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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 19-20, 2016
Atlanta, Georgia

FINAL - October 14 2016

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329
October 19-20, 2016

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, October 19			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Hepatitis Vaccines**		
	Introduction	Information & Discussion	Dr. José Romero (ACIP, WG Member)
	Updated hepatitis B vaccine recommendations	**Vote**	Dr. Sarah Schillie (CDC/NCHHSTP)
	VFC resolution	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
9:30	**Pertussis Vaccines**		
	Introduction	Information & Discussion	Dr. Laura Riley (ACIP, WG Member)
	Guidance on timing of Tdap administration during pregnancy		Dr. Jennifer Liang (CDC/NCIRD)
	Public comment		
	Updated ACIP statement for pertussis, tetanus and diphtheria vaccines	**Vote**	Dr. Jennifer Liang (CDC/NCIRD)
10:40	***Break***		
11:10	**Human Papillomavirus (HPV) Vaccines**		
	Introduction	Information & Discussion	Dr. Allison Kempe (ACIP, WG Chair)
	Review of evidence for 2-dose vaccination schedule		Dr. Lauri Markowitz (CDC/NCIRD)
	Proposed recommendations for 2-dose HPV vaccination		Dr. Elissa Meites (CDC/NCIRD)
	Public comment		
	Recommendation vote	**Vote**	Dr. Elissa Meites (CDC/NCIRD)
	VFC resolution	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
12:30	***Lunch***		
1:45	**Meningococcal Vaccines**		
	Introduction	Information & Discussion	Dr. David Stephens (ACIP, WG Chair)
	Impact of MenB-FHbp (Trumenba) on meningococcal carriage		Dr. Heidi Soeters (CDC/NCIRD)
	Immunogenicity studies of two MenB vaccines in adults		Dr. Dan Granoff (Children's Hospital Oakland Research Institute)
	MenB-FHbp update		Dr. Laura York (Pfizer)
	Considerations for use of 2- and 3-dose schedules of MenB-FHbp		Ms. Jessica MacNeil (CDC/NCIRD)
	Public comment		
	Recommendation vote	**Vote**	Ms. Jessica MacNeil (CDC/NCIRD)
	VFC resolution	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
3:30	***Break***		
4:00	**Herpes Zoster Vaccines**		
	Introduction	Information & Discussion	Dr. Edward Belongia (ACIP, WG Chair)
	Herpes zoster background		Dr. Kathleen Dooling (CDC/NCIRD)
	Herpes zoster vaccine update: Herpes Zoster Subunit (HZ/su) Vaccine		Dr. Romulo Colindres (GlaxoSmithKline)
5:15	**Yellow Fever Vaccine**		
	Update on vaccine supply	Information	Dr. Mark Gershman (CDC/NCEZID)
5:30	**Public Comment**		
5:45	**Adjourn**		

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Thursday, October 20

8:00	**Update: Zika Virus**	Information	Ms. Stacey Martin (CDC/NCEZID)
8:15	**Agency Updates** CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); CDC and Ex *Officio M* embers
8:30	**Child/adolescent Immunization Schedule** Introduction	Information & Discussion	Dr. José Romero (ACIP, WG Chair)
	Child/adolescent immunization schedule	**Vote**	Dr. Candice Robinson (CDC/NCIRD)
9:30	**Adult Immunization Schedule** Introduction	Information & Discussion	Dr. Laura Riley (ACIP, WG Chair)
	Adult immunization schedule	**Vote**	Dr. David Kim (CDC/NCIRD)
10:15	***Break***		
10:30	**Pneumococcal Vaccine** Introduction Direct and indirect impact of PCV13 use on invasive disease among adults and children in the US Changes in invasive disease burden among adults with and without indications for PCV13 use Outline of research agenda to inform potential policy change in 2018 for PCV13 use among adults	Information & Discussion	Dr. Allison Kempe (ACIP, WG Member) Ms. Tamara Pilishvili (CDC/NCIRD) Dr. Sana Ahmed (CDC/NCIRD) Ms. Tamara Pilishvili (CDC/NCIRD)
11:30	**Influenza** Introduction Epidemiology/surveillance update Afluria quadrivalent influenza vaccine	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair) Ms. Lynette Brammer (CDC/NCIRD) Seqirus - Dr. Gregg Sylvester
12:30	***Lunch***		
1:30	**Respiratory Syncytial Virus (RSV) Vaccine** Introduction Burden of disease in older adults Update on Novavax RSV vaccine development programs	Information & Discussion	Dr. Robert Atmar (ACIP, WG Chair) Dr. Ann Falsey (University of Rochester) Novavax - Dr. Jeffrey Stoddard, Vice President, Medical Affairs
2:45	**Evidence Based Recommendations**	Information & Discussion	Dr. Wendy Carr (CDC/NCIRD)
3:00	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
3:10	**Public Comment**		
3:30	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
Tdap	Tetanus, Diphtheria, Acellular Pertussis Vaccine
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
VFC	Vaccines for Children
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AASLD	American Association for the Study of Liver Diseases
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Events
aHCST	Autologous Hematopoietic Stem Cell Transplant
AIM	Association of Immunization Managers
ALT	Alanine Aminotransferase
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BV	Baculovirus
BBB	Blood-Brain Barrier
BIO	Biotechnology Innovation Organization
BLA	Biologics License Application
CAP	Community-Acquired Pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
CCA	Chimpanzee Coryza Agent
CDC	Centers for Disease Control and Prevention
C-Section	Cesarean Section
CHeRP	Center for Healthcare Research in Pediatrics
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CISA Project	Clinical Immunization Safety Assessment Project
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
cLIA	Competitive Luminex Immunoassay
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
DFO	Designated Federal Official
DGSOM	David Geffen School of Medicine
DIR	Division of Intramural Research
DLA	Defense Logistics Agency
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
ED	Emergency Department
EHDB	Enteric and Hepatic Diseases Branch
eHMP	Enterprise Health Management Platform
EHR	Electronic Health Record

EIA	Enzyme Immunoassay
EMR	Electronic Medical Record
EPS	Enhanced Pertussis Surveillance
EtD	Evidence to Decision
EtR	Evidence to Recommendation
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
Fiocruz	Fundacao Oswaldo Cruz-Fiocruz
FIM	Fimbria
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GID	Global Immunization Division
GMC	Geometric Mean Concentrations
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HBeAg	Hepatitis B e Surface Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Vaccine
HCP	Healthcare Personnel
HCV	Hepatitis C Virus
HepB	Hepatitis B
HepB-BD	HepB Birth Dose
HZ	Herpes Zoster
HZ/su	HZ Subunit Vaccine
HHS	(Department of) Health and Human Services
HI	Hemagglutination Inhibition
Hib	*Haemophilus Influenzae* Type B
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
hMPV	Human Metapneumovirus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Human Complement Serum Bactericidal Antibody
ICD	International Classification of Diseases
ICG	International Coordinating Group
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IHR	International Health Regulations
IHS	Indian Health Service
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IMS	Insurance Management Services
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
ISO	Immunization Safety Office
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
LRTI	Lower Respiratory Tract Illness
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MI	Myocardial Infarction

MIWG	Maternal Immunization Working Group
MMWR	*Morbidity and Mortality Weekly Report*
MoH	Ministry of Health
MSM	Men Who Have Sex With Men
msLRTD	Moderate to Severe Lower Respiratory Tract Disease
mTVC	Modified Total Vaccinated Cohort
NACCHO	National Association of County and City Health Officials
NAIIS	National Adult and Influenza Immunization Summit
NAM	National Academy of Medicine
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NCQA	National Committee for Quality Assurance
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Immunization Conference
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNDSS	National Notifiable Diseases Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OMB	Office of Management and Budget
PAHO	Pan American Health Organization
PCA	Palivizumab-Competing Antibodies
PCR	Polymerase Chain Reaction
PCV13	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PhRMA	Pharmaceutical Research and Manufacturers of America
PHR	Public Health Reports
pIMDs	Potential Immune Mediated Diseases
PPSV23	Pneumococcal Polysaccharide Vaccine 23
PPB	Prime-Prime-Boost
PRN	Pertactin
PT	Pertussis Toxin
QALYs	Quality Adjusted Life Years
QIV	Quadrivalent Influenza Vaccine
qPCR	Real-Time Polymerase Chain Reaction
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RSV-ARD	RSV-Acute Respiratory Disease
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts on Immunization
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate

SES	Socioeconomic Status
SGA	Small for Gestational Age
SME	Subject Matter Experts
Sf9	*Spodoptera frugiperda* Cell Line
SSUAD	Serotype-Specific Urine Antigen Detection
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
TVC	Total Vaccinated Cohort
UAT	Urine Antigen Test
UCLA	University of California at Los Angeles
UCSF	University of California, San Francisco
UK	United Kingdom
UN	United Nations
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VistA	Veterans Information Systems and Technology Architecture
VLP	Virus-Like Particle
VSD	Vaccine Safety Datalink
VSV	Vesicular Stomatitis Virus
VZV	Varicella Zoster Virus
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WNV	West Nile Virus
WRAIR	Walter Reed Army Institute of Research
YF	Yellow Fever
ZIP	Zika in Infants and Pregnancy Study

Call To Order, Welcome, Overview / Announcements, & Introductions

Call To Order / Welcome

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett called the October 2016 Advisory Committee on Immunization Practices (ACIP) meeting to order and welcomed those present.

Overview / Announcements

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn welcomed everyone to the October 2016 ACIP meeting. She indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She then recognized several others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Ms. Natalie Greene and Dr. Jean Clare Smith. She noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes after being made visually accessible to all viewers, including the visually disabled. The live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following this meeting. Members of the media interested in conducting interviews with ACIP members were instructed to contact Ian Branam, located at the press table, for assistance in arranging interviews.

The next ACIP meeting will be convened at the Centers for Disease Control and Prevention (CDC) on Wednesday and Thursday, February 22-23, 2017. Registration for all meeting attendees is required. The registration deadline for Non-US citizens is February 1, 2017 and for US citizens registration closes February 13, 2017. Registration is not required for webcast viewing. As a reminder for non-United States (US) citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms are submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to help with any questions about the process.

Dr. Cohn introduced and welcomed Dr. Allen Craig who recently joined the National Center for Immunization and Respiratory Diseases (NCIRD) as the Deputy Director. Dr. Craig was most recently part of CDC's Global Immunization Division (GID) where he served as the Africa Team Lead in the Polio Eradication Branch since 2013. After completing his medical residency, Dr. Craig joined the Indian Health Service where he served as the Acting Chief Medical Officer from 1993 to 1995. In 1995, he joined the Tennessee Department of Health and later became a State Epidemiologist before returning to CDC in 2007. He was an ACIP member for a short duration of time before he joined CDC.

Dr. Cohn introduced the following guests attending this ACIP meeting:

- Dr. Lu Ming, EPI Division Director, Ministry of Health (MoH)
- Dr. Feng Zijian, Deputy Director of China CDC
- Dr. Wang Huaqing, National Immunization Program Director, China CDC
- Dr. An Zhijie, Vaccine Evaluation Division Director, China CDC
- Dr. Xu Keming, External Affairs and Communication Division Director, Ministry of Health
- Dr. Xia Wei, National Professional Officer, World Health Organization (WHO) China Office
- Dr. Su Qiru, Epidemiologist, China CDC
- Dr. Lance Rodewald, CDC Medical Officer on Secondment to WHO China

Dr. Cohn reported the following *Ex Officio* and Liaison Representative substitutions during this meeting:

Ex Officio Members

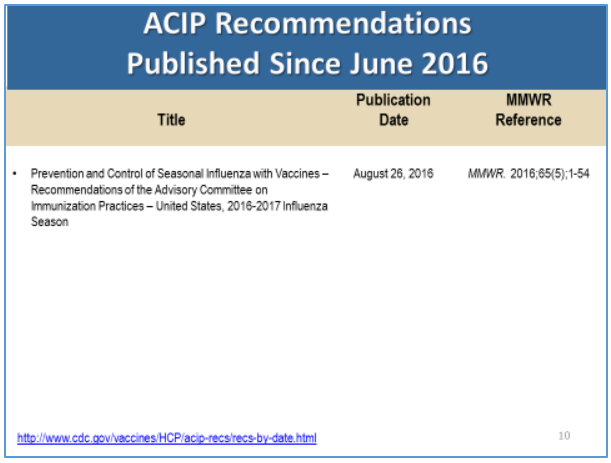
- Ms. Kathleen Pittman is representing the US Department of Veterans Affairs (DVA)
- Dr. Gus Birkhead is representing the National Vaccine Program Office (NVPO)

Liaison Representatives

- Dr. Corey Robertson is representing Pharmaceutical Research and Manufacturers of America (PhRMA)
- Dr. Bonnie Maldonado is representing the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP)
- Dr. Greg Frank is representing Biotechnology Innovation Organization (BIO)
- Dr. Susan Lett is representing the Association of Immunization Managers (AIM)

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

Recommendations and immunization schedules can be downloaded from the ACIP website. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, revised, or retired. During every meeting, an update is provided on the status of ACIP recommendations. There was one ACIP publication since the June 2016 meeting, which is reflected in the following table:



Applications for ACIP membership are due no later than August 2, 2017 for the 4-year term beginning July 1, 2018. 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: www.cdc.gov/vaccines/acip/index.html

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

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

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

Introduction of New Members / Roll Call

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett introduced the following new ACIP members, who will serve a 4-year term from July 2016 through June 2020:

- Robert Atmar, MD is Board Certified in Internal Medicine and Infectious Diseases, has served joint appointments since 2006 as Professor of Medicine and Professor of Molecular Virology and Microbiology at the Baylor College of Medicine. He has served since 2007 as Chief of the Infectious Diseases Service at Ben Taub General Hospital. In addition to his

strong record of basic and clinical research, Dr. Atmar has contributed generously to the administrative, clinical, and educational missions of the college.

- Paul Hunter, MD is Board Certified in Family Medicine. He has served since 2009 as Associate Medical Director of the City of Milwaukee Health Department in Milwaukee, Wisconsin, Wisconsin's largest and most ethnically diverse city, with public health problems related to disparities within the city's population. He also is Associate Professor in the Department of Family Medicine and Community Health, School of Medicine and Public Health, at the University of Wisconsin Madison. Dr. Hunter has completed many projects related to population health, health disparities, and immunization initiatives.

- Grace Lee, MD, MPH is Board Certified in Pediatrics and Pediatric Infectious Diseases. She is the Director of the Center for Healthcare Research in Pediatrics (CHeRP) at Harvard Medical School where she has been conducting analyses for more than a decade on clinical and policy issues in immunization and infectious disease. She also is Associate Professor of Population Medicine and Pediatrics, Department of Population Medicine, Harvard Medical School, Boston, Massachusetts. She served on The Institute of Medicine (IOM) Committee on Review of Priorities in the National Vaccine Plan (NVP), and the IOM Board on Population Health and Public Health Practice. Dr. Lee also has participated extensively in activities related to immunization safety, including the Vaccine Safety Datalink (VSD) project.

- Peter Szilagyi, MD, MPH is Board Certified in Pediatrics. He is Professor and Vice-Chair for Clinical Research in the Department of Pediatrics, David Geffen School of Medicine (DGSOM) at the University of California at Los Angeles (UCLA). He brings extensive experience as both an immunization delivery researcher and a primary care clinician. He has carried out a large body of work over more than 25 years dedicated to immunization practices and policies. He also is an expert on children's health insurance plans.

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

- Robert Atmar receives research support from Takeda Vaccines
- Dr. Belongia has a conflict for respiratory syncytial virus (RSV) due to receiving research support from Novavax
- Dr. Romero has a conflict for RSV for funding non-related to vaccine trials and therapeutics
- The remainder of the ACIP members declared no conflicts

Dr. Bennett then requested that the liaison and *ex officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaisons are included in the appendixes at this end of this document.

Hepatitis Vaccines

Introduction

José Romero, MD, FAAP, FIDSA, FPIDS
ACIP Hepatitis Work Group Member

Dr. Romero reminded everyone that the ACIP Hepatitis Work Group (WG) Terms of Reference are to:

- Update ACIP recommendations for hepatitis B (HepB) vaccine:
  - Current ACIP recommendations
    - ACIP Routine Recommendation for HepB vaccine (Infants/Children). *MMWR* 2005 Dec 23;54(RR-16):1-33.
    - ACIP Routine Recommendation for HepB vaccine (Adult). *MMWR* 2006 Dec 8;55(RR-16):1-33.
    - Use of HepB vaccine for adults with diabetes mellitus: recommendations of the ACIP. *MMWR* 2011 Dec 23;60(50):1709-11.
  - Current CDC Guidelines
    - CDC guidance for evaluating health-care personnel for HepB virus (HBV) protection and for administering postexposure management. *MMWR* 2013 Dec 20;62(RR-10):1-19.
    - Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to HepB-Infected Mothers. *MMWR* 2015 Oct 9;64(39):1118-20.

The objectives for this session were to: 1) vote on removing the permissive language for the HBV birth dose to be administered after hospital discharge; and 2) vote to approve the revised HBV statement.

From February through September 2016, the WG deliberated on HepB vaccine recommendation topics and held five teleconference meetings. The WG and ACIP members reviewed and commented on a draft of the statement prior to the ACIP's October 2016 meeting. The key updates to the HepB vaccine recommendations include the following:

- Removal of permissive language for delaying birth dose
- Provide examples of chronic liver disease (CLD), including recommending HepB vaccine for persons with hepatitis C virus (HCV) infection
- Postvaccination serologic testing for infants whose mother's hepatitis B surface antigen (HBsAg) status remains unknown indefinitely
- Testing HBsAg-positive pregnant women for HBV deoxyribonucleic acid (DNA)
  - Guidance on the use of maternal antiviral therapy during pregnancy

Updated Hepatitis B Vaccine Recommendations

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

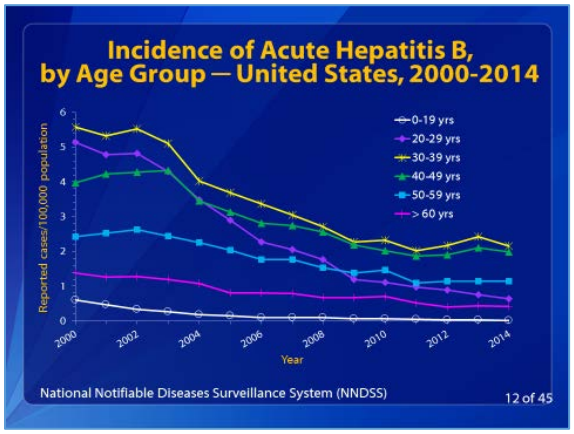
Dr. Schillie discussed Hepatitis B Virus (HBV) background, epidemiology, and prevention; existing HepB recommendations; and the revisions deliberated by the WG. The Hepatitis WG has drafted a revised statement for HepB vaccine recommendations. The revised statement is a single document containing guidance for HepB vaccination of infants, children, adolescents, and adults; testing of pregnant women for hepatitis B surface antigen (HBsAg), and, if positive, HBV DNA; HepB pre-vaccination and post-vaccination serologic testing; and HBV post-exposure prophylaxis for occupational and non-occupational exposures. The revised statement incorporates previously-published recommendations from ACIP and CDC, and is augmented with the American Association for the Study of Liver Diseases (AASLD) recommendation 8A: *The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL* [Terrault et al. Hepatology 2015].

The single revised statement will update the two existing ACIP HepB statements for infants, children and adolescents published in 2005 and for adults published in 2006. The revised statement also will incorporate previous ACIP guidance for HepB vaccination of adults with diabetes published in 2011, ensuring HBV protection among healthcare personnel (HCP) published in 2013, and CDC guidance for shortening the interval for post-vaccination serologic testing for infants born to HBsAg-positive mothers published in 2015.

HBV is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. The virus is highly infectious and remains viable on environmental surfaces for at least 7 days. HBV can be transmitted in the absence of visible blood [Bond et al. Lancet 1981]. Approximately 3,000 cases of acute HBV were reported to CDC in 2014, accounting for an estimated 19,200 new cases when considering under-ascertainment and underreporting. It also is estimated that 952 perinatal HBV infections occur annually. According to analyses from the National Health and Nutrition Examination Survey (NHANES), approximately 850,000 persons in the US have chronic HBV infection. Other studies have yielded higher estimates. Persons with chronic infection serve as the main reservoir for transmission. Imported chronic HBV accounts for approximately 95% of new cases in the US [National Notifiable Diseases Surveillance System (NNDSS); Ko et al. JPIDS 2016; Roberts et al. Hepatology 2016; Mitchell et al. PLoS One 2011].

