Rubin made a motion to approve the recommendations for a Yellow Fever vaccine booster dose. Dr. Belongia seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Bocchini, Belongia, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Public Comment

No public comments were offered during this specific session. Given that all public comments presented during this meeting pertained to meningococcal vaccine, they are included within the meningococcal section of this document.

Certification

Upon reviewing the foregoing version of the February 26, 2015 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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