The rate of reported acute HBV infections has declined by 90.6% since recommendations for HepB vaccine were first issued in 1982. The rate has been fairly stable from 2010-2014, although increases occurred in some populations such as white persons 30 through 39 years of age reporting injection drug use in Kentucky, Tennessee, and West Virginia [NNDSS; Harris et al. *MMWR* 2016].

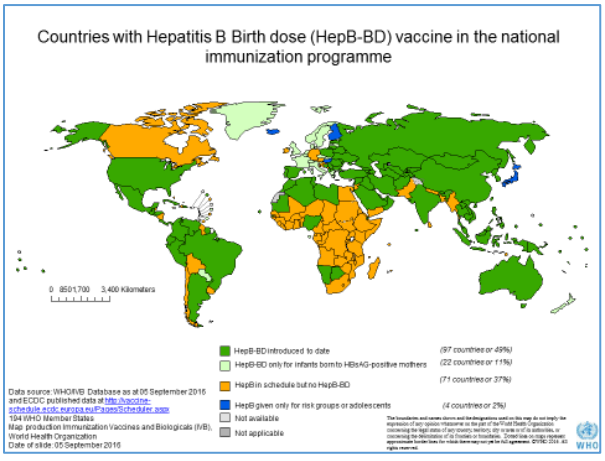
This graphic depicts the decline of acute HBV since 2000. Note that the rate is lowest for persons 19 years of age and younger, which is likely the result of routine vaccination:



Chronic HBV infection develops in approximately 90% of infected infants, 30% of infected children less than 5 years of age, and in less than 5% of infected persons 5 years of age and older. The risk of premature death from cirrhosis or liver cancer with chronic HBV infection is approximately 25% if infected during childhood, and approximately 15% if infected after childhood [Mast et al. *MMWR* 2005; Goldstein et al. Int J Epidemiol 2005].

Perinatal transmission occurs primarily from mucosal exposure to infected blood and other body fluids during delivery. Without post-exposure prophylaxis (PEP), perinatal HBV infection develops in approximately 90% of infants born to mothers who are HBsAg-positive and hepatitis B e antigen (HBeAg)-positive, and 5% to 20% of infants born to mothers who are HBsAg-positive and HBeAg-negative [Nelson et al. JPIDS 2014; Mast et al. MMWR 2005].

The WHO recommends all infants receive their first dose of HepB vaccine as soon as possible after birth, preferably within 24 hours [WHO Hepatitis B Vaccines Position Paper. Weekly Epidemiological Record 2009]. Countries in which a HepB birth dose (HepB-BD) vaccine has been implemented in the national immunization program are depicted in the following map in green, reflecting 49% of countries:



PEP shortly after birth is efficacious in preventing perinatal HBV transmission. HepB vaccine alone is 75% effective in preventing perinatal HBV transmission, and HepB immune globulin (HBIG) alone 71% effective. The combined efficacy is 94% [Beasley et al. Lancet 1983; Lee et al. BMJ 2006].

Serologic evidence of vaccine-induced protection is assessed by the level of antibody to hepatitis B surface antigen (anti-HBs) measured 1 to 2 months after HepB vaccination. Anti-HBs of ≥10mIU/mL corresponds to vaccine-induced protection. Protection exists for 30 years or longer among immunocompetent vaccine responders [Leuridan et al. CID 2011; Bruce et al. JID 2016].

The 3-dose vaccine series results in protective anti-HBs in 98% of healthy infants and 90% to 95% of healthy children and adults aged 40 years and younger. Lower seroprotection is associated with prematurity, advanced age, diabetes, obesity, chronic illness, and smoking [Schillie et al. Vaccine 2012; Mast et al. MMWR 2006].

Anti-HBs after the HepB vaccine series wanes over time. However, even when levels wane to less than <10 mIU/mL, breakthrough HBV infections are uncommon in immunocompetent vaccine responders [Middleman et al. Pediatrics 2014; Leuridan et al. CID 2011].

In terms of existing HepB recommendations, the national strategy to eliminate HBV transmission in the US encompasses the following: 1) screen all pregnant women for HBsAg and provide prophylaxis consisting of HepB vaccine and HBIG within 12 hours of birth for all infants born to HBsAg-positive women; 2) universal vaccination of all infants beginning at birth, before hospital discharge, as a safety net; 3) routine vaccination of previously unvaccinated children and adolescents aged 19 years and less; and 4) vaccination of adults at risk for HBV infection, including those requesting protection from HBV without acknowledgment of a specific risk factor [Mast et al. *MMWR* 2005; Mast et al. *MMWR* 2006].

To identify HBV infected pregnant women, all women should be tested routinely for HBsAg during pregnancy during an early prenatal visit. Testing should occur during every pregnancy, even if the woman has been previously vaccinated or tested. For infants born to HBsAg-positive mothers, ACIP recommends HepB vaccine and HBIG within 12 hours of birth. For those infants with birthweights <2000 grams, the birth dose is not counted as part of the vaccine series. Infants born to mothers with unknown HBsAg weighing ≥2000 grams should receive HepB vaccine within 12 hours of birth. Infants weighing <2000 grams should receive both HepB vaccine and HBIG within 12 hours of birth. For those infants weighing <2000 grams, the birth dose is not counted as part of the vaccine series. Infants weighing ≥2000 grams who are born to HBsAg-negative mothers should receive HepB vaccine before hospital discharge. For infants weighing <2000 grams born to HBsAg-negative mothers, the first dose of HepB vaccine should be delayed until 1 month of age or hospital discharge.

The existing recommendations contain permissive language to delay the birth dose. The language states that, “On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 grams and whose mother is HBsAg-negative.” A physician’s order to withhold the birth dose should be present, along with a copy of the original maternal HBsAg-negative laboratory report. The birth dose should be administered by 2 months of age, and should not be delayed in high risk situations, such as high risk maternal behavior or expected poor compliance with follow-up.

The HepB vaccine series is completed at age 6 months for infants born to HBsAg-positive or unknown mothers, or at age 6 to 18 months for infants born to HBsAg-negative mothers. Post-vaccination serologic testing consisting of testing for anti-HBs and HBsAg is recommended at age 9 to 12 months, or 1 to 2 months after the final dose of the vaccine series if delayed, for infants born to HBsAg-positive mothers. Three-dose revaccination followed by repeat post-vaccination serologic testing is recommended for infants with anti-HBs <10mIU/mL. HepB vaccination is recommended for all children and adolescents aged <19 years. Those not previously vaccinated should be vaccinated routinely at any age using an appropriate dose and schedule.

Adults recommended for HepB vaccination include those at high risk for infection by sexual exposure, such as sex partners of HBsAg-positive persons and men who have sex with men (MSM); those at risk for infection by percutaneous or mucosal exposure to blood, such as injection-drug users, health-care and public safety workers, persons with end-stage renal disease, and adults with diabetes; international travelers to regions with high or intermediate HBV endemicity, defined as HBsAg-positive prevalence ≥8% and ≥2%, respectively; persons with chronic liver disease; persons with HIV infection; and all persons seeking protection from HBV infection even without acknowledgement of a specific risk factor. All adults in certain settings also are recommended for HepB vaccination, including the following:

- ❑ Sexually transmitted disease treatment facilities
- ❑ HIV testing and treatment facilities
- ❑ Facilities providing drug-abuse treatment and prevention services
- ❑ Health-care settings targeting services to injection-drug users
- ❑ Correctional facilities
- ❑ Health-care settings targeting services to men who have sex with men
- ❑ Chronic-hemodialysis facilities and end-stage renal disease programs
- ❑ Institutions and nonresidential day care facilities for developmentally disabled persons

Vaccination of persons who are immune to HBV infection due to past infection or vaccination does not increase risk for adverse events (AEs). However, pre-vaccination serologic testing might reduce costs by avoiding vaccination of persons who already are immune. Pre-vaccination serologic testing is recommended for household, needle-sharing, or sex contacts of HBsAg-positive persons; persons born in regions of high HBV endemicity; and HIV-positive persons. The existing recommendations also state that pre-vaccination serologic testing might be cost-effective for injection drug users, incarcerated persons, MSM, and persons born in regions of intermediate HBV endemicity. The first vaccine dose typically should be administered immediately after the collection of blood for serologic testing.

Post-vaccination serologic testing for immunity is not recommended after routine vaccination of infants, children, adolescents, and adults. Post-vaccination serologic testing is recommended for infants born to HBsAg-positive mothers, HCP, chronic hemodialysis patients, HIV-infected and other immunocompromised persons, and sex partners of HBsAg-positive persons. Testing is recommended 1 to 2 months after the final dose of the vaccine series or at age 9 to 12 months for infants of HBsAg-positive mothers. Revaccination is recommended if anti-HBs is <10 mIU/mL.

In terms of post-exposure prophylaxis following occupational exposures, unvaccinated HCP exposed to blood or body fluids from a source patient positive for HBsAg should receive 1 dose of HBIG and initiate vaccination. Those exposed to a source patient negative for HBsAg should initiate vaccination. A previously vaccinated HCP who is a known vaccine responder requires

no PEP regardless of source patient status. Previously vaccinated HCP who are known non-responders after 3 vaccine doses and exposed to a positive source patient should receive 1 dose of HBIG and initiate revaccination. Those exposed to a source patient negative for HBsAg should initiate revaccination. Previously vaccinated HCP who are known non-responders after 6 vaccine doses and exposed to a positive source patient should receive 2 doses of HBIG separated by 1 month. Those exposed to a source patient negative for HBsAg require no prophylaxis.

With regard to post-exposure recommendations following non-occupational exposures, an unvaccinated person exposed to a HBsAg-positive source should receive a HepB vaccine series and HBIG. A previously vaccinated person exposed to a HBsAg-positive source should receive a dose of HepB vaccine. An unvaccinated person exposed to a source with an unknown HBsAg status should receive the HepB vaccine series, while a vaccinated person exposed to a source with unknown status requires no prophylaxis.

Dr. Schillie then discussed the revisions to the recommendations deliberated upon by the WG. The WG deliberated upon and supports guidance for testing HBsAg-positive pregnant women for HBV DNA. DNA testing identifies infants at greatest risk for perinatal HBV infection and prioritizes women for referral for antiviral therapy in accordance with AASLD's suggestion for maternal antiviral therapy to reduce the risk of perinatal transmission when maternal HBV DNA is >200,000 IU/mL.

The WG also deliberated upon and supports guidance for post-vaccination serologic testing for infants whose mother's HBsAg status remains unknown indefinitely, such as infants surrendered anonymously shortly after birth. Note that all 50 states have some form of safe-haven law to reduce the risk of infant abandonment, and that medical data on these infants is lacking.

The WG also deliberated on removal of the permissive language for birth dose administration after hospital discharge. The following table reflects the existing and proposed language. Note the proposed revised language on the right, which reflects removal of the permissive paragraph from the existing language regarding delaying birth dose administration:

Existing Language	**Revised Language (proposed)**
For all medically stable infants weighing ≥2,000 grams at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered before hospital discharge. Only single-antigen HepB vaccine should be used for the birth dose. On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 grams and whose mother is HBsAg-negative.	For all medically stable infants weighing ≥2,000 grams at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered before hospital discharge. Only single-antigen HepB vaccine should be used for the birth dose.

Included in the WG's deliberations was a study demonstrating an increase in HBV infections for infants born to HBsAg-positive mothers with increasing age at first dose of vaccination. The adjusted odds ratio for an increase in infection was 4.3 (95% CI, 2.2-8.4) [Marion et al. Am J Epidemiol 1994]. Birth dose coverage in the US is currently 72.4% and has remained relatively stable in recent years. Note that current coverage is below the Healthy People 2020 target of 85%.

The WG also discussed the safety net provided by birth dose prior to hospital discharge, including when infants born to infected mothers are not identified due to errors in maternal HBsAg testing or transcription or reporting of test results. Note that the WG did not reach consensus on removal of the permissive language.

The WG deliberated upon and supports providing examples of chronic liver disease (CLD) in the statement. The existing guidance recommends HepB vaccination for persons with CLD. The WG supports providing examples of CLD such as cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and liver function tests >2 times the upper limit of normal. Three-dose HepB vaccine coverage among adults aged ≥19 years with chronic liver conditions is slightly less than 30% [Williams et al. *MMWR* 2016].

CDC supports explicit language for recommending HepB vaccination for persons with HCV infection. The increasing incidence of HBV and HCV infections have been noted in young, non-urban adults who inject drugs in Kentucky, Tennessee, and West Virginia. Concurrent HepB virus infection may increase the risk for liver disease progression among HCV-infected persons [Zibbell et al. *MMWR* 2015; Harris et al. *MMWR* 2016; Bell et al. Acta Gastroenterol Belg 2000.; Oh et al. BMC Cancer 2012].

For discussion and vote, Dr. Schillie posed the following questions:

- ❑ Does ACIP approve removing the permissive language for the HepB vaccine birth dose to be administered after hospital discharge?

- ❑ Does ACIP approve the revised HepB statement?

Discussion Points

Dr. Belongia requested insight as to why the original language was included regarding the permissive birth dose prior to discharge, and an example of what would be a circumstance that would have been considered reasonable not to vaccinate prior to hospital discharge.

Dr. Schillie replied that she had no insight as to why the language originally was placed in the recommendation. That was from the 2005 recommendations. Some of the WG deliberations in favor of not removing the permissive language was for mothers who feel that they know that they are negative for HBV, and that perhaps those mothers should not be required to have their infant vaccinated before hospital discharge. Perhaps they should have the choice to have the infant vaccinated later in life.

Dr. Hunter asked whether there were any data that would suggest that removing the birth dose permissive recommendation would change the overall completion rate of the 3-dose infant series and, if not, whether there were any plans to study this question.

Dr. Schillie responded that there are studies which are 10 to 15 years old that showed an association with receipt of the birth dose and timely completion of the vaccine series.

Speaking on behalf of some mothers she has spoken to about the birth dose, Dr. Even (ACHA) reported that these mothers have concern about vaccinating a child at birth in terms of their immune system not being ready for vaccine, and that the infant's immune system should be more mature before beginning vaccination.

While they may have concerns, Dr. Moore said she did not believe there was any scientific evidence to support that. She reminded everyone that having a clear recommendation does not mandate anything. People make their own choices all of the time about whether to refuse something that is recommended. It did not seem to her that removal of the permissive language would result in a compulsion of parents to immunize who are resistant to that any more than any other recommendation does. However, in her experience, clinicians may choose to have a patient get their vaccine at the doctor's office at the 2-week visit. That may be for convenience for the clinicians, and so that the clinician is paid for that visit instead of it being something that the hospital takes care of. Other issues may come into play in terms of pediatric practice. A clear recommendation without the permissive language may make it easier to make vaccination routine in hospitals prior to discharge.

Regarding the recommendation for infants <2000 grams born to seronegative mothers, Dr. Walter pointed out that the language stated "delay dose of HepB vaccine until age 1 month or hospital discharge." He asked what the intent was, especially for a child who is approximately 2000 grams or just under that who may be discharged at 2 to 3 weeks of age.

Dr. Schillie replied that among term infants, vaccine response is normal when it is administered early in life. Vaccine response among low birthweight infants improves quite a bit when vaccination is delayed until about 1 month of life. When low birthweight babies are immunized in the first couple of days of life, 60% to 65% might achieve seroprotective antibody levels. When vaccination in those infants is delayed starting at 1 month of life, 90% or more achieve seroprotective levels.

Dr. Walter asked whether they should be vaccinated at 1 month or at hospital discharge, which may be before 1 month. The language is somewhat confusing.

Dr. Schillie clarified that the language shown on the slide was taken verbatim from the existing recommendation, which do not specify a preference. It states either "1 month of life or hospital discharge." The WG could certainly entertain a preference.

Regarding testing post-vaccination for infants born to HBsAg-positive mothers, Dr. Kimberlain (AAP) noted that one of Dr. Schillie's slides illustrated that the recommendation is 9 to 12 months or 1 to 2 months of the final dose of the vaccine series. Pointing out that it used to be 9 to 18 months, he asked whether Dr. Schillie could comment on why it changed from 18 to 12 months.

Dr. Schillie indicated that in 2015, CDC issued a recommendation to shorten that interval from 9 to 18 months to 9 to 12 months for two reasons. One, there were new data that showed the decline in anti-HBs over time when post-vaccination testing was done at increasing intervals following vaccination. Infants were falsely identified as non-responders and were being revaccinated unnecessarily due to the decline in anti-HBs over time. Second, COMVAX®

production was discontinued. With COMVAX®, the last dose was given at age 15 months. So, one reason the interval was extended out to 18 months was to accommodate intervals completing vaccination with COMVAX®.

Dr. Kimberlain (AAP) pointed out that the 2015 STI guidelines do not specifically state this, but points to the 2005 *Morbidity and Mortality Weekly Report* (*MMWR*), not the 2015 document. If there is a living document with the STI guidelines, he suggested that it might be worth adding that in.

Dr. Messonnier asked whether COID has language pertaining to this in the Red Book, and if there is an opinion and / or agreement about the permissive language.

Dr. Maldonado (AAP) replied that COID discussed this on a conference call the previous week, and was in agreement with the recommendation. Discussion regarding the 2005 recommendations pertained to the difficulty among practitioners and hospitals in developing a birth dose within their systems and capturing every child. The idea was to allow some permissiveness. Since that point, most hospitals and practices have been able to make that switch.

Dr. Kimberlain (AAP) added that the Red Book currently contains permissive language, but they are working actively on the 2018 edition and would be delighted to incorporate this in should ACIP vote in favor of removing the permissive language.

Dr. Thompson (NVAC) asked what is known about the fraction of births that occur outside of what would be captured as hospitals in terms of whether a small part of the population is being missed who might be relevant to uptake, and what is being done to improve uptake.

Dr. Schillie replied that while the WG focused primarily on infants born in the hospital, certainly they are concerned about those born outside the hospital as well. However, she said she did not have data on the proportion of infants born outside of hospitals and their HepB birth dose coverage rates. In terms of what is being done to improve rates of birth dose before discharge, educational efforts are underway to try to educate mothers and providers about the importance of the birth dose as a safety net. Birth dose coverage before hospital discharge also is a quality metric for hospitals that choose to use that measure.

Dr. Schaffner (NFID) said he was supportive of removing the permissive language regarding the HepB birth dose. He requested a brief discussion of adult immunization, because he was disappointed in the WG's report because he thought an opportunity had been missed. Part of the title of the document is "A Strategy to Interrupt Transmission." As was demonstrated, there have been flat rats in the adult population for some time. Indeed, rates are increasing in some parts of the country in some age groups. This is an opportunity to move forward in the strategy to interrupt transmission in a more innovative and assertive way. After the 19th birthday, in a way that differs from all other vaccine recommendations, an adult has to acquire risk before being eligible for immunization. However, individuals do not have to wait to be exposed to measles before receiving measles vaccine. Also, it is known that this risk-based strategy is honored most often in the breech rather than the observance. Therefore, it is a strategy that is stuck or even failed. It has been about 15 years since universal immunization has been recommended of everyone up to the 19th birthday. He has never understood why, once someone turns 19 years of age plus one day, they are no longer eligible. He suggested taking that universal recommendation with that cohort and moving it forward with them. This is an opportunity to move universal immunization up to age 35, 40, 50. That would be innovative and

strategic rather than lethargic. He urged the colleagues to re-deliberate and do something innovative regarding this continuing concern about HepB acutely occurring in adult age groups.

Dr. Schillie thought Dr. Schaffner raised an excellent point. Certainly, there are areas in which HBV is increasing among young adult populations such that immunization of adults 30 through 39 years of age would help to address the increasing HBV prevalence among those populations.

Dr. Wexler (Immunization Action Coalition) pointed out that the permissive language was developed as restrictive language. She has been attending ACIP meetings since before 2000, and she has been following the HepB birth dose issue since 1991. She recalled that before the thimerosal controversy, there were very high rates of HepB vaccination at birth. The rate was approaching 80%, decreased to zero with thimerosal, and then increased only to about 40% after the 1998 thimerosal fiasco. In 2002, ACIP recommended the birth dose for every baby. Rates began to increase again, but not very quickly. The purpose of the language in 2005 being referred to as "permissive" that actually was "restrictive" was to say, "Do not give the birth dose later. Give it at birth, except in rare circumstances and on a case-by-case basis." As a result of that, the birth dose rate has been increasing gradually and is approximately 72%. That is within 3 days of birth, not before hospital discharge. Dr. Wexler emphasized that she wanted to set the stage for how important it is to give this birth dose in the hospital. She said she had just received an email from a Perinatal HepB Coordinator who has been to every hospital in her state, and is fighting to get the birth dose implemented. Private doctors are still delaying the dose and giving it in their practices at the 1-week visit. She is hungry for help about what to do. In light of the former restrictive language and perhaps moving toward the language of everybody giving the vaccine, programmatically it would be very helpful to Perinatal HepB Coordinators for ACIP to explain what it means to administer the dose before hospital discharge—either before 12 hours of age or before 24 hours of age. That would help Perinatal HepB Coordinators and everyone else be very clear in what they are trying to implement rather than stating "before hospital discharge."

Dr. Decker (Sanofi Pasteur) added that another factor which played into this that Dr. Wexler did not mention, which was an economic / political issue. At the time, there was the original recommendation and hospitals adopted it widely. When the thimerosal issue arose, hospitals leapt at the opportunity to keep this out of their programs because it was an unfunded mandate. When it occurs during the birth process, it was capitated for the mother but nobody was paying for the injection to the baby. Another reason there was the language in 2005 was because it was part of political compromise. This is 11 years later and in order to make progress, it is necessary to move to mandatory language. He agreed that rather than stating "before discharge" they should state "within the first 24 hours of life." He emphasized that they must be very specific and concrete if they wanted to get it done.

Dr. Fryhofer (AMA / ACP) noted that on page 5 of the handout in terms of adults recommended for HepB vaccine, an example was not given for the bullet "persons at risk for infection by sexual exposure" through having more than one sex partner within the last six months. This relates to what Dr. Schaffner was saying. Even patients in their 50s, 60s, and up may experience changes in their situations and that may apply to them. She applauded the WG for highlighting fatty liver as an indication as an example of CLD, because an increasing number of patients with fatty liver are being seen in practices because of the obesity crisis.

Dr. Hunter asked why the cutoff for the upper limit of normal of liver function tests as a risk was twice the upper limit of normal versus three times the upper limit of normal, which is what most clinicians use as a decision factor in clinical situations.

Dr. Schillie replied that the number was chosen fairly arbitrarily. There are some clinical guidelines that use greater than two times the upper limit of normal in some of the decision factors. Unrelatedly, an algorithm for prenatal testing was issued that received some comments that the alanine aminotransferase (ALT) cutoff was perhaps too low. It is important to capture a level that is not too high or too low, and the WG is open for feedback on that level.

Dr. Hunter added that for primary care physicians, he was arguing in general to try to make the recommendations as uniform as possible for correct implementation.

Dr. O'Leary (PIDS) noted that the 2005 guidelines have fairly extensive guidance for hospitals on policies to increase the uptake of the birth dose, screening, et cetera, and included recommending the use of standing orders. He wondered whether that would be included in the new guidelines. Dr. Schillie replied that it would.

Regarding Dr. Schaffner's comments, Dr. Ward (Director, Division of Viral Hepatitis) noted that the major gap in HepB coverage is among adults. That is where most cases are being observed in states such as Tennessee, which is heavily related to the opioid abuse crisis and the injection of those medications or heroin. There has been an elimination goal, although it is one that has been proposed without a numerical target, since the infant vaccine was recommended by ACIP in about 1992. This elimination target has taken on some renewed interest. The IOM, now known as the National Academy of Medicine (NAM), has convened a panel to set elimination targets for HepB and HepC elimination and is framing it as the elimination of HepB transmission and disease as a public health threat in the US. This is proposed to be coming out from that panel in Spring 2017. A more ambitious HepB vaccination policy for the most vulnerable parts of the population, in this case young, middle-aged, and even older adults, would be very appropriate. He suggested that the WG could reconvene to assess stronger recommendations for adults, while still hopefully having ACIP agree with what already was before them during this session.

Regarding measurement, Dr. Lee pointed out that it would be helpful to understand whether the rate of 72% for the birth dose excludes premature populations. That is, if 10% actually are premature, vaccination rates may be higher. It also might give them a better sense of where to target improvement efforts. From a systems level perspective, it seemed like they were trying to bridge the gaps and that minimizing permissive use would be helpful in that instance. It also might be helpful to assess the impact of alternative vaccination strategies, particularly in terms of the adult disease burden. She asked whether the WG would consider that.

Dr. Moore completely supported the idea of having the WG consider an age-based recommendation for adults. As the Program Manager for Tennessee, she reported that they are one of the three states that are struggling mightily with this. Risk-based strategies have not helped them. Reminding everyone that the proposed language specified hospitals and excluded children born outside of the hospital setting, she emphasized that the concern was not about the setting. It was about protecting the infant at birth. She asked whether there would be opposition to proposing, especially from a programmatic standpoint, the clear-cut communication message that the first dose should be administered within 24 hours of life rather than before hospital discharge. That would eliminate the setting of the birth from consideration in the protection of the newborn.

Dr. Hunter indicated that the American Congress of Obstetricians and Gynecologists (ACOG) website reported that there are about 35,000 births per year outside of the hospital setting, which is about 0.9% of births.

Dr. Belongia supported the suggested amendment of the inclusion of "within 24 hours of life" and elimination of setting, given that it does not matter whether the birth occurs in the hospital.

Dr. Messonnier pointed out that the language "within 24 hours of birth" is consistent with the WHO. In order to facilitate the upcoming Vaccines for Children (VFC) vote, she requested that the specific language preferred be utilized in terms of "within 24 hours of birth" or "before hospital discharge."

Dr. Lee asked whether there were any implementation issues of concern with regard to the proposed change to "within 24 hours of birth" versus "before hospital discharge."

Dr. O'Leary (PIDS) said he would argue that the suggested change would make things clearer for hospitals and clinicians, because there is confusion regarding whether they should wait for 72 hours if it is a Cesarean section (C-section) for example.

Dr. Riley added that from a programmatic standpoint, it would just mean changing standing orders. She did not think this would be problematic. However, she was not wildly optimistic that people who deliver outside of the hospital suddenly will be the ones who get vaccinated. The very people who deliver outside of the hospital generally are not people who are tremendously excited about organized medicine, and the need to get vaccinated.

Dr. Stephens emphasized the need to keep in mind Dr. Schaffner's point about universal vaccination.

Dr. Kempe reiterated the importance of the WG returning to the adult recommendations at a later time.

Dr. Szilagyi agreed, stressing that risk-based strategies typically are not effective.

In terms of implementation considerations, Patsy Stinchfield (NAPNAP) underscored that a lot of education will be needed for those who do not meet the 24-hour stipulation. For example, a birth center might ask, "We're at hour 25. What do we do?"

Christina Hildebrand (A Voice for Choice Advocacy) expressed concern about the 24 hours, pointing out that the US has the highest rate of infant mortality within the first day of birth and also is one of the few countries that has a HepB vaccine given within the first 24 hours of birth. She wondered whether CDC and / others have conducted research to assess this. It concerns her that there may be a correlation, and she requested that consideration be given to this before making that recommendation.

Dr. Schillie replied that CDC continuously monitors the safety of HepB vaccine, including when administered shortly after birth. It is a very safe vaccine. Anaphylaxis occurs in about 1 out of a million cases, and CDC will continue to monitor this. There are data to support the safety of the vaccine being given so shortly after birth, including that it does not increase the work-up for sepsis in young infants.

Dr. Riley noted that in addition to the safety data, it would be important to point out that most infant mortality in the US is in pre-term infants who are not the babies being vaccinated within the first 24 hours of life because they are <2000 grams.

Vote: Hepatitis B Vaccine Birth Dose Amendment

Dr. Romero made a motion to approve the advised recommendation as stated, "For all medically stable infants weighing ≥2,000 grams at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered before hospital discharge. Only single-antigen HepB vaccine should be used for the birth dose." Dr. Atmar seconded the motion. Dr. Moore offered an amendment to the proposed language to replace the statement "before hospital discharge" with the statement "within 24 hours of birth." Dr. Belongia seconded the suggested amendment. Dr. Bennett called for a vote on the amendment. The motion carried unanimously with 14 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Vote: Hepatitis B Vaccine Amended Birth Dose & Removal of Permissive Language

Dr. Romero motioned to approve the overall birth dose recommendation as amended, "For all medically stable infants weighing ≥2,000 grams at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered within 24 hours of birth. Only single-antigen HepB vaccine should be used for the birth dose" and to remove the permissive language reading "On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 grams and whose mother is HBsAg-negative." Dr. Atmar seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Vote: Hepatitis B Vaccine Overall Recommendations

Dr. Romero motioned to approve the overall recommendations for Hepatitis B vaccination. Dr. Atmar seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution

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

Dr. Santoli indicated that the purpose of this resolution was to align the VFC resolution with the ACIP's updated HepB recommendations. The eligible groups for this resolution are all children and adolescents birth through 18 years of age. The tables below list the acceptable vaccination schedules for children and adolescents birth through 18 years of age, which are directly from the draft of the recommendations that ACIP has reviewed, discussed, and approved. The change will be made that was just discussed and voted upon, such that "birth" is replaced with "within 24 hours" through all parts of the tables:

Table 1, Part I: Infants

		Single antigen vaccine		Single-antigen[1] and combination vaccine[2,3]	
Birth weight	Maternal HBsAg status	Dose	Age	Dose	Age
≥2000 g	Positive	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Unknown	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Negative	1	Birth (before discharge)[1]	1	Birth (before discharge)[1]
		2	1-2 months	2	2 months
		3	6 -18 months	3	4 months
				4	6 months

Table 1, Part 2: Infants

<2000 g	Positive	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1 month	2	2 months
		3	2-3 months	3	4 months
		4	6 months	4	6 months
	Unknown	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1 month	2	2 months
		3	2-3 months	3	4 months
		4	6 months	4	6 months
	Negative	1	Age 1 month or at hospital discharge[1]	1	Age 1 months or at hospital discharge[1]
		2	2 months	2	2 months
		3	6 -18 months	3	4 months
				4	6 months

Table Notes:
1. Only a single antigen hepatitis B vaccine (ENGERIX-B® or RECOMBIVAX HB®) can be given at birth.
2. Pediarix® [DTaP-IPV-HepB] is licensed for children 6 weeks through 6 years of age.
3. Use of brand names is not meant to preclude the use of other comparable US licensed vaccines.

Table 2: Children and Adolescents

Age	Schedule[1, 6]
Children (1 through10 years)	0, 1, and 6 months[2] 0, 2, and 4 months[2] 0, 1, 2, and 12 months[2,4]
Adolescents (11 through 18 years)	0, 1, and 6 months[2] 0, 1, and 4 months[2] 0, 2, and 4 months[2] 0, 12, and 24 months[2] 0 and 4-6 months[3] 0, 1, 2, and 12 months[2,4] 0, 7 days, 21-30 days, 12 months[5]

Table Notes
1. Children and adolescents may be vaccinated according to any of the schedules indicated, except as noted. Selection of a schedule should consider the need to optimize compliance with vaccination.
2. Pediatric/adolescent formulation.
3. A two-dose schedule of Recombivax-HB Adult Formulation is (10 micrograms) is licensed for adolescents aged 11 through 15 years. When scheduled to receive the second dose, adolescents aged > 15 years should be switched to a three-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.
4. A four-dose schedule of Engerix B® is licensed for all age groups.
5. Twinrix® can be administered to persons 18 years of age before travel or any other potential exposure on an accelerated schedule at 0, 7, and 21-30 days, followed by a dose at 12 months.
6. Use of brand names is not meant to preclude the use of other comparable US licensed vaccines.

The only items to be added to Table 2 will be at the bottom of the Adolescent part of the table, which is the accelerated schedule that can be used when administering Twinrix®. This does apply to 18 year olds who are covered by the VFC program.

There also is information about interrupted schedules and minimum dosing schedules that comes from the current version of the recommendations that was voted on and approved, as well as prior versions of the recommendations:

Interrupted Schedules and Minimum Dosing Intervals

- When the HepB vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least eight weeks. If only the third dose has been delayed, it should be administered as soon as possible.

- The third dose of vaccine must be administered at least eight weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is four weeks. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be re-administered, using the correct dosage or schedule.

- Vaccine doses administered ≤4 days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix®, the four-day guideline does not apply to the first three doses of this vaccine when administered on a 0 day, 7 day, 21-30 day, and 12 month schedule.

- In infants, administration of the final dose is not recommended before age 24 weeks (164 days).

There also is guidance about revaccination to make sure those doses are included in the VFC program, which is taken directly out of the statement in various categories for which revaccination would be recommended:

Revaccination

Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, or adolescents. Revaccination when anti-HBs is <10 mIU/mL is recommended for the following:

- Infants born to HBsAg-positive mothers. HBsAg-negative infants with anti-HBs <10 mIU/mL should be revaccinated with a second three-dose series and retested (HBsAg and anti-HBs) 1-2 months after the final dose of vaccine.

- Hemodialysis patients. For hemodialysis patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.

- Other immunocompromised persons. For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. When anti-HBs levels decline to <10 mIU/mL, annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.

- ❑ Persons with postvaccination serologic testing results that do not demonstrate protection. This includes children and adolescents through age 18 years who are chronic hemodialysis patients, HIV-infected, otherwise immunocompromised (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), or sex partners of HBsAg-positive persons. Persons in these groups found to have anti-HBs concentrations of <10 mIU/mL after the primary vaccine series should be revaccinated.

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 Hepatitis B 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.]

Vote: VFC Resolution for Hepatitis B Vaccine Recommendations

Dr. Stephens motioned to approve the VFC Resolution for the Hepatitis B Vaccine Recommendations. Dr. Romero seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Pertussis

Introduction

Laura Riley, MD
ACIP Pertussis Vaccine Work Group

Dr. Riley reminded everyone of the following terms of reference for the Pertussis Vaccine WG, indicating that only the first term of reference remained to be completed, and that the draft of the updated statement would be presented during this session:

- ❑ Review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate into a single statement

- ❑ Review new data on Tdap including
  - Effectiveness of ACIP recommendations
  - Interval between Td booster and Tdap
  - Use of Tdap in adults ages 65 years and older
  - Pregnant and breastfeeding women
    - Use of Tdap
    - Cocooning strategies
  - Vaccinated HCP and need for post-exposure prophylaxis
  - Tdap revaccination
    - Pregnant women
    - Healthcare personnel
    - "Cocooning"

- ❑ Review updated epidemiology of tetanus and diphtheria in the US

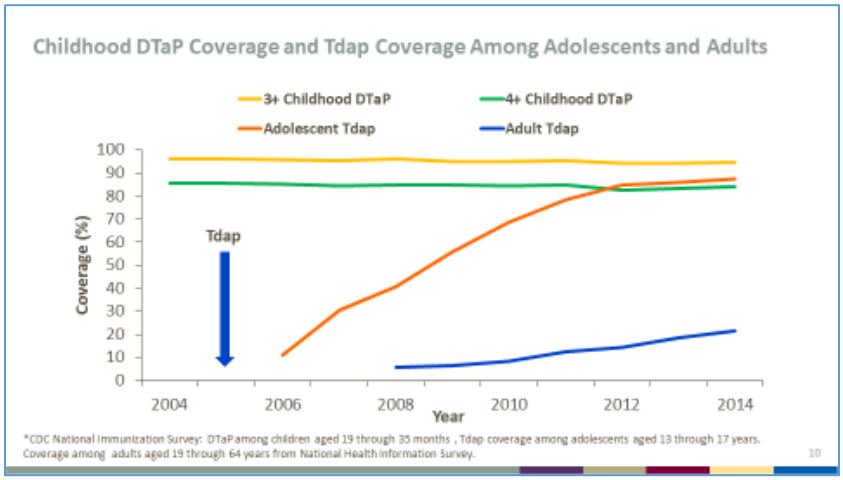
As a reminder, there are two types of pertussis, tetanus, and diphtheria vaccines. The first is DTaP (diphtheria and tetanus toxoids and acellular pertussis), which is the pediatric vaccine. The second is Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis), which is the same as DTaP but with reduced quantities. This is the adolescent and adult vaccine that is licensed for single use only.

In the time since ACIP recommended Tdap for pregnant women, additional studies have assessed the safety and immunogenicity of Tdap vaccination during pregnancy, and the effectiveness of preventing infant pertussis. It was timely and critically important for the WG to review these data, given that the updated statement for pertussis, tetanus, and diphtheria vaccines was being prepared for ACIP's review and affirmation.

Tdap coverage among pregnant women has steadily increased. The current estimate during influenza season from an Internet Panel Survey is 48.8% [CDC. Internet Panel Survey. Women aged 18–49 years pregnant at any time since August of prior year (e.g. 2015 for the April 2016 survey)].

With regard to the updated statement and the historical background of the ACIP statements, the first acellular DTaP vaccines were licensed by the Food and Drug Administration (FDA) and recommended by ACIP for the 4th and 5th dose in 1991. In 1997, ACIP recommended DTaP for all 5 doses in the childhood schedule. In 2005, Tdap was first licensed by the FDA and then recommended by ACIP for a single dose for adolescents and adults. Since the 2005 Tdap recommendations, ACIP has expanded and updated the Tdap recommendations, which were published as Policy Notes in the *MMWR*. In 2010, ACIP recommended that Tdap should be administered regardless of interval since last tetanus or diphtheria toxoid-containing vaccine. This included a permissive Tdap recommendation for adults aged 65 years or older, as well as a catch-up schedule for children aged 7 through 10 years to receive a single dose of Tdap[1]. In 2011, ACIP recommended a dose of Tdap during pregnancy for women who previously have not received Tdap[2]. In 2012, ACIP routinely recommended a single dose of Tdap for adults aged 65 and older and a dose of Tdap during every pregnancy[3,4] [[1]CDC. *MMWR* 2011;60;13–5; [2]CDC. *MMWR* 2011;60:1424–6; [3]CDC. *MMWR* 2012;61;468-470; and [4]CDC. *MMWR* 2013;62;131-135].

Vaccination rates among children are high. Unlike Tdap coverage among adults, adolescent Tdap immunization has increased steadily since its introduction:



This session focused on the guidance for the use of Tdap in pregnant women; and the updated ACIP statement for pertussis, tetanus, and diphtheria for a vote.

Guidance on Timing of Tdap Administration During Pregnancy

Jennifer L. Liang, DVM, MPVM
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

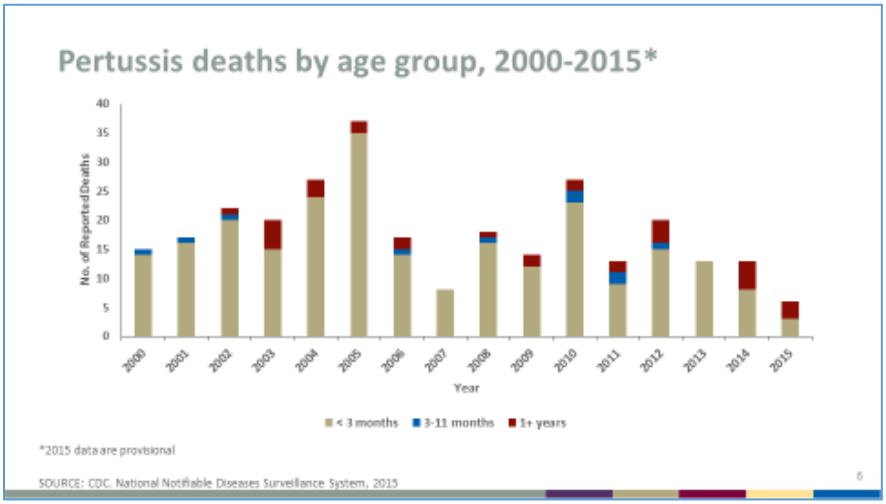
Before focusing on the topic of timing of Tdap administration during pregnancy, Dr. Liang indicated that because the pertussis WG had not presented to ACIP in over a year, she would give an overview of the epidemiology of pertussis in the US, the current ACIP Tdap recommendation and guidance for use for pregnant women, and the safety of Tdap administration to mothers and their infants.

Following the introduction of whole-cell pertussis vaccines (DTP) in the late 1940s, there was a dramatic decline in cases reported through the NNDSS. In the 1990s, the US transitioned from whole-cell to acellular pertussis vaccine (DTaP). By 1997, all 5 doses of the childhood series were DTaP. Tdap vaccine was introduced in 2005. Since the late 1980s, the burden of disease has been increasing, with notable epidemic years in 2004, 2010, and most recently in 2012, with over 48,000 cases reported. The increases in reported pertussis cases over the last two decades are likely the result of a number of factors, including improved surveillance capacity; changes in diagnostic testing and reporting; increased public and provider awareness; and probably most importantly, waning protection from acellular pertussis vaccines.

Historically, rates of pertussis have remained about the same for all age groups until more recent years when the emergence of disease has been observed in 7 to 10 year olds and 11 to 19 year olds. A growing body of evidence, which has been presented to ACIP throughout the years, strongly suggests that the change in vaccines from whole-cell to acellular pertussis vaccines in the childhood vaccine series has caused the age-specific increases due to waning immunity. Infants continue to have the highest risk for disease [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System].

Published studies have found that acellular pertussis vaccines provide protection within the first year of receipt, but that effectiveness wanes over time. Vaccine effectiveness for DTaP was evaluated by time since the 5th DTaP dose[1]. Tdap vaccine effectiveness was evaluated in adolescents who received only acellular pertussis vaccines for the primary DTaP series[2] [[1]Misegades LK, et al. JAMA. 2012 Nov 28;308(20):2126-32; [2]Acosta AM, et al. Pediatrics. 2015;135:981–9].

As previously mentioned, infants continue to have the highest risk for disease. This graph shows the number of reported deaths by age group and year. Infants less than 3 months of age (in beige) account for the greatest number of reported deaths from pertussis:



Of reported infant pertussis cases who were hospitalized, more that 50% were less than 2 months of age. Of those who died, 86% were less than 2 months of age. These infants were too young to have received any doses of pertussis vaccines. Because young infants are vulnerable to pertussis infection and have the highest morbidity and mortality rates of pertussis, as a strategy to prevent infant pertussis, ACIP first recommended a single dose of Tdap for pregnant women in 2011. Prior to this recommendation, Tdap was recommended to be given to women postpartum. In 2012, ACIP expanded the recommendation to a dose of Tdap during every pregnancy. This is the ACIP Tdap recommendation for pregnant women and guidance for use:

ACIP Tdap Recommendation for Pregnant Women

- ❑ *ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap.*

Guidance for Use

- ❑ *To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.*

The focus of the WG's review and discussion is the language in the guidance for use that states, "To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy."

As a reminder, 2 Tdap vaccines are available in the US: Sanofi Pasteur's ADACEL™ and GlaxoSmithKline's (GSK's) BOOSTRIX®. Both provide protection to pertussis, diphtheria, and tetanus. For pertussis antigens, both products contain pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN). ADACEL™ also contains fimbriae (FIM).

When ACIP first recommended Tdap to pregnant women, safety data, although reassuring, were limited. ACIP stated the need for enhanced monitoring and safety studies of Tdap given during pregnancy, especially to women who have received prior Tdap vaccination. In response to ACIP's comments, the CDC Immunization Safety Office (ISO) developed an immunization safety plan for this population through 3 established post-licensure vaccine safety monitoring infrastructures:

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Clinical Immunization Safety Assessment (CISA) Project

CDC monitoring activities for maternal Tdap safety include ongoing monitoring through VAERS and VSD. VSD provides available coverage data, as well as surveillance and research on safety signals including: preterm delivery and small for gestational age (SGA), acute vaccine-related AEs, obstetric events, and birth defects. VSD also has access to electronic medical records (EMRs) and medical records to validate cases and denominators for rates. CISA currently has 2 projects: 1) Tdap safety in pregnant women; and 2) the safety of simultaneous Tdap Inactivated Influenza Vaccine (IIV) in pregnant women. Safety data from these monitoring activities have been presented to ACIP at past meetings.

Safety data collected in the US on Tdap in pregnant women and infants continue to be reassuring. The pattern of AEs observed in VAERS in pregnant women receiving Tdap and their infants is consistent with expectations. Studies of over 50,000 women receiving Tdap during pregnancy in the VSD show no increased risk for adverse maternal or infant health outcomes. A clinical study in the CISA Project shows that Tdap was well-tolerated in both pregnant and non-pregnant women, including pregnant women receiving a repeated Tdap dose [Kharbanda EO et al. JAMA. 2014;312(18):1897-904.; Sukumaran L, et al. JAMA. 2015 314(15):1581-7, Sukumaran L, et al. ObGyn. 2015;126(5): 1069–1074; Kharbanda EO et al. Vaccine 2016; 34: 968-73].

Although pertussis-specific antibodies likely would confer protection and modify the severity of pertussis illness, when ACIP first recommended Tdap for pregnant women, the effectiveness of Tdap vaccination during pregnancy to prevent infant pertussis was not known. Since then, effectiveness data and additional immunogenicity data have become available. Recent immunogenicity studies have assessed the optimal timing of Tdap administration during pregnancy to provide maximal transfer of maternal antibodies to infants. Before presenting a summary of these studies, Dr. Liang highlighted some additional information.

For pertussis, there are no well-defined serologic correlates of protection. PT is suggested to be the most important virulence factor. After receipt of Tdap, a minimum of 2 weeks is needed to mount a maximal immune response to the vaccine antigens. During the course of pregnancy, active immunoglobulin G (IgG) transport begins around 17 weeks gestation and increases with gestational age, with accelerated uptake starting around 34 weeks. The immune response in pregnant women to Tdap immunization is similar to non-pregnant women, and vaccine-induced pertussis antibodies are efficiently transplacentally transferred from a woman to her fetus. Studies report higher antibody concentration in infant cord blood compared to maternal serum.

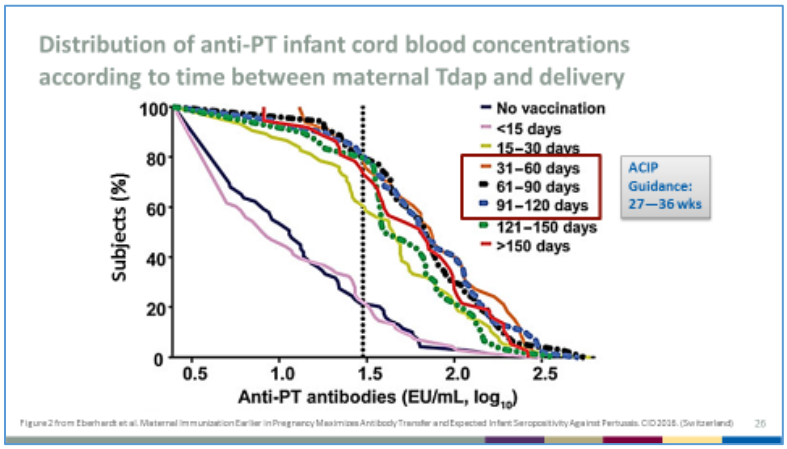
An Australian study from Naidu et al examined and compared cord blood pertussis antibody levels for PT, FHA, and PRN in infants of unvaccinated and vaccinated mothers. Compared to the no Tdap group, cord blood antibody levels were significantly higher in the vaccinated groups. By multivariable analysis, when adjusted for maternal pre-vaccination levels, pertussis toxin approached significance and PRN was significantly higher in the early versus late vaccination group. Naidu et al also found a modest to significantly positive correlation between the number of weeks exposed to Tdap and infant cord blood levels for the three pertussis antibodies. These findings suggest that longer exposure to vaccine allows for higher vaccine-induced antibody levels produced by the mother and transferred to the infant, which supports earlier vaccination within the 27 through 36 week window [Naidu et al. Pertussis vaccination during pregnancy. *Am J Obstet Gynecol* 2016. (Australia)].

As with the previous study, a study from Abu Raya et al found both maternal and infant cord blood sera concentrations were higher in the Tdap vaccinated groups versus the unvaccinated group. Within the 27 through 36 week window of Tdap administration, the cord blood GMC for PT was higher in infants whose mothers received Tdap at 27 through 30 weeks compared to 31 through 36 wks. It is unclear why the GMCs are higher for Tdap after 36 weeks, but this is from a smaller group and the findings are not consistent with other studies [Abu Raya et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study. *Vaccine* 2014. (Israel)].

A study by Dr. Mary Healy from Baylor College of Medicine looked at anti-PT specific IgG levels in cord blood from infants born to women who received Tdap during weeks 27 through 36 weeks gestation compared with infants of unvaccinated mothers. As part of this study, Dr. Healy assessed the optimal gestation for Tdap administration between 27 through 36 weeks. This study shows that immunization earlier within the 27 through 36 weeks appears to allow for maximal anti-PT IgG antibodies in infants [Unpublished data courtesy of CM Healy, Baylor College of Medicine].

The aim of a Swiss study by Eberhardt et al was to determine whether Tdap vaccination as early as 13 through 25 weeks would elicit non-inferior geometric mean concentrations (GMCs) of infant cord blood antibodies compared with immunization after 25 weeks gestation. Within the current ACIP guidance, infant cord blood GMCs for PT and FHA tended to be higher for infants whose mothers received Tdap between 26 through 33 weeks compared to infants whose mothers received Tdap after 33 weeks gestation. Eberhardt also found that the GMCs were non-inferior for infants whose mothers received Tdap earlier than 26 weeks [Eberhardt et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *CID* 2016. (Switzerland)].

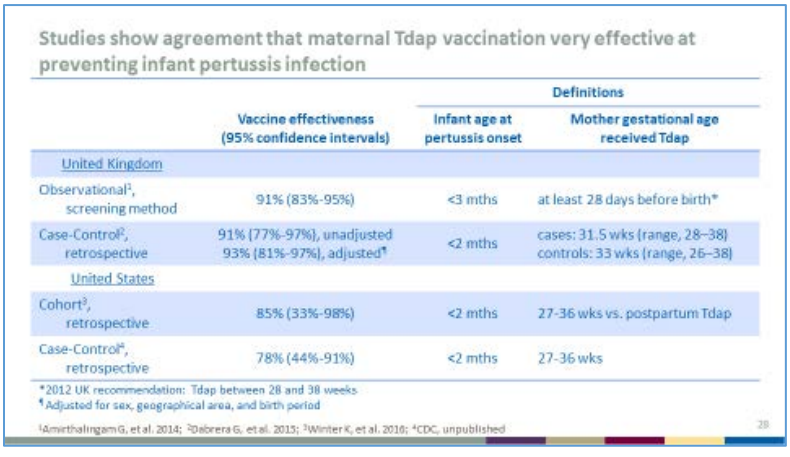
From the Eberhardt et al study, these curves represent the distribution of individual anti-PT antibody GMCs at various time intervals between maternal Tdap immunization and delivery:



There is a red box around the days that would fall within the 27 through 36 week window. Compared to no vaccination and less than 15 days before delivery (pink and blue lines), a longer time between maternal Tdap and before delivery resulted in similar distribution of anti-PT infant cord blood concentrations. Antibody concentrations markedly increased with intervals greater than 14 days, reaching optimal GMC with intervals between 31 and 120 days.

In summary of the immunogenicity studies, infants of mothers vaccinated with Tdap during pregnancy were born with significantly higher anti-pertussis antibodies compared to infants of unvaccinated mothers. Within the 27 though 36 week window, the concentration of anti-pertussis antibodies in infant cord blood were generally higher when mothers were vaccinated earlier. In addition, longer exposure to vaccine allows for higher vaccine induced antibody levels produced by mother and transferred to infant. One study found infant cord blood concentration of anti-pertussis antibodies non-inferior when maternal Tdap was administered before 27 weeks.

Although the methodologies differ, several studies have shown that vaccinating women during pregnancy is very effective at preventing infant pertussis, from 78% to 93% effective. The majority of women from these studies were vaccinated within the current guidance window of 27 through 36 weeks:



Studies show agreement that maternal Tdap vaccination very effective at preventing infant pertussis infection

	Vaccine effectiveness (95% confidence intervals)	Definitions: Infant age at pertussis onset	Definitions: Mother gestational age received Tdap
United Kingdom			
Observational[1], screening method	91% (83%-95%)	<3 mths	at least 28 days before birth*
Case-Control[2], retrospective	91% (77%-97%), unadjusted 93% (81%-97%), adjusted¶	<2 mths	cases: 31.5 wks (range, 28–38) controls: 33 wks (range, 26–38)
United States			
Cohort[3], retrospective	85% (33%-98%)	<2 mths	27-36 wks vs. postpartum Tdap
Case-Control[4], retrospective	78% (44%-91%)	<2 mths	27-36 wks

*2012 UK recommendation: Tdap between 28 and 38 weeks
¶Adjusted for sex, geographical area, and birth period

[1]Amirthalingam G, et al. 2014; [2]Dabrera G, et al. 2015; [3]Winter K, et al. 2016; [4]CDC, unpublished

A retrospective cohort study from California evaluated whether infants born to mothers who received Tdap during pregnancy had less severe pertussis compared to infants born to unvaccinated mothers. Infected infants of vaccinated mothers were older when they developed disease and were less likely to have classic pertussis symptoms. They also were at significantly lower risk of hospitalization and intensive care unit (ICU) admission. None of these infants developed seizures, required intubation, or died [Winter K, et al. Effectiveness of prenatal Tdap vaccination on pertussis severity in infants. *Clin Infect Dis*. 2016 Sep 13. (Epub ahead of print)].

After review of available data on immunogenicity and effectiveness, the WG was cautious with how these immunogenicity data might relate to effectiveness. Again, the minimal concentration of antibodies to confer protection is unknown. Because of this unknown, the WG noted that it is important to ensure enough time between mother's receipt of Tdap and infant's birth to allow for maximizing the concentration of maternal antibodies. This may be better achieved by vaccinating at an earlier gestational age (e.g., before 27 weeks gestation). However, vaccination too early during pregnancy may not allow for sustained levels of antibodies to provide protection through the infant's first DTaP dose at age 2 months due to maternal antibody decay. Data are not yet available to address this concern.

Based on review of the immunogenicity and effectiveness data, the WG considered the following options to modifying the current window:

1. Expanding the window to include earlier Tdap administration (e.g., as early as 22 weeks)
2. Narrowing the window to 27 through 32 weeks
3. No change to the current window of 27 through 36 weeks, but emphasize earlier administration within the window

When reviewing these 3 options, the WG considered what the impact any modification to the guidance window would have on the current program. ACIP has been recommending Tdap for pregnant women since 2011. Since then, Tdap uptake in pregnant women has steadily increased. As Dr. Riley presented earlier, the current estimate from the 2015-2016 influenza Internet Panel Survey was 48%. During the previous flu season, Tdap coverage was 23%. The WG did not want to potentially disrupt this trend. Earlier administration of Tdap might increase the opportunity to educate and vaccinate pregnant women and increase protection among preterm infants. Vaccinating pregnant women earlier might provide protection to the earliest preterm infants, but the great majority of preterm infants are provided protection under the current 27 through 36 week window. When considering narrowing the window, the WG was concerned this would decrease the opportunity to vaccinate pregnant women.

The WG is encouraged that vaccinating pregnant women with Tdap is effective at preventing pertussis in infants. The WG also was reassured that if infected with pertussis, infants born to vaccinated mothers are less likely to develop severe pertussis compared to infants born to unvaccinated mothers. Although there is variation between immunogenicity studies, and the studies are limited by small to modest samples sizes, these studies have shown that vaccinating earlier within the 27 through 36 week window or even before 27 weeks may be beneficial in optimizing the production and transfer of maternal antibodies to infants. However, it is unclear at this time how the immunogenicity data from earlier administration will translate to effectiveness in preventing infant pertussis. The current strategy is effective at preventing infant pertussis, so the WG was reluctant to modify the current window. Again, the WG was cautious not to equate higher concentration of maternal antibodies from earlier vaccination to similar or better effectiveness without knowing whether the durability and concentration of maternal antibodies would be maintained until an infant is old enough to receive his or her first DTaP.

Without effectiveness data specific to vaccinating women earlier during pregnancy, the WG is cautious to over-interpret results from these studies.

After considering the proposed options, the WG did not support expanding the window to include earlier Tdap administration. Although the WG thought that vaccinating earlier within the current window likely would provide maternal antibodies for the majority of infants including those born preterm, WG members differed in how to modify the current guidance of 27 through 36 weeks. A minority of the WG supported narrowing the current window to 27 through 32 weeks; whereas, a majority supported no change to the current window of 27 through 36 weeks, but including language to emphasize earlier administration within this window. This option also was supported by the American Congress of Obstetricians and Gynecologists (ACOG) and the American College of Nurse Midwives (ACNM) WGs. Therefore, the language Dr. Liang presented was modified accordingly.

As a reminder, here is the current ACIP Tdap recommendation for pregnant women along with the guidance for use. The underlined sentence in the Guidance for Use is the language the WG is updating:

ACIP Tdap Recommendation for Pregnant Women

- *ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap.*

Guidance for Use (CURRENT)

- *To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.*

The drafted change to the Guidance for Use is shown below. The underlined sentence is the WG's proposed updated language:

Guidance for Use (DRAFTED CHANGE)

- *Tdap should be administered between 27 and 36 weeks gestation, although it may be given at any time during pregnancy. Currently available data suggest that vaccinating earlier in the 27 through 36 week window will maximize passive antibody transfer to the infant. For women not previously vaccinated with Tdap, if it is not administered during pregnancy, Tdap should be administered immediately postpartum.*

This guidance language will be included in the updated ACIP statement for pertussis, tetanus, and diphtheria vaccines, which Dr. Liang presented following this discussion.

Discussion Points

Acknowledging that there are not specific data about duration of maternal antibody if given earlier, Dr. Kempe said she would not expect this to be very different from other situations. She asked Dr. Liang to talk about what the subject matter experts (SMEs) thought about duration (e.g., the comparison between 22 weeks or 27 weeks).

Dr. Liang replied that while the immunogenicity showing equivalent or non-inferior concentration to earlier administration were promising, the WG was concerned that without knowing the durability and timing of maternal antibody decay, whether that higher concentration would translate to durability from time of birth to 2 months of age when the infant would be recommended to receive the first dose of DTaP.

Dr. Walter asked whether that was the WG's main consideration in not narrowing the window to an earlier time.

Dr. Liang responded that that was one of the considerations. The other concerns regarded potential programmatic disruption. Any change potentially could cause confusion. They have heard anecdotally that even with the current guidance window, providers are not necessarily targeting between the 27 through 36 weeks. Any other change potentially would result in misinterpretation. Because the data are not available at this time, the WG did not want to change the recommendation drastically.

Dr. Riley added that the concern was that it would be making another small change in the context of only 48% uptake with a fairly new recommendation, which could cause more confusion. It has been observed that when people do not understand a change, they tend to do nothing. The goal is to get people vaccinated. Even if women are vaccinated at 36 weeks, it is better than not getting vaccinated at all. Because of the goal to shift vaccination to the earlier end of the range, ACOG intends to tell obstetricians that if this is paired with the glucose test that everyone has at approximately 27 to 28 weeks, this would be an ideal time to give Tdap as well. The hope is that people will vaccinate earlier in the window. The other concern is that when vaccination is given at 34 and 36 weeks, it misses all of the late pre-term infants who get nothing.

Dr. Liang said that given the various studies that have evaluated the effectiveness in preventing pertussis in infants, and because those evaluations were done within the current window of administration, the WG felt that was reassuring and showed that the current program is working. Whether to shift it to make it earlier, they didn't have these data. Within the US, the evaluations—the coverage, they are still learning about impact. They know that it works in the individual infant, but in terms of overall numbers of cases reported in infants, we're just starting to be able to evaluate that as coverage increases and moving forward through time.

Dr. Szilagyi asked whether there are any healthcare utilization data that would suggest what percentage of pregnant women would not be seen at all if the window were narrowed, resulting in a missed opportunity to vaccinate them.

Dr. Liang replied that they do not have these data. While it is known that there are providers who are administering Tdap, it is not known when specifically they are administering it even during pregnancy. There is a lot of variability. One of the limitations of the coverage data is that while it is known that pregnant women are receiving Tdap, when they receive it during pregnancy is unknown.

Dr. Hunter asked whether it would be possible to acquire data about frequency by week of pregnancy. He noticed on one of slides that there were data about that in a small group. It looked like it was between 27 and 30 weeks, and then dropped off after that. He assumed that had to do with the protocols of when it is given, and group-by-group how practices decide to set things up in their clinics.

Dr. Riley responded that it probably reflects how people are implementing the protocol. The thought is that if the ACOG statement stresses that earlier in the existing window is better for X, X, and X reasons and it is paired with the glucose test, more women will receive the vaccine at 27 to 28 weeks. The WG discussed making it 26 weeks. The concern is that little changes make people do odd things.

Dr. Messonnier emphasized that studying this is very difficult and there is a lot of variability in the datasets about when people get vaccinated. While there are data on the overall vaccine efficacy of the program, there are no data that take timing into account. It also is important to remember that there are two vaccines, and there are some data to suggest that the kinetics of the vaccines differ. The UK will be changing their window, so this is a case in which additional data will be available in a couple of years from a setting of high vaccination coverage.

Dr. Stanley Plotkin (Audience Member) said he thought the recommendation to maintain 27 to 36 weeks was a reasonable public health recommendation. However, he objected to the mantra that the correlates of protection are unknown. Obviously, this is known. The fact that maternal immunization protects infants shows that, in fact, antibody is the correlate of protection. What is not known is an absolute threshold for the antibody. But it is very clear that antibodies to PT, FIM, and PRN are protective. Personally, he believes that vaccinating early in the third trimester is better than vaccinating later because of the antibody data. He thinks it is a reasonable compromise under the current circumstances to maintain the breadth of the recommendation, particularly since the impact on later vaccination of the infant has to be taken into account in making the overall recommendation.

Having reviewed the data as the WG has, Dr. Neuzil (IDSA) also believes that it appears that earlier is better though how early is not quite clear. However, she was not certain that the statement reflected the WG's intent and that it may not be strong enough. While she appreciated the issue of not wanting to tweak, she asked whether consideration was given to recommending that the vaccine should be administered during the first visit of the third trimester, or as early as possible in the third trimesters, and then putting that 27 through 36 in parentheses. As Dr. Riley said, it is very protocol-driven in obstetrics. If they could get it right there with the first third trimester visit, that might accomplish this without causing confusion.

Dr. Belongia supported that. He suggested that the second sentence would be stronger if it read, "Vaccine should be administered as early as possible within the 27 through 36 week window."

Dr. Hayes (ACNM) emphasized that the WG felt that they should be careful about recommendation fatigue, which was one of the primary reasons that this was not changed. In regard to the question about data and utilization, ACNM has a Maternal Immunization Working Group that is trying very hard to get a quality data measurement on this. They were not happy because they have been working for a year and a half on this language, which is what they planned to measure. She issued a plea on behalf of the ACNM Maternal Immunization Working Group not to change the language. She did agree that the language could be stronger.

Dr. Riley said she was perfectly fine with saying "earlier within the window." She cautioned against saying "the first visit in the third trimester" because that definition is a moving target. Some people say the third trimester is 24 weeks, some say 26, and others say 28. If the recommendation is too literal, someone at 25 weeks might not get the vaccine.

Dr. Bennett noted that the plan was to vote on the updated statement, not this particular wording.

Dr. Friedland (GSK) mentioned that in addition to the safety programs outlined by Dr. Liang, GSK maintains a pregnancy registry for the use of BOOSTRIX® in the US and in other parts of the world. They have ongoing pharmacovigilance systems in place to monitor the safety of the use of BOOSTRIX® in pregnant women around the world.

Dr. O'Leary (PIDS) thought that "earlier in the window" was vague. He asked whether there was discussion about being more specific, such as stating 27 to 30 weeks, or 27 to 29 weeks, just thinking about the protocolization.

Dr. Riley stressed that from a programmatic standpoint, if it is timed with the glucose loading test that obstetricians do at a certain time all of the time, this probably would be earlier in the window.

An inquiry was posed regarding what the wording is on the glucose testing, and whether it is tied to a trimester.

Dr. Riley replied that it is generally given at 26 to 28 weeks gestation.

Dr. Wexler (IAC) said that they do receive a lot of questions about the last statement, "For women not previously vaccinated with Tdap, if it is not administered during pregnancy, Tdap should be administered immediately postpartum." Providers want to know, even if women were vaccinated at 11 or 12 years of age, why not protect them immediately with a dose of Tdap.

Dr. Belongia asked what is known about co-administration of influenza vaccine and Tdap in pregnancy, and whether there is a specific recommendation and if there is any evidence that receipt of one might influence the immunologic response to the other.

Dr. Liang replied that at this time, a CISA study is just beginning to assess this. Currently, there is no language that states not to co-administer Tdap with influenza vaccine. One study has evaluated co-administration of these two vaccines in non-pregnant populations, which found that there was a slight decrease in the response in one of the pertussis antigens. However, it is not known what that translates to in terms of clinical outcome or the impact of the response.

Updated ACIP Statement for Pertussis, Tetanus, and Diphtheria Vaccines

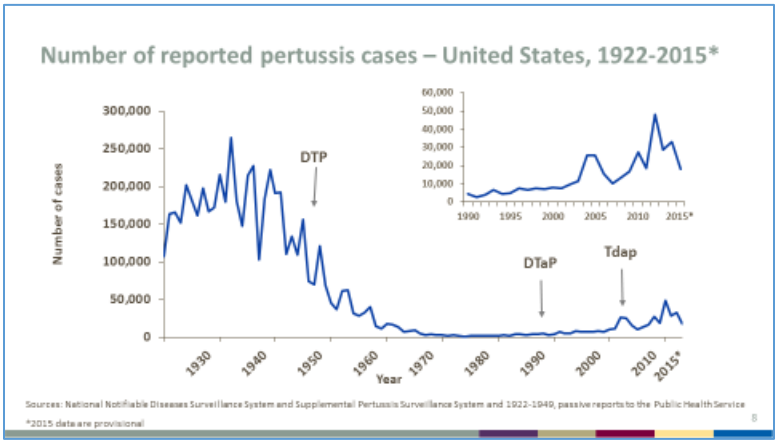
Jennifer L. Liang, DVM, MPVM
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Liang explained that the updated statement compiles and summarizes all previously published recommendations from CDC's ACIP regarding prevention and control of pertussis, tetanus, and diphtheria in the US, specifically after the introduction of acellular pertussis vaccines, and does not contain any new recommendations. This document also provides an overview of the current epidemiology of tetanus, diphtheria, and pertussis; and an updated list of current vaccines and recommendations for routine vaccination and guidance for use. The statement also describes the process undertaken and the rationale used in support of these recommendations, and is intended for use by clinicians and public health providers as a resource. This statement is the product of the review of published DTaP and Tdap vaccine

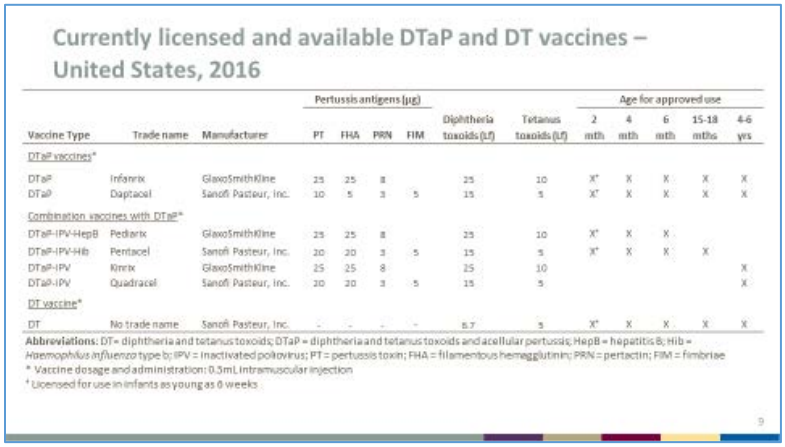
recommendations, peer-reviewed literature, and surveillance data from NNDSS and Enhanced Pertussis Surveillance (EPS). The WG reviewed the draft statement and provided comments. Prior to this meeting, ACIP voting members reviewed the draft statement and provided comments.

To summarize the updated statement, after the introduction of universal immunization with tetanus toxoid-containing vaccines in the mid-1940s, the incidence of reported tetanus in the US declined by more than 98%. Deaths from tetanus also declined similarly during this period. Currently, tetanus is rare in the US and occurs primarily among older adults. From 2005-2015, an average of 28 tetanus cases per year are reported.

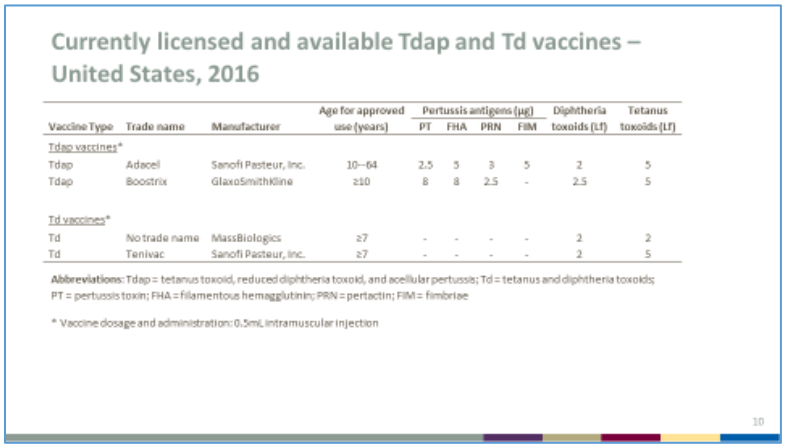
In the US, reported diphtheria cases from all anatomical sites declined from over 200,000 in 1921 to 15,536 in 1940. This decline continued after the introduction of universal childhood immunization in the late 1940s. In 1980, only two cases of diphtheria were reported. During 1996–2004, 11 cases were reported. From 2004-2011 no cases were reported, but in 2012, there was a probable case of nontoxigenic diphtheria, and in 2014 a confirmed case positive by culture with non-toxigenic *C. diphtheriae*. As previously presented, the following graph shows the number of reported pertussis cases in the US from 1922-2015:



Listed here are the currently licensed and available DTaP vaccines, combination vaccines with DTaP, and DT vaccines in the US:



Following is a list of the currently licensed and available Tdap and Td vaccines in the US:



Currently licensed and available Tdap and Td vaccines – United States, 2016

Vaccine Type	Trade name	Manufacturer	Age for approved use (years)	Pertussis antigens (µg)				Diphtheria toxoids (Lf)	Tetanus toxoids (Lf)
				PT	FHA	PRN	FIM		
Tdap vaccines*									
Tdap	Adacel	Sanofi Pasteur, Inc.	10–64	2.5	5	3	5	2	5
Tdap	Boostrix	GlaxoSmithKline	≥10	8	8	2.5	-	2.5	5
Td vaccines*									
Td	No trade name	MassBiologics	≥7	-	-	-	-	2	2
Td	Tenivac	Sanofi Pasteur, Inc.	≥7	-	-	-	-	2	5

Abbreviations: Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td = tetanus and diphtheria toxoids; PT = pertussis toxin; FHA = filamentous hemagglutinin; PRN = pertactin; FIM = fimbriae

* Vaccine dosage and administration: 0.5mL intramuscular injection

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Note that monovalent tetanus toxoid vaccine manufacturing was discontinued and has not been available in the US since 2013.

The consolidated updated statement will contain the routine recommendations for DTaP, DT when indicated, Tdap, and Td which were last published in separate statements. The statement also includes Tdap recommendations made after the 2005 recommendations and published in *MMWR* Policy Notes. Again, there are no changes to these previously published recommendations. The statement also contains updates such as DTaP vaccines that became available after the 1997 DTaP statement, and updates to label indications for various DTaP and Tdap products. Also included in the statement are the following updates:

- ❑ Mention of the discontinuation of monovalent tetanus toxoid (TT) vaccine
- ❑ Contraindications and precautions for DTaP are now consistent with AAP's Red Book
- ❑ For persons aged 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose may be given at age 11 through 12 years; this guidance is now in line with guidance given on children for which Tdap is inadvertently administered

Dr. Liang explained that the ACIP vote for this session would be to affirm the updated statement, which does not contain any new vaccine recommendations. The statement will be updated with the modified Guidance for Use language of Tdap for pregnant women, along with a summary of supporting data. A table summarizing safety studies on use of Tdap in pregnant woman and their infants also will be included. Before the vote, Dr. Liang recognized and acknowledged all of the WG members from past and present who have been part of this process since 2009. She also thanked the previous WG chair, Dr. Mark Sawyer and current WG chair Dr. Art Reingold for their leadership. In addition, she acknowledged several CDC groups and CDC contributors on the WG for providing subject matter expertise.

Discussion Points

Given that the guidance is part of the recommendations, Dr. Kempe asked for clarity regarding whether they were in fact voting on the language of the guidance as well.

Dr. Cohn indicated that they were separating out recommendations from Guidance for Use. The Guidance for Use are CDC recommendations about how to implement the recommendations the ACIP votes on. It sounded like the WG could incorporate some of the discussion from earlier to modify that language.

Ms. Stinchfield (NAPNAP) noted that a very common situation that she did not hear discussed regarded how to handle an adolescent who has not had a primary DTaP series, who presents to catch-up.

Dr. Liang replied that there is catch-up language for a child, adolescent, or adult who presents wanting to receive any pertussis-containing vaccines that the catch-up series includes one dose of Tdap.

Public Comment

Christina Hildebrand
A Voice For Choice Advocacy

I was very interested in what you presented today, and I thank you for allowing me to give you public comment. I have some questions which seem to be left unanswered by the presentation. You said that you're going to give a summary of Tdap safety studies. The vaccine package inserts for both Tdap studies state that there will be no clinical trial or studies on pregnant women for both of those studies, so I'm curious to get those Tdap safety studies that you mentioned. The studies that were outlined in the presentation have extremely small sample sizes, so I would hope that the studies that you are referring to have larger sample sizes. I also wonder whether there has been review of the number of miscarriages. The studies that I've seen actually took out stillborn deaths, and I wonder if we have any studies on the number of stillborn deaths and miscarriages that happen after vaccination versus those people who are not vaccinated. The other piece that I would ask that you address is that both Tdap vaccines include aluminum—we know aluminum crosses the blood-brain barrier (BBB)—and whether that has been studied in fetuses and whether the aluminum from the Tdap vaccine dose, in fact, crosses the BBB and what that does to the fetus. And then the other question that I have for you is that there have been studies in baboons that have shown that the DTaP and Tdap vaccines actually show that you can be an asymptomatic carrier of pertussis and you can actually give pertussis to someone else. And so, I wonder whether that has been addressed and whether the giving of Tdap and DTaP among infants, specifically Tdap among the parent, whether they can be an asymptomatic carrier to their infant, as well as whether giving the Tdap actually stops the infant from getting pertussis—whether in that first 6 months of life, whether those infants that have had higher antibodies have actually been stopped from getting pertussis. Also, because we know right now, most people and—most adults and most teenagers that are getting pertussis are getting it having been fully vaccinated. Thank you.

Dr. Meissonier thanked Ms. Hildebrand for her questions and comments. She said she thought that one issue was that a lot of the information she was asking about was presented during a previous ACIP meeting. All of the ACIP members have seen those data and have had deliberations on it. That information is available online. In addition, she said that CDC's SMEs

would be happy to speak with Ms. Hildebrand during the break and share data. The pharmaceutical companies also collect data pertaining to some of Ms. Hildebrand's points. If the information is not clear in the package insert, she was sure the manufacturers would be happy to provide more information about that as well.

James Grundvig
Freelance Journalist, New York City
Epoch Times, Financial Times, Foreign Direct Investment (FDI) Magazine

My green investors would like to know why Zika wasn't discussed with this particular vaccine. Apparently the microcephaly problems in Northeast Brazil has not been confirmed yet whether it's Zika, whether it's other toxins, or whether the vaccine was given down there to pregnant women.

Dr. Bennett thanked Mr. Grundvig for his comment. She explained that ACIP focuses its attention on vaccine recommendations in the US, and that there would be an update on Zika during the second day of the ACIP meeting.

Vote: Updated Statement for Pertussis, Tetanus, and Diphtheria Vaccines

Dr. Walter motioned to approve the updated statement for pertussis, tetanus, and diphtheria vaccines. Dr. Riley seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Kempe reminded everyone that since 2006, HPV vaccination has been recommended as a 3-dose series. The ACIP HPV Vaccines WG and ACIP have reviewed data on 2-dose schedules over the last year, and a vote is scheduled for this meeting.

During the February 2016 meeting, there were presentations and deliberations on the background on 2-dose schedules, 9vHPV 2-dose immunogenicity trial data, and 2-dose data for the 2vHPV and 4vHPV.

During the June 2016 meeting, there were presentations and deliberations on HPV vaccine supply, duration of protection after a 3-dose series of 2vHPV and 4vHPV vaccination; impact and cost-effectiveness modeling for 2-dose schedules; review of post-licensure vaccine

effectiveness studies of 2vHPV and 4vHPV; Grading of Recommendation Assessment, Development and Evaluation (GRADE) for 2-dose schedules; and initial considerations for recommendations.

Since June 2016, the WG has held monthly conference calls to review further data from the 9vHPV 2-dose trial, including follow-up data through month 12 and data on intervals between doses; discussed policy options; and drafted recommendations.

The FDA approved a 2-dose series for persons age 9 through 14 years on October 7, 2016. The updated 9vHPV label includes immunogenicity data from the trial and an updated Dosage and Administration section shown below:

---------- DOSAGE AND ADMINISTRATION ----------
For intramuscular administration only. (2)
Each dose of GARDASIL 9 is 0.5-mL
Administer GARDASIL 9 as follows: (2.1)

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 26 years	3-dose	0, 2, 6 months

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. (14.2 and 14.5)

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

Potential future issues for the HPV Vaccines WG are to: 1) revisit the wording for the routine recommended age groups; and 2) revisit the upper age recommendation for males, as some WG members and liaison members feel strongly about this. The WG felt that these issues would require more data and more discussion; therefore, it was decided that these topics be tabled for future meetings.

Review of Evidence for a 2-Dose Vaccination Schedule

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

In this presentation, Dr. Markowitz provided an overview of evidence for 2-dose schedules. She started with some background information on HPV vaccines and recommendations, and then provided a summary of evidence of data presented to ACIP over the last two meetings on 2-dose schedules, as well as some new data from the 9vHPV vaccine 2-dose trial. She ended with data on vaccine coverage in the US and programmatic considerations.

By way of review, there are 3 HPV vaccines licensed in the US: bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV). These are all virus-like particle (VLP) vaccines composed of the L1 major capsid protein. The 2vHPV is produced by GSK and 4vHPV and 9vHPV are produced by Merck. While all are VLP vaccines, they differ in the types they target, their production systems, and adjuvants. The first vaccine licensed was 4vHPV in 2006, and the most recent was 9vHPV in 2014.

In terms of changes in the recommendations since the beginning of the program, in 2006, 4vHPV was licensed and recommended for routine vaccination of females. In 2009, 2vHPV was recommended as one of the vaccines that could be used for females. Also in that year, the 4vHPV was licensed for use in males and ACIP made a statement that the vaccine may be given to males. In 2011, 4vHPV was recommended for routine vaccination of males. In 2015, after licensure of 9vHPV, that vaccine was recommended as one of 3 vaccines that could be used for females and one of 2 for males. Since the beginning of the program, a 3-dose series has been recommended.

ACIP currently recommends routine vaccination at age 11 or 12 years. The vaccination series can be started beginning at age 9 years. Vaccination is recommended through age 26 for females and through age 21 for males not vaccinated previously. A 3-dose series is recommended at an interval of 0, 1-2 months, and 6 months. Since 2015, any of the three vaccines are recommended for females and 4vHPV or 9vHPV for males [*MMWR* 2015;64:300-4].

Vaccine use and availability in the US is changing. Through 2014, almost all HPV vaccine used was 4vHPV. In 2016, almost all HPV vaccine used is 9vHPV (>90%). GSK made the decision to stop supplying 2vHPV in US due to low demand. In the US, 2vHPV supplies are expected to be used up by November 2016. Only 9vHPV has been on the CDC contracts since April 2016. Merck will distribute only 9vHPV in the US after October. 2vHPV and 4vHPV will continue to be available outside the US.

In terms of the evidence considered by ACIP for the 2-dose recommendation over the past two meetings, for initial licensure of the HPV vaccines as a 3-dose schedule, efficacy and immunogenicity data were obtained. These included efficacy data from large randomized controlled trials (RCT) trials in 15 through 26 year olds, with trial endpoints of cervical pre-cancer lesions and well as some other pre-cancers and genital warts for 4vHPV v [Future II Study Group, *NEJM* 2007; Garland *NEJM* 2007; Paavonen *Lancet* 2007], and data from bridging immunogenicity trials in 9 through 15 year olds. Licensure in 9 through 15 year olds was based on non-inferior antibody response compared with young adult women in the efficacy trials.

The 3-dose schedule for which vaccines were originally tested and licensed at a 0, 1 to 2, and 6 months schedule can be considered a prime-prime-boost, with the first 2 doses being the priming doses and the third being the boost. The 2-dose schedules that are being studied, such as the 0, 6 months schedule, can be considered a prime boost with the second prime being eliminated. Memory B cells require at least 4 to 6 months to mature and differentiate into high-affinity B cells. The approximate 6-month interval between the first and last dose allows the last dose to reactivate memory B cells efficiently.

The evidence reviewed for 2-dose schedules by the WG and ACIP include data on immunogenicity, post-hoc analyses of efficacy data, and post-licensure effectiveness data, and data from modeling and duration of protection. Dr. Markowitz reviewed each of these briefly. Most of the data used for evidence on 2-dose schedules are immunogenicity data. Immunogenicity trials comparing 2 and 3 doses have been conducted for all three HPV vaccines. The main analyses, and those considered by regulatory agencies, are comparisons of the antibody response after 2 doses in young adolescents about 9 through 14 years of age, with 3 doses in young adult women about 16 through 26 years of age. Again, the comparison group in these immunobridging analyses is the age group and the vaccine schedule for which

efficacy demonstrated in large RCTs. Immunobridging analyses are used because although the basis of protection after vaccination is thought to be due to the neutralizing antibody after vaccination, there is no established minimum threshold for protection. Trials of all three HPV vaccines found the antibody response after 2 doses given at a 0, 6 or 0, 12 month interval in those approximately 9 through 14 years of age to be non-inferior to the antibody response after 3 doses in the older age group. Some trials also compared 2 and 3 doses in those approximately 9 through 14 years of age, with the results varying by trial. Antibody titers were lower after 2 doses versus 3 dose for some the HPV types in some of the trials. Based on data from immunogenicity trials, regulatory authorities have approved 2-dose vaccination schedules for HPV vaccines. These schedules are being used in multiple countries worldwide.

With regard to the study design of the 9vHPV trial which led to FDA approval of a 2-dose schedule, there were 5 study arms. Three arms were among 9 through 14 year olds: 1) girls who received vaccine at a 0, 6 months interval; 2) boys who received vaccine at a 0, 6 months interval, and 3) a combined group of girls and boys who received vaccine at 0, 12 months interval. Two groups received a 3-dose schedule: 1) females 16 through 26 years of age, who were defined as the control group, and 2) females 9 through 14 years of age, who were used for an exploratory comparison. The primary analyses were at 1 month post-last dose. These were the data reviewed by the FDA and results were presented to CDC and ACIP in February 2016. Follow-up to assess antibody persistence is planned at months 12, 24, and 36.

At one month after the last dose, there were non-inferior geometric mean titers (GMTs) in girls who received 2 doses at 0,6 months compared with women who received 3 doses at 0,2,6 months. The GMTs were, in fact, higher at the younger age. The GMT ratios range from 1.60 to 2.96 for the different types, with lower bound of the confidence interval (CI) above 1 for all types. The results for the comparison with the boys who received vaccine at 0, 6 months were similar. There were similar findings in the 2-dose 0,12 month group with non-inferior GMTs at one month post-last dose in girls and boys who received 2 doses at 0,12 months compared with women who received 3 doses at 0,2,6 months. Again, the GMTs were not only non-inferior, but also were higher in the younger age group that received 2 doses. The GMT ratios for each of the 9 types ranged from 1.96 to 6.31 [http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf].

At the time of the presentation to ACIP in February 2016, only the data from 1 month after the last dose were available. Recently, the WG reviewed data from 6 months after the last dose. Data from 6 months after the last dose are not yet available for the 2-dose 0, 12 month group. Just looking at HPV6 as an example, GMTs decreased in all groups between these two time points, consistent with what has been seen for other HPV vaccination follow-up studies. At month 12, which is 6 months after the last dose, GMTs in both of the 2-dose groups were non-inferior and higher than those in women who received 3 doses. The GMT ratios for girls compared with women was 2.15 at month 7 and 1.69 at month 12. There were similar findings for HPV 11 and 16. In terms of the other types targeted by the 9vHPV at 1 and 6 months after the last dose (months 7 and 12), for types 18, 31, and 33, GMTs were higher in the 2-dose groups compared with women who received 3 doses at both time points. For types 45, 52, and 58 comparing the 2-dose 9 through 14 year olds and the 3-dose 16 through 26 year olds, GMTs decreased between 1 month and 6 months after the last dose. This is not unexpected and also was seen in the 4vHPV 2-dose trial in which GMT ratios also decreased initially, but stabilized between months 24 and 36.

Additional data reviewed by the WG from the 9vHPV 2-dose trial included data on GMTs by the interval between dose 1 and dose 2 in the 2-dose groups. This was to inform decisions about minimum intervals. In the 2-dose trial, the interval between 2 doses in the 0, 6 month group was 6 months plus or minus 4 weeks. Over half of the vaccinees received dose 2 between 5 and less than 6 months after dose 1. This table shows GMTs for 4 of the types by interval between dose 1 and dose 2 in the 0, 6 month 2-dose group:

Assay (cLIA)	(0, 6) Girls		(0, 2, 6) Women
	5 months to <6 months (N=162)	≥6 months to 7 months (N=112)	5 months to 7 months (N=286)
Anti-HPV 6	**1613**	**1720**	**771**
Anti-HPV 11	**1333**	**1468**	**581**
Anti-HPV 16	**7845**	**8238**	**3154**
Anti-HPV 18	**1821**	**1949**	**762**
N=number of subjects in the per-protocol population for ≥1 HPV type cLIA = Competitive Luminex immunoassay GMTs expressed in milli-Merck units per milliliters (mMU/mL)			

GMTs were similar if dose 2 was administered at 5 to less than 6 months or ≥6 months to 7 months after dose 1. For both intervals and all HPV types, GMTs were numerically higher than in women who received 3 doses, shown in the last column above. The updated 9vHPV label indicates a 2-dose series at 0 and 6-12 months and also states a minimum interval between dose 1 and dose 2 of 5 months.

In summary, in the 9vHPV immunogenicity trials, immunogenicity is 97.8% to 100% seropositive to all 9 types 1 month after last dose. Compared with 3 doses in 16 through 26 year olds, antibody titers were non-inferior and significantly higher 1 month after the last dose. After2-doses (0, 6 months or 0, 12 months) in the 9 through 14 year olds GMTs remained non-inferior and higher 6 months after the last dose. GMTs by interval between 2 doses in the 2-dose 0, 6 month group support a minimum interval of 5 months between the two doses. Follow-up of the 9vHPV 2-dose trial will continue through 36 months. As Dr. Kempe showed earlier, the FDA approved a 2-dose schedule for persons age 9 through 14 years on October 7, 2016. The label includes data from the 2-dose trial, as well as an updated Dosage and Administration section that states a 0, 6-12 month regimen and the minimum interval between doses.

ACIP also reviewed immunogenicity data on 2-dose vaccination schedules for 2vHPV and 4vHPV. As just discussed, in all trials, 2 doses at 0, 6 or 0, 12 months in those 9 through 14 years of age were non-inferior to 3 doses in older age group. These trials provide important information because there is longer follow-up than in the trial of the 9vHPV vaccine. While there are differences in the vaccines, these studies do provide relevant data on persistence of antibody after vaccination. The longest follow-up for the 2vHPV is 60 months, for 4vHPV is 36 months, and for 9vHPV vaccine is 12 months [Romanowski, *Hum Vaccin Immunother* 2016; Puthanakit, *JID* 2016; Lazcano-Ponce, *Vaccine* 2014; Dobson, *JAMA* 2013; Hernández-Ávila, *Hum Vaccin Immunother* 2016]. Another reason that these data were reviewed is that although 4vHPV will not be marketed in the US after October, many individuals have received 4vHPV in the US and some have not completed the 3-dose series. Recommendations will need to be

made for those individuals. Data from the 2vHPV and 4vHPV immunogenicity trials were included in the WG's GRADE evaluation.

Regarding the GMTs through 60 months of follow-up in one of the 2vHPV trials, for the group who received 2 doses on a 0, 6 month schedule at age 9 through 14 years and the group who received a 3 dose schedule at 15 through 25 years of age, the antibody kinetics were identical in the two groups with the peak titers 1 month after the last dose, a decline, and then plateau at about 18 to 24 months [Romanowski, *Hum Vaccin* 2016]. A similar curve of the antibody kinetics has been seen in all of the HPV vaccine trials.

GMTs through 36 months of follow-up in one of the 4vHPV trials was also shown. In this trial, there were 3 groups: a group that received a 0, 6 month schedule at 9 through 13 years of age, a group that received a 3-dose schedule at age 9 through 13 years of age and a group that received a 3-dose schedule at 16 through 26 years of age. The antibody kinetics were similar in the groups with the peak titers one month after the last dose, a decline, and then plateau at about 18 to 24 months. The 2-dose group remained higher than the 3-dose women [Adapted from: Dobson, JAMA 2013].

As discussed during past ACIP meetings, there are no data from RCTs trials of 2- vs 3-doses of HPV vaccines evaluating efficacy against infection or disease outcomes. For the 2vHPV, there are data from post-hoc analyses of a 3-dose efficacy trial. These were some of the first data that stimulated interest in reduced dose schedules. For the 4vHPV, data are available from analysis of an interrupted 2- vs 3-dose efficacy trial that was analyzed as an observational study. All of these analyses suggest efficacy with less than a 3-dose schedule [Kreimer, *Lancet Oncol* 2011; Kreimer, *JNC*I 2015; Sankaranarayanan, *Lancet Oncol* 2016; Markowitz, presented at February 2016 ACIP].

Post-licensure studies have been used to evaluate other vaccines; however, these types of studies are challenging for HPV vaccines at this point in the program. There are 10 published studies that have evaluated post-licensure effectiveness by number of doses in settings of a recommended 3-dose schedule for 2vHPV or 4vHPV. All of these found that 2 doses were not as effective as 3 doses. However, there are many limitations for post-licensure effectiveness studies at this time in the vaccination program. First of all, most 2-dose vaccinees had received vaccine at a 0, 1 month or a 0, 2 month interval since these studies were in the setting of a 3-dose recommendation. Persons who received only 2 doses differed from those completing the schedule. In some studies, they were older, of lower socioeconomic status (SES), and had earlier cervical cancer screening, suggesting differences in exposure to HPV prior to vaccination. One study evaluated different intervals between 2 doses, and found that effectiveness increased as the interval between doses increased [Herweijer, 2014; Dominiak-Felden 2015; Blomberg, 2015; Gertig, 2013; Crowe, 2014; Brotherton, 2015; Kavanagh, 2014; Cuschieri, 2016; Hofstetter, 2016; Pollock, 2014; Oliver, presented at June 2016 ACIP].

The WG's conclusion is that there are many challenges for vaccine effectiveness evaluations in the context of a 3-dose program. Data from these effectiveness studies may not be directly applicable to the currently policy question of a 2-dose recommendation due to differences in age at vaccination, the interval between the 2 doses, and differences in population in the populations receiving 2 doses and 3 doses in these studies. The WG did not include post-licensure effectiveness evaluations in its GRADE evaluation.

To examine different aspects of shifting to a 2-dose schedule, results were considered from health economic models. The model used was an individual-based transmission-dynamic model. This model takes into account the direct effects of vaccination, as well as herd immunity effects. This model uses a variety of inputs and includes 6 important components: demographics, sexual behavior and HPV transmission, natural history, vaccination, screening and treatment of cervical lesions and cervical cancer, and economics. The objective was to evaluate the population-level effectiveness and cost-effectiveness of a 3-dose versus 2-dose 9-valent vaccination program in the US.

To summarize the modeling results, the conclusions were that if efficacy and duration of protection after 2 doses are similar, 2 doses would be cost-saving compared with 3 doses. Exploration of important parameters showed that the incremental health benefits and cost-effectiveness of a 3rd dose of HPV vaccine depend most on relative duration of efficacy provided by a 2-dose versus 3-dose schedule. Vaccination is predicted to reduce HPV-burden of disease substantially after any schedule if protection is at least 20 years. A 2-dose vaccination program would provide similar population-level health benefits to 3-dose vaccination, unless 2 doses provide shorter duration of protection and do not enable higher vaccination coverage. A 3-dose vaccination program is predicted to have high incremental cost per Quality Adjusted Life Years (QALY) gained of over $118,000 compared to a 2-dose vaccination program, except when 2-dose protection is less than 20 years [Laprise, *JID* 2016; Brisson, presented at June 2016 ACIP].

Because duration of protection is found in the model to be the most important parameter influencing population impact, the WG reviewed data on duration of protection for HPV vaccines with the ACIP during the last meeting. Most of these data came from follow-up of clinical trials. In summary of what was presented to ACIP in June 2016, there is no evidence of waning protection after a 3-dose schedule to date. Data are available through about 10 years after the 2vHPV and 4vHPV became available. Longer follow-up, through about 14 years, is on-going in some of these studies. Antibody responses are maintained over time after a 3-dose schedule. Again, data are available for about 10 years for 2vHPV and 4vHPV. Longer follow-up, through 14 years, is on-going in some studies. Waning of detectable antibody to HPV 18 by competitive luminex immunoassay (cLIA) in 4vHPV v is not associated with loss of protection. For 2-dose schedules, long-term protection data are not available yet from 2-dose trials. However, antibody kinetics shown earlier are similar between 2-dose and 3-dose schedules with 2vHPV and 4vHPV , which suggests that duration of protection will be very similar for a 2-dose and 3-dose schedule [Markowitz, presented to June ACIP 2016].

Evidence was evaluated using GRADE and was presented to ACIP in June 2016. The main policy question was: “Should 2 doses of any HPV vaccine be recommended for 9 through 14 year-olds?” The population was girls and boys aged 9 through 14 years. The intervention was 2 doses of HPV vaccine separated by 6 to 12 months. The comparison was 3 doses of HPV vaccine at 0, 1–2, and 6 months among women in the age group in which efficacy has been demonstrated. The outcome was immunogenicity.

For the GRADE summary, for 2 doses of HPV vaccine in girls or boys aged 9 through 14 years compared with 3 doses of HPV vaccine in women about 15 through 26 years of age, the age group in which clinical efficacy was demonstrated, data were available on immunogenicity outcomes for 9vHPV vaccine from 1 study, 4vHPV from 2 studies, and 2vHPV from 4 studies. All of these studies found evidence of non-inferior immunogenicity with 2 doses. These were observational studies, because it was not possible to randomize participants in two different age groups. The overall evidence type is 3.

For the summary of considerations for formulating recommendations, if benefits are expected to be the same and the potential AEs are lower, the balance of benefits over harms is greater. Again, the evidence type for benefits was type 3. The workgroup placed a high value on programmatic considerations, as well as prevention of outcomes due to HPV vaccine types. A 2-dose schedule is likely to be cost-effective compared to 3 doses. The proposed recommendation is a Category A. The specific recommendation language follows in Dr. Meites' presentation.

Dr. Markowitz briefly mentioned some programmatic considerations. In terms of vaccine coverage from 2006-2015, in spite of HPV vaccine recommendations for females being published around the same time as those for Tdap and quadrivalent meningococcal conjugate vaccine (MenACWY), HPV vaccination coverage in females has increased at a comparatively slow pace. Coverage for at least 1 and 3 dose among females has reached 62% for 1 dose and 42% for 3 doses. Coverage among males began to increase after 2011 when the routine recommendation was made for males. In 2015, it was 50% for at least one dose and 28% for 3 doses [Reagan-Steiner *MMWR* 2016]. A variety of efforts are ongoing to increase coverage, and these have been reviewed with ACIP in the past.

It is unknown how a 2-dose recommendation would impact vaccination initiation or series completion in the US, although it is generally thought that a 2-dose schedule would be easier to implement and would be more acceptable. Many other countries have switched to a 2-dose schedule. Most of these have school-based vaccination and many already had high coverage, so information may not inform the situation in the US. In the US, a 2-dose 0, 6-12 month schedule would allow flexibility and vaccinations could coincide with preventive health care visits.

Examination of current coverage data can provide information on the impact of a potential change in recommendation on current coverage estimates, and also on the need for recommendations that address incomplete schedules. In terms of the percentage of girls and boys who received 3, 2, and 1 doses as determined in the 2015 National Immunization Survey-Teen (NIS-Teen), about 10% to 11% received only 2 doses and an additional 10% to 11% percent received only 1 dose. Recommendations will need to be made for these individuals as well. With regard to the interval in months between the first and second dose among teens who started the HPV vaccination series before age 15 years in the US, most received a second dose close to the recommended interval of 2 months in the current 3-dose schedule. These data include persons who completed a 3-dose schedule as well as those who did not. When looking at teens who completed only 2 doses, there is a slightly different picture. Among teens who received 2 doses only and the percent who received 2 doses only both at least 5 months apart and started the series before age 15, 10.6% of 13 through 17 year olds received only 2 doses, and 5.4% received only 2 doses at least 5 months apart and started the series before age 15 years [NIS-Teen, United States, 2015]. If ACIP votes to accept a 2-dose schedule, these individuals could be considered fully vaccinated, and the other 2-dose vaccinees would be recommended to receive a third dose in this age group.

In summary, although three HPV vaccines are licensed for use in the US, after the end of 2016 only 9vHPV will be available in the US. In October 2016, FDA approved 9vHPV as a 2-dose series for persons aged 9 through 14 years. During the past year, ACIP has been reviewing data related to 2-dose schedules, including immunogenicity, post-hoc analyses of efficacy trials, post-licensure effectiveness, health economic models, and duration of protection. Importantly, trials of all HPV vaccines found that the antibody response after 2 doses at 0, 6 months or 0, 12

months in 9 through 14 year olds is non-inferior to the response after 3 doses in the group in which efficacy was demonstrated. Post-licensure studies examining HPV vaccine effectiveness by number of doses are difficult to interpret at this time in the vaccination program. Data from follow-up of 3-dose vaccine trials show that duration of protection after HPV vaccination is long lasting. Data from follow-up of immunogenicity trials suggest that duration of protection will be the same after 2-dose and 3-dose schedules. ACIP used GRADE to evaluate evidence on 2-dose HPV vaccination schedules. The HPV Vaccines WG proposes a Category A recommendation for a 2-dose schedule for persons initiating the series at age 9 through 14 years. A 2-dose HPV vaccination schedule might facilitate vaccine initiation and series completion in the US.

Proposed Recommendations for 2-Dose HPV Vaccination

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Dr. Meites reminded everyone that three HPV vaccines are licensed for use in the US: 2vHPV, 4vHPV, and 9vHPV. Recently, on October 7th, 9vHPV was approved by the FDA for use in a 2-dose series for girls and boys at ages 9 through 14 years. The current ACIP recommendations are as follows:

- HPV vaccine is recommended for routine vaccination at age 11 or 12 years. The vaccination series can be started beginning at age 9 years.

- ACIP also recommends HPV vaccination for:
  - Females aged 13 through 26 years not vaccinated previously,
  - Males aged 13 through 21 years not vaccinated previously*
  - Immunocompromised persons (including those with HIV infection) and men who have sex with men through age 26 years, if not vaccinated previously

  * Males aged 22 through 26 years may be vaccinated

The rationale for the vote during this session is that HPV vaccines are highly effective and safe, and a powerful prevention tool for reducing the burden of HPV infections and associated disease; evidence suggests that a 2-dose schedule (administered at 0, and 6–12 months) will have efficacy equivalent to a 3-dose schedule (administered at 0, 1–2, and 6 months) if the HPV vaccination series is initiated before the 15th birthday.

Here is the outline of the proposed recommendations that would be included in a Policy Note:

- Routine and catch-up age groups (no changes)
- Dosing schedules
- Persons with prior vaccination
- Interrupted schedules
- Special populations
- Medical conditions
- Contraindications and precautions (no changes)
- Summary

No changes are proposed to the routine and catch-up age groups for HPV vaccination. Major additions are proposed to the sections on dosing schedules and persons with prior vaccination. Clarifying language is proposed for the sections on interrupted schedules, special populations, and medical conditions. For contraindications and precautions, no changes are proposed. The summary includes the proposed recommendation category.

The routine and catch-up age groups, for whom HPV vaccination is recommended, would not change. The text of this section would continue to emphasize that:

- ACIP recommends routine HPV vaccination for girls and boys at age 11 or 12 years. Vaccination can be given starting at age 9 years.

- ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not adequately vaccinated previously. Males aged 22 through 26 years may be vaccinated.

- Additional details will be presented in the sections on Special Populations, and Medical Conditions.

Beginning with the section on dosing schedules, underlined text indicates new information or changes to the current recommendations. Based on the evidence previously presented to ACIP on 2-dose immunogenicity, efficacy, cost-effectiveness, duration of protection, GRADE evaluation, and additional considerations, the proposed dosing schedules for HPV vaccination are:

- For persons initiating vaccination before the 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule).*

- For persons initiating vaccination on or after the 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).*

* See footnote defining minimum intervals

The next section with major changes is on evaluating persons with prior vaccination. This is a new section proposed to address questions about persons who have received any HPV vaccine in the past. The proposed text is:

- Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before the 15th birthday, and received 2 doses at the recommended dosing schedule, or 3 doses at the recommended dosing schedule, are considered adequately vaccinated.

- Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after the 15th birthday, and received 3 doses at the recommended dosing schedule, are considered adequately vaccinated.

In addition, this section could formalize current CDC supplemental guidance for vaccination providers which appears online at: www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf. This states that 9vHPV may be used to continue or complete a series started with 4vHPV or 2vHPV.

Furthermore, the workgroup would like to include an explicit statement that for persons who have been adequately vaccinated with 2vHPV or 4vHPV, there is currently no ACIP recommendation regarding additional vaccination with 9vHPV.

In the section on interrupted schedules, the following is proposed:

- If the vaccine schedule is interrupted, the vaccination series does not need to be restarted.

- Number of recommended doses is based on age at administration of the first dose.

Before presenting the proposed minimum intervals, Dr. Meites reviewed the current recommendations and evidence considered on this topic. In current guidelines, the minimum interval between the 1st and 3rd dose in a 3-dose series is given at 24 weeks, slightly less than 6 months. The WG noted that in both the new 2-dose and the original 3-dose trials of 9vHPV, doses given at a target 6-month interval were scheduled for 180 days after the first dose, which is equivalent to 26 weeks. However, participants were included if they received vaccine within 4 weeks of this target date, and many participants in the 2-dose trial did receive their second dose in this window. Therefore, the 9vHPV trial data support a minimum interval of 5 months, which is equivalent to 22 weeks. Furthermore, the updated FDA-approved label for 9vHPV vaccine states a minimum interval of 5 months between doses in a 2-dose series. For these reasons, the WG proposed that a footnote defining the minimum intervals include the following:

- In a 2-dose series of HPV vaccine, the minimum interval is 5 months between the first and second dose.

- In a 3-dose series of HPV vaccine, the minimum intervals are:
  1 month between the first and second doses,
  3 months between the second and third doses, and
  5 months between the first and third doses.

- A vaccine dose administered at a shorter interval should be re-administered at the recommended interval.

The section on special populations is largely unchanged. Currently, for children with a history of sexual abuse or assault, ACIP recommends routine HPV vaccination beginning at age 9 years. In addition, ACIP currently recommends an extended catch-up age range for MSM, and for immunocompromised persons. The WG proposed to add clarifying text to the current guidance that defines these populations more clearly.

To the current recommendation for MSM, the proposed clarification would add terms that are used elsewhere to recognize diversity in sexuality and gender identity and expression among men whose behavior may include sex with men. The proposed text is:

- For gay, bisexual, and other men who have sex with men (MSM), ACIP recommends routine HPV vaccination as for all adolescents, and initiation of vaccination through age 26 years for those who were not adequately vaccinated previously. For transgender persons, ACIP recommends HPV vaccination through age 26 years for those who were not adequately vaccinated previously.

For immunocompromised persons, the WG did not feel that a 2-dose schedule should be recommended for all types of immunocompromise. The purpose of this addition is to clarify which immunocompromising conditions should continue to receive 3 doses, based on expert opinion and consistent with the Infectious Disease Society of America (IDSA) clinical practice guidelines for vaccination of the immunocompromised host. The current recommendation with the full text of the proposed clarifying addition and footnote is:

- ACIP recommends HPV vaccination for immunocompromised females and males aged 9 through 26 years with three doses of HPV vaccine (0, 1–2, 6 months). Persons who should receive 3 doses are those with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy, since immune response to vaccination may be attenuated.*

  * The recommendation for a 3-dose schedule does not apply to children aged <15 years with asplenia, asthma, chronic granulomatous disease, chronic heart/liver/lung/renal disease, CNS anatomic barrier defects (e.g., cochlear implant), complement deficiency, diabetes, or sickle cell disease.

Finally, contraindications and precautions, including those related to pregnancy, are unchanged from previous recommendations. Standard language is included on the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by telephone (1-800-822-7967) or online (https://vaers.hhs.gov).

To summarize, the proposal is for ACIP to recommend a 2-dose schedule of HPV vaccine for girls and boys who initiate the vaccination series at ages 9 through 14 years. The proposed category is a Category A recommendation, for everyone in this age range. As discussed in this presentation, the WG proposed text for each of the sections shown here, for ACIP to consider:

- Routine and catch-up age groups (no changes)
- Dosing schedules
- Persons with prior vaccination
- Interrupted schedules
- Special populations
- Medical conditions
- Contraindications and precautions (no changes)
- Summary

In terms of next steps, the WG anticipates that a Policy Note could be published in the *MMWR* before the end of this year, and detailed methods and GRADE tables would be linked and posted online.

Discussion Points

Regarding the 6 to 12 month interval and how this may play out in the real world, Dr. Szilagyi pointed out that education for pediatricians and family physicians is important. He suspects that many practitioners will bring adolescents back at their next well-child visit. There is one complication with that in that some commercial insurance plans will not pay for a well-child visit if it is within 12 months. That does not include Medicaid or public health insurance, so he did

not know what percentage of the population that would include, but thought that it would be small but measurable. That means that many practitioners may bring their adolescents back at 13, 14, or 15 months.

Dr. Hunter asked about the current rates of 1-dose vaccination amongst 9 through 14 year olds, especially in comparison to whether that is higher than the current rates of 3-dose vaccination amongst 15 through 26 year olds to understand how much rates may bump up. Dr. Markowitz replied that those are not the age groups in NIS-Teen, but Dr. Wharton could provide additional information.

Dr. Messonnier added that there may be people who are not initiating the series because of the complicated schedule. While this question can be answered based on who is getting the vaccine now, the hope is that by simplifying the regimen, more people will access it and this will help providers make a stronger vaccine recommendation. Dr. Wharton indicated that reported in the most recent publication of NIS-Teen, was that 3-dose coverage in the 13 to 15 year old age group, which corresponds to the Healthy People 2020 target, coverage was pretty low at 27% coverage in males and 37% coverage in females. She emphasized the point that Dr. Messonnier made, that a recommendation for a 2-dose series at younger ages might very well result in better completion than with the current recommendation.

Ms. Pellegrini stressed that the 0, 2, 6 month schedule is very hard for families with teenagers. Going to the pediatrician 3 times in 6 months is very difficult. The more flexible schedule and wider interval proposed would allow for the next well-child visit, sports physical, or sick visit could make a real difference in increasing the completion rates in a timely fashion and in incentivizing families to begin the schedule. There are people who look at the 0, 2, 6 schedule and say they know they cannot do it and will not start it.

Dr. Lett (AIM) heard that ACIP would not be considering recommendations to change the wording of the age at which to begin HPV vaccine in this statement. She asked if there was any other permissive use language that could be considered including in the statement about starting the vaccination earlier.

Dr. Bennett emphasized that the goal for this session was to focus on the 2-dose schedule; however, the WG does intend to reassess the language around the recommended age parameters downward and upward (within the 9 through 26 year age range). That probably will be brought back at a later time.

Referring to Slide 9 regarding persons with prior vaccination, Dr. O'Leary (PIDS) thought the wording might be confusing. The statement in the first bullet might be interpreted by providers as the old recommended schedule of 2 doses at 0 and 1-2 months. He suggested specifying the number of months so providers understand whether it indicates the old schedule (0, 1-2, 6 months) versus the newly recommended schedule (0, 6-12 months).

Dr. Gemmill (NACI) reported that while Canada took a different route, they came to the same position in time. They went to a 2-dose schedule with the 4vHPV vaccine, and are now discussing for future consideration the same thing ACIP was discussing during this session. He thought he heard stated that anybody who had 2 or 3 doses with any vaccine is considered to be completely immunized. Inevitably, some people who have had 2vHPV+ or 4vHPV will want protection from the other types. He asked whether there would be a permissive recommendation that would allow for this and, if so, what it would be. Canada is struggling with this.

Dr. Meites replied that the current proposal includes the language that, for those who have been adequately vaccinated previously, there is no ACIP recommendation regarding additional vaccination with 9vHPV.

Referring to Slide 13 regarding minimal intervals, Dr. Walter pointed out that the third bullet may need further clarification: "A vaccine dose administered at a shorter interval should be re-administered at the recommended interval." For example, if someone gave a vaccine at 0 and 4 months, he would assume that would mean the next dose should be given at 5 months. However, someone might assume that this meant 6 from the dose given at 4 months.

Dr. Meites pointed out that the text on Slide 13 was abbreviated to avoid distracting from the main presentation, and explained that the full text of the footnotes (shown on Slide 27) would include full details about the recommended minimum intervals between each dose for both 2-dose and 3-dose schedules, along with guidance on re-administration of an early dose.

Dr. Hayes (ACNM) said she thought there was an International Classification of Diseases (ICD)-10 code so that a well-child visit does not have to be coded in order to give the vaccine. She said she loved the liberal language about recommended time frames for giving the vaccine, in that if the child presents late it can still be given. When administering the vaccine at family planning visits at the same time as giving Depo-Provera, her colleagues were unclear about whether a second dose of vaccine could be given a year later.

Dr. Messonnier pointed out that a number of complicated clinical decision issues could come from this policy change. CDC will try to work through all of those with the professional organizations. She requested that any questions be submitted to Dr. Wharton, and CDC will try to ensure that they are included in the massive health communication materials that CDC will develop to help clinicians work their way through this.

Referring to Slide 9, Dr. Hahn (CSTE) commented that someone she knows has had the first 2 doses at 2 months apart, and she suggested that it read "and received 2 doses at least 5 months apart" to be more clear.

Dr. Middleman (SAHM) read the following statement into the record: "Members from the Society for Adolescent Health and Medicine, including the Vaccination Committee and the President-elect and current President have significant concerns regarding the new policy's use of the labels "gay" and "bisexual" as proxies for behavior that places men 22 to 26 years of age at increased risk of HPV acquisition. Labels that characterize sexual orientation do not necessarily characterize behavior. If a behavior puts a person at greater risk for disease and greater need for vaccination, then it is more accurate to describe the specific behavior, for example "men who may have or have had sex with men." Men who identify as gay or bisexual may not engage in behaviors that place them at increased risk for HPV acquisition and conversely, men who do not identify as gay or bisexual may engage in sexual behaviors that place them at increased risk. Importantly, many HCP do not routinely screen their patients in great detail regarding sexual orientation or sexual behaviors. The evolving nature of sexual and gender expression makes generalizing with the use of labels obsolete and inaccurate. We potentially miss vaccinating many young men who should be protected against disease. Furthermore, we know from past experiences, as Dr. Schaffner noted earlier today, that targeting vaccination for specific groups has not been an effective public health strategy. The most inclusive and effective strategy to protect young men is to avoid assumptions based on generic labels. We recommend: 1) eliminate imprecise labels from vaccination

recommendations that falsely assume an equivalence between sexual orientation and risk behaviors, potentially resulting in missed opportunities for vaccination; and 2) update the recommendations for young men, hopefully at the next meeting, to include catch-up for all 22 to 26 year olds in order to protect all young men, including those whose behaviors defy labels, from the morbidity and mortality associated with HPV infection. We have an extremely effective vaccine that is more cost-effective than initially predicted. The number of vaccines distributed for 22 to 26 year old males is reportedly extremely low, implying poor uptake among this group of men. The goal for our young men at this point should be to use fewer labels, make fewer assumptions, have fewer restrictions, and strive to be more inclusive, immunize more men, and save more lives. Thank you."

Dr. Meites thanked Dr. Middleman for her commitment to this issue and her work with adolescent patients. She stressed that it certainly was the intent of the proposal to make the language inclusive of the populations who should receive vaccine. As far as the particular phrasing of the terms, she pointed out that these terms are widely used at CDC. She showed an assortment of websites from different CDC programs that focus on lesbian, gay, bisexual, and transgender (LGBT) health. She pointed out that the language included in the CDC fact sheet on "HPV in Men," under the heading "Can I get an HPV vaccine?" already specifically includes, "Gay, bisexual, and other men who have sex with men." Dr. Meites explained that the focus for this session was to propose formalizing the language already in use to describe the existing ACIP recommendation for MSM. As mentioned, the topic of recommendation language over the full age range for which HPV vaccine is licensed (i.e., for males ages 22 through 26 years) is a topic that the WG would like to continue discussing in the future.

Dr. Messonnier thanked the HPV WG and expressed appreciation for SAHM's concern, recognizing that SAHM is an incredibly important partner for this age group and on this vaccine. CDC wants to find a way to make this work. The WG came to this language as everyone heard, but outside of the bullet, there is clinical language that CDC uses in its health communication materials that derive from the kind of conversations they have, but the wording is not always exactly what is voted on. CDC commits to SAHM that the agency will engage with the experts who are putting out this information to try to find something that is acceptable to SAHM and also meets the purpose of the WG, which is actually to be more inclusive, not less inclusive.

Dr. Middleman (SAHM) expressed her appreciation, and said that SAHM appreciates the opportunity to contribute.

Dr. Bennett thanked Dr. Middleman for raising this important issue.

Referring to Slide 13 regarding minimum intervals, Dr. Wexler (IAC) pointed out that this was a divergence from how CDC usually writes recommendations for spacing minimum intervals. Usually, ACIP would say 4 weeks instead of 1 month and 12 weeks instead of 3 months. Language in the childhood schedule says, "For purposes of calculating intervals between doses, 4 weeks equals 28 days. Intervals of 4 months or greater are determined by calendar months." That is, 4 months is the cutoff for using month terminology.

Dr. Meites said it was also her understanding that these were used interchangeably. Since preferable, she expected the WG would be supportive of using the terms "4 weeks" and "12 weeks" rather than the terms "1 month" and "3 months."

Dr. Offit (Children's Hospital Philadelphia) said that while he understood that there was no additional recommendation for those who have completed either the 2vHPV or 4vHPV series, it was not clear to him why. There is a 9vHPV vaccine that will protect against an additional several thousand cases of cancer and presumably hundreds of deaths. One could argue that the best medical recommendation is for someone who has completed either 2vHPV or 4vHPV to get 2 doses of 9vHPV vaccine separated by at least 6 months. That would save lives. He asked whether the reason the WG was not making that recommendation was programmatic or financial. Dr. Markowitz replied that this had not been brought before the entire ACIP, and for a variety of reasons was not part of the earlier recommendations. However, the WG may revisit this discussion going forward.

Regarding Slide 15 on special populations, Dr. Thompson (NVAC) said she did not understand why there was different language used for these different populations of gay, bisexual, and other MSM and transgender individuals. The language in the slide differed in a way that did not make sense to her, and she wondered what the rationale was for the actual language on which the committee would be voting. That is, why was vaccination for all adolescents recommended for the first group but not the second? She also wondered about the language for proposed medical conditions in terms of what evidence there is about the 3-dose schedule in these special populations with respect to the timing. Is it better for these individuals to have the 0, 1-2, and 6 month schedule or 0, 6 to 12 month and then a booster later. If this is not known, she asked whether any research is being done to figure out the right timing for immunocompromised populations.

Dr. Meites replied that the language in the two sentences on Slide 15 originally was one sentence, and the WG revised it into two sentences for clarity. They certainly could repeat, "ACIP recommends routine HPV vaccine as for all adolescents" in the second sentence.

Dr. Cohn said that she wanted to make it clear that the proposed recommendation from the WG was solely about the 2 doses, and that all of the clinical guidance language they were seeing could be modified before publication of the *MMWR*.

Regarding Dr. Thompson's second question on the timing of the 3-dose regimen for those who are immunocompromised, Dr. Meites referred to Slide 28. She pointed out that it is known that HPV vaccines are non-infectious. The concern is that the immune response following vaccination may be attenuated in persons with certain immunocompromising conditions; that is, they might produce lower GMTs and antibody responses if their cell-mediated or humoral immune responses are reduced. As far as the timing of doses, she said she was not aware of any studies that have evaluated a 6 to 12 month schedule in immunocompromised patients. For these reasons, the standard 3-dose recommendation has been left in place for these persons as well as for those who initiate the vaccine series as an older teen.

Dr. Maldonado (AAP) indicated that COID met to discuss the proposed wording. COID strongly supports the 2-dose recommendation, taking into account the other issues that were brought up around operational issues, opportunities for missed second doses, et cetera. In particular, one of the areas that COID is concerned about and would recommend some thoughtful consideration is expanding to the larger age range for the purposes of including optimal vaccination periods for younger children.

Requesting that Slide 27 with the full footnotes for minimum intervals be redisplayed, Dr. Lett (AIM) asked if the proposed minimum interval was 4 months.

Dr. Meites indicated that this slide articulates the proposed minimum intervals and proposed language about what to do if a vaccine dose has been administered at an interval that was shorter than that. The proposal was, in a 2-dose schedule, "If the second dose is administered at a shorter interval, an additional dose should be administered at least 4 months later," and in a 3-dose schedule, "If a vaccine dose is administered at a shorter interval, it should be re-administered after another minimum interval."

Dr. Lett (AIM) emphasized that this would be important for individuals who had not had their vaccines on time.

Public Comments

Christina Hildebrand
A Voice For Choice Advocacy

I agree with dosing going down to 2. My concern, and I know this isn't your choice, but with the 9vHPV vaccine being the only one available, the increase in aluminum is double for every dose. That is a concern, and I wonder if the safety studies have been done surrounding the aluminum specifically and looking at things like premature ovarian failure and other adverse reactions that have been reported, and looking at the long-term. I know that the 2-dose brings it down, but it's still higher than the 3-doses of the initial 4- or 2-variant GARDASIL®.

Dr. Bennett thanked Ms. Hildebrand for her comments and referred her to the SMEs and CDC's vaccine safety personnel to discuss that issue.

Kristen Morelli
Richmond, Rhode Island
Submitted Via Email to be Included in the Record

I am deeply concerned about the safety, effectiveness, and necessity for the HPV vaccine for the following reasons.

- Concern was publicly raised about ovarian failure related to the HPV vaccine. This should not be ignored and further detailed studies should be done immediately, and prior to more vaccines being recommended.
- Advertising the HPV vaccine for cancer prevention should cease immediately. Not one study proves cancer prevention, it is an assumed result that does not have solid proof yet. This is extremely misleading to the public and does not permit proper informed consent.
- CDC should cease and desist on any form of advertising of any vaccines to the public. Vaccine manufacturers are free from liability when a vaccine causes a negative side effect. They benefit full profits of all vaccine sales. Our tax dollars and government agencies should not be paying to advertise a product that produces billions in profits for the manufacturer.
- Multiple countries are no longer recommending the HPV vaccine due to a high level of young adults having serious side effects of the vaccine. The CDC and ACIP need to take this seriously and show the US public that they do care about the youth, and will also do more follow up studies and further investigation of the HPV vaccine.

The fact that vaccine manufacturers are not liable in a similar fashion to all other pharmaceutical manufacturers is also a big concern for me. These ARE pharmaceuticals, being shot into the veins of small children. Testing should be as thorough as any other pharmaceutical.

Vote: 2-Dose HPV Vaccination Recommendations

Dr. Kempe motioned to approve the proposed 2-Dose HPV Vaccination Recommendations. Dr. Lee seconded the motion. The motion carried unanimously with 13 affirmative votes, 0 negative vote, and 1 abstention. The disposition of the vote was as follows:

13 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Stephens, Szilagyi, Walter
0 Opposed: N/A
1 Abstained: Romero (due to non-vaccine-related

VFC Resolution

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 resolution was to reflect the new dosing schedules for HPV vaccine. Eligible groups include all children 9 through 18 years of age. ACIP recommends routine HPV vaccination at age 11 or 12 years, and vaccination can be given starting at age 9 years. ACIP also recommends vaccination for females and males aged 13 through 18 years who were not adequately vaccinated previously. The table below summarizes the recommended number of HPV vaccine doses and schedule for specific groups of children:

Recommended number of doses	Recommended dosing schedule	Population
2	0, 6–12 months[1]	Persons initiating vaccination at age 9 through 14 years, except immunocompromised persons[2]
3	0, 1–2, 6 months[3]	Persons initiating vaccination at age 15 through 18 years, and immunocompromised persons[2] initiating vaccination at 9 through 18 years

Table Notes:
1. In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and the second dose.
2. Persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity.
3. In a 3-dose schedule of HPV vaccine, the minimum intervals are 1 month between the first and second dose, 3 months between the second and third dose, and 5 months between the first and third dose.

Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before the 15th birthday, and received 2 doses at the recommended dosing schedule, or 3 doses at the recommended dosing schedule, are considered adequately vaccinated. Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after the 15th birthday, and received 3 doses at the recommended dosing schedule, are considered adequately vaccinated. Vaccine doses administered at shorter than minimum intervals should be re-administered as recommended. 9vHPV may be used to continue or complete a series started with another HPV vaccine. If the vaccine schedule is interrupted, the series does not need to be restarted.

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 Hepatitis B 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.]

Vote: VFC Resolution for 2-Dose HPV Vaccination Recommendations

Ms. Pellegrini motioned to approve the VFC Resolution for the 2-Dose HPV Vaccination Recommendations. Dr. Walter seconded the motion. The motion carried unanimously with 13 affirmative votes, 0 negative vote, and 1 abstention. The disposition of the vote was as follows:

13 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Stephens, Szilagyi, Walter
0 Opposed:	N/A
1 Abstained:	Romero (due to non-vaccine-related funding support)

Meningococcal Vaccines

Introduction

David S. Stephens, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

Dr. Stephens reminded everyone that a revised dosing schedule was approved for Trumenba®, Pfizer Vaccines' MenB-FHbp vaccine. The dosing schedule was approved by FDA on April 14, 2016 to change the original language of the 3-dose schedule from 0, 2, and 6 month to 0, 1-2,

and 6 months and to approve a 2-dose schedule with administration at 0 and 6 months. The revised schedule indicates that the choice and dosing schedule may depend upon the risk of exposure and the patient's susceptibility to serogroup B meningococcal (MenB) disease.

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

- ❑ Impact of MenB-FHbp (Trumenba®) on meningococcal carriage
- ❑ Immunogenicity studies of two MenB vaccines in adults
- ❑ MenB-FHbp update
- ❑ Considerations for use of 2- and 3-dose schedules of MenB-FHbp
- ❑ ACIP and VFC votes anticipated

The policy options for 2- or 3-dose schedules of MenB-FHbp (Trumenba®) are:

- ❑ For persons at increased risk and for use during outbreaks:
  - ➢ Preference for 3-dose schedule (0, 1-2, 6 months)

- ❑ When given to healthy adolescents:
  - ➢ Preference for 2-dose schedule (0, 6 months)

OR

  - ➢ Option for 2- (0, 6 months) or 3-dose (0, 1-2, 6 months) schedule

OR

  - ➢ Preference for 3-dose schedule (0, 1-2, 6 months)

Additional WG activities include a Policy Note regarding the recommendations for use of meningococcal conjugate vaccines in HIV-infected persons, which is to be published in the *MMWR* on November 4, 2016. The WG is continuing to review additional data on MenB vaccines as it becomes available, and considering the issue of booster doses of MenB vaccine for persons at increased risk.

Impact of MenB-FHbp (Trumenba®) on Meningococcal Carriage

Heidi M. Soeters, PhD, MPH
Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Soeters discussed a meningococcal carriage evaluation conducted in response to a serogroup B meningococcal disease outbreak and the resulting mass vaccination campaign that occurred at a college in Rhode Island.

In terms of background and context, meningococcal disease most commonly takes the form of meningitis or bacteremia. It often starts with influenza-like symptoms but can progress within hours to a serious illness that can include high fever, severe headache, stiff neck, confusion, and a purpuric rash. This disease has a 10% to 15% case-fatality ratio, even with appropriate antibiotic treatment. Of survivors, 11% to 19% have permanent sequelae, such as cognitive deficits or amputations due to necrosis of the extremities. Meningococcal disease is caused by

the bacterium *Neisseria meningitidis*, which is a gram-negative diplococcus. Invasive meningococci generally have a polysaccharide capsule surrounding the cell, which confers the serogroup. Of the 12 different serogroups of meningococci that have been identified, only 6 primarily cause invasive disease.

Traditionally, meningococcal vaccines are based on the capsular polysaccharide that is specific to each serogroup. Therefore, the resulting protection is serogroup-specific. There are polysaccharide vaccines composed of purified capsular polysaccharide. Formulations include monovalent A, monovalent C, bivalent A-C, and quadrivalent A-C-W-Y. There also are conjugate vaccines, where the capsular polysaccharides are conjugated to proteins, such as tetanus or diphtheria toxoids. These vaccines achieve similar or greater immunogenicity and duration of protection than polysaccharide vaccines, and are formulated as monovalent A, monovalent C, or quadrivalent A-C-W-Y. The conjugate quadrivalent ACWY, or MenACWY, vaccine is routinely recommended for adolescents in the US. This same approach of basing a vaccine on the capsular polysaccharides has not worked for serogroup B, because the serogroup B polysaccharide antigen is similar to human antigens, leading to poor immunogenicity and concerns about potential autoimmunity.

As a result, serogroup B, or MenB, vaccines have to take a different approach and focus on outer membrane proteins. These antigens have multiple alleles and variable expression in different strains of the bacteria. Not all serogroup B bacteria will express the antigens that are present in a particular vaccine, and the serogroup B polysaccharide capsule, which is required for virulence, is not contained in MenB vaccines. Unlike vaccines for other meningococcal serogroups, MenB vaccines are not expected to be protective against all serogroup B strains in circulation. Also, since they are based on outer membrane proteins, and not on the serogroup-specific capsule, they may help protect against other serogroups as well.

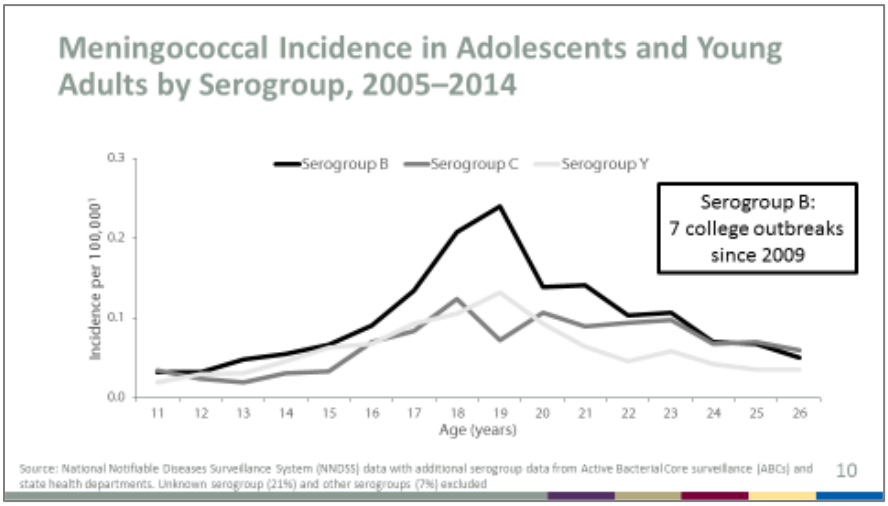
There are two MenB vaccines licensed in the US: MenB-FHbp (Trumenba®) and MenB-4C (Bexsero®). MenB-FHbp is a 2-component vaccine, containing a FHbp variant from each subfamily A and B. It is given in 2 or 3 doses. Bexsero® is a 4-component vaccine, containing NadA, a FHbp from subfamily B, NHBA, and porA and is given in 2 doses.

In terms of transmission, meningococcal bacteria are carried in the human nasopharynx, and most carriers remain completely asymptomatic. Less than 1% of persons exposed to the organism develop invasive disease. The bacteria are spread through close contact, specifically via respiratory or oral secretions from patients or asymptomatic carriers. Important risk factors for both disease and carriage among adolescents include age[1,2], social mixing[3], and smoking[1]. As the majority of transmission is thought to be attributable to asymptomatic carriers, decreasing carriage is the main way to provide herd immunity against meningococcal disease [[1]Harrison et al. *JID* 2014. (US); [2]Jeppesen et al. *J Infect* 2015. (UK); and [3]Mandel et al. *JID* 2013. (US)].

Looking at what we know about vaccine impact on meningococcal carriage, in the United Kingdom (UK), vaccines targeting serogroup C were shown to decrease nasopharyngeal carriage of serogroup C by 66% one year post-vaccination, thereby decreasing transmission and providing herd protection[1]. MenA conjugate vaccine nearly eliminated serogroup A carriage[2,3]. The understanding of MenB vaccine impact on carriage is currently limited. The only previous study was conducted using MenB-4C, and found an 18% reduction in carriage of any meningococcal bacteria, and no effect specifically on serogroup B carriage by 3 months after completion of the 2-dose series[4]. To date, no data has been published regarding the effect

of MenB-FHbp on carriage [[1]Maiden et al. *Lancet* (2002); [2] Daugla et al. *Lancet* (2014); [3] Kristiansen et al. *CID* (2013); [4]Read et al. *Lancet* (2014)].

In the US, 3 serogroups (B, C, and Y) are the primary causes of meningococcal disease. This graph shows the incidence of these serogroups in adolescents and young adults following the introduction of conjugate MenACWY vaccine in 2005:



While incidence of all serogroups is low, serogroup B (in black) is the leading cause of meningococcal disease in this age group. In fact, serogroup B caused 7 outbreaks on college campuses since 2009, resulting in 41 cases and 3 deaths [Source: NNDSS data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments. Unknown serogroup (21%) and other serogroups (7%) excluded].

To provide some background on this particular outbreak at Providence College in Rhode Island, 2 cases of serogroup B occurred in undergraduate students on January 31 and February 5, 2015. The cases resided in different dormitories and had no known epidemiologic links. Both were determined to have a rare sequence type, ST-9069, never before seen in the US. Both case-patients survived. These 2 cases among a population of 4500 students indicated an attack rate of 44 cases per 100,000, nearly 500 times higher than the national incidence among persons aged 17 through 22 years. In response to the outbreak, Providence College rapidly implemented a mass vaccination campaign using MenB-FHbp. The three doses were provided in February, April, and September of 2015, with remarkably high vaccination coverage of 94% with the first dose, 80% with the second, and 77% with the third. Incoming freshman in the fall of 2015 also were offered to begin the series.

CDC incorporated a meningococcal carriage evaluation into this vaccination campaign. It had 2 objectives, which were to: 1) determine the baseline prevalence of nasopharyngeal carriage of *Neisseria meningitidis*, and 2) assess the impact of MenB-FHbp vaccination on carriage. The evaluation consisted of a short questionnaire assessing risk factors for meningococcal carriage and disease, followed by an oropharyngeal swab. All undergraduate students at Providence College and graduate students who lived on campus were eligible to participate. Specimens were evaluated using culture, slide agglutination, real-time polymerase chain reaction (rt-PCR), and whole genome sequencing.

As mentioned, 2 methods were used to determine the serogroup of each isolate: rt-PCR and slide agglutination. PCR is a genotypic test that detects the presence of capsule biosynthesis genes for each serogroup, regardless of whether they are expressed. PCR can detect serogroups A, B, C, W, X, and Y and any specimen that does not contain the genes for one of these serogroup capsules is considered non-groupable. Slide agglutination, on the other hand, is a phenotypic test which uses antiserum to look for expression of each serogroup, and can detect the same 6 serogroups as PCR, in addition to serogroups E and Z, which rarely cause invasive disease. Any specimen that does not clump with the antiserum for any of the serogroups is considered non-groupable according to slide agglutination. Meningococcal bacteria can possess the genes for a serogroup but not be expressing them in their current environment, which would produce discordant results according to these 2 methods. Therefore, both methods were used in conjunction to get a more precise picture of meningococcal dynamics in this setting.

Additionally, meningococcal vaccination records were abstracted for each participant, recording the doses and dates of previous MenACWY or MenB vaccination. This process was repeated 4 times, resulting in 4 cross-sectional snapshots of carriage on-campus. Round 1 occurred in February 2015, the week after the outbreak and dose 1 clinics. Round 2 occurred in conjunction with dose 2 in April. Round 3 occurred in September, as upperclassmen received dose 3 and incoming freshmen received dose 1. Round 4 occurred one year post-outbreak, including fully vaccinated upperclassmen and freshmen receiving dose 3.

For analysis, descriptive statistics were performed on participant characteristics. The proportion of students were assessed in terms of overall meningococcal carriage and specifically serogroup B carriage, and how this changed over time. Prevalence ratios were estimated using general estimating equation methods for repeated measures. Finally, as a number of students participated in multiple rounds, within-individual changes in carriage over time are being examined.

The number of participants in each round ranged from 622 to 878. In total, 2843 swabs were collected from 2014 unique individuals. This table shows participant characteristics across the 4 rounds:

Carriage Evaluation Participant Characteristics

Characteristic	Round 1: Feb '15, N (%)	Round 2: Apr '15, N (%)	Round 3: Sept '15, N (%)	Round 4: Mar '16, N (%)
Graduation Year				
2019	0 (0)	0 (0)	50 (8)[1]	322 (51)[1]
2018	192 (27)	239 (27)	204 (33)	99 (16)
2017	283 (39)	250 (28)	134 (22)	97 (16)
2016	118 (16)	192 (22)	198 (32)	106 (17)
2015	121 (17)	194 (22)	27 (4)[2]	0 (0)[2]
Graduate Student	3 (0.4)	3 (0.3)	9 (2)	2 (0.3)
Live on campus	655 (91)	734 (84)	452 (73)	557 (89)

[1]Incoming freshmen; [2]Graduated seniors

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Note that as the evaluation took place across 2 academic school years, the class of 2019 was only included in rounds 3 and 4. The proportion of participants who lived on campus was high, but varied each round. Of the participants, 34% to 42% were male. Recent antibiotic use and recent upper respiratory symptoms were both highest during round 1, which took place during the winter. A high proportion of students smoked or had second-hand smoke exposure. Social mixing was common, as 67% to 74% of students reported visiting bars, clubs, or parties at least once per week.

Also assessed were meningococcal vaccine doses received at least 2 weeks prior to specimen collection, to allow time to mount an immune response. A high proportion of students had documented MenACWY vaccine, which generally was received the summer before college entry. In round 1, no students had received MenB-FHbp more than 2 weeks prior. In round 2, most participants had received 1 dose. In round 3, most had received 2 doses. In round 4, the majority had received either 2 or 3 doses.

In terms of overall meningococcal and serogroup B carriage, in round 1, 24% of participants were carrying *Neisseria meningitidis*. This proportion remained fairly stable over the next year, with 24% carriage in round 2, 20% carriage in round 3, and 21% carriage in round 4. When looking at serogroup B carriage, 4% of participants carried serogroup B by PCR in each of the 4 rounds. By slide agglutination, just over 1% of students were carrying bacteria that express the serogroup B capsule in each round.

Regarding serogroup results by PCR over time, as with previous meningococcal carriage studies, most isolates were non-groupable, meaning the bacteria are unencapsulated and therefore better adapted for colonizing the nasopharynx. Serogroup B was the most common, and a handful of serogroups C, Y, W, and X were detected in each round. The majority of isolates were non-groupable according to slide agglutination as well. With respect to the groupable isolates, serogroup B was the most commonly expressed capsule, though serogroup E increased over time and a handful of isolates expressed serogroups X, Y, C, and Z as well.

Next, associations with carriage of any meningococcal bacteria were examined. As compared with round 1, there was no difference for rounds 2 or 4, but round 3 had a slight association with decreased carriage. In comparison to the class of 2018, who were freshmen during outbreak, the class of 2017 had the highest carriage prevalence. Male sex, smoking, and partying at least once per week were associated with increased carriage. Recent antibiotic use was associated with decreased carriage. Receipt of 1, 2, or 3 MenB-FHbp vaccine doses was not significantly associated with carriage.

When the same models were repeated with the outcome of serogroup B carriage by PCR instead of any meningococcal carriage, very similar associations were observed. During the evaluation, only 1 individual was found to be carrying the outbreak strain. This individual participated only in rounds 2 and 3, and was carrying this strain during both rounds. The carried strain was serogroup B by PCR, but was non-groupable by slide agglutination. Whole genome sequencing (WGS) revealed that this was due to phase-variation in the capsule locus, meaning the bacteria were temporarily not expressing the capsule. It is unclear whether this change in expression occurred in vivo or after the specimen was collected and cultured.

In total, 615 students participated in multiple carriage evaluation rounds. Of these students, 71% were not carrying any meningococcal bacteria during any round; 14% were consistently carrying meningococcal bacteria during each round in which they participated, though not necessarily the same strain or serogroup; 8% were carrying meningococcal bacteria during one

round, but then were not carrying any meningococci during a later round; and 7% did not have carriage, but then acquired carriage that was detected during a later round.

Of the 50 students who lost meningococcal carriage, 13 lost carriage after one MenB-FHbp dose, 32 after two doses, and 5 after three doses. Of the students, 45 acquired meningococcal carriage (20 after one dose, 16 after two doses, and 9 after three doses). Looking at serogroup B, 11 students lost serogroup B carriage (2 after one dose, 8 after two doses, and 1 after three doses), and 10 students acquired serogroup B carriage (3 after one dose, 4 after two doses, and 3 after three doses).

In conclusion, in each round, 20% to 24% of students carried meningococcal bacteria and 4% specifically carried serogroup B by PCR. This overall carriage prevalence is comparable to previously reported prevalences of up to 34% among university students in the UK. However, the observed carriage prevalence was quite a bit higher than recent US estimates of 1% to 8% among the general population. Despite this high carriage prevalence, only 1 carrier of the outbreak strain was identified and no further serogroup B cases associated with the college have occurred. No evidence was found that MenB-FHbp vaccination impacts carriage, at either the population or individual level.

These results help inform US MenB vaccine guidelines, both for use in adolescents and young adults, and specifically in outbreak settings. Also, if MenB vaccines do not appear to affect carriage and therefore provide some herd immunity, this reinforces the need for high vaccination coverage during outbreaks to protect each individual and emphasizes the role of chemoprophylaxis for close contacts. WGS is underway to further characterize the isolates, compare carriage versus invasive isolates, examine within-individual longitudinal data, and investigate MenB vaccine antigens among the carriage isolates. Additionally, concurrent meningococcal carriage evaluations were conducted at two other universities, and the findings will be compared from all 3 evaluations once they are complete.

Immunogenicity Studies of Two MenB Vaccines in Adults

Dan Granoff, MD, FPIDS
Center for Immunobiology and Vaccine Development
UCSF Benioff Children's Hospital Oakland

Dr. Granoff noted that Men A, C, Y and W capsular based vaccines have minimal antigenic variability within a capsular group. For disease-causing MenB strains, protein antigens have large variability in amino acid sequence and expression, which can affect susceptibility to serum bactericidal activity. For MenB vaccine licensure, efficacy was inferred based on data against a limited number of reference strains. Gaps in knowledge include the extent of protection against more diverse disease-causing strains, as well as the effect of vaccination schedules (2 doses versus 3 doses), and duration of protection.

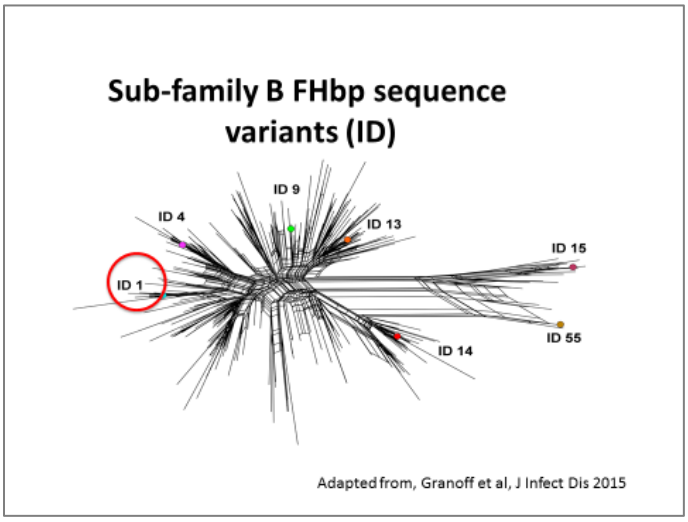
During this session, Dr. Granoff discussed the results from three MenB immunogenicity studies in adults. These studies were not designed to provide comparison data between vaccines. Each study tested one vaccine. The studies were performed independent of industry. Dr. Granoff pointed out that he has no relevant potential conflicts of interest other than being the inventor on patents related to meningococcal vaccines.

Dr. Granoff began by sharing the conclusions so that everyone could be thinking about them while he described the studies. One month post-dose 2, both vaccines elicited protective bactericidal antibody (titers ≥1:4) against most strains. Some strains are relatively resistant to bactericidal activity despite prediction of susceptibility by sequence analysis and antigen expression. After dose 2, titers can decline within 4 to 6 months, especially for strains with low antigen expression.

Study 1 was of MenB-4C (BEXSERO®) to assess immunogenicity in adults. There were two studies sites: Oxford Vaccine Clinic, UK (N=15) and University of California, San Francisco (UCSF) Benioff Children's Hospital Oakland (N=5). The median age was 29. Of the participants, 12 (60%) were healthcare or laboratory workers. Participants received 2 doses on either a 0,1 or 0, 2 schedule. As noted earlier, MenB-4C vaccine contains four components that are largely responsible for bactericidal antibody: FHbp (sub-family B), NHba, NadA, and PorA (P1.4). A reference strain for FHbp would be considered one that was absent of NadA, PorA that did not have P1.4, and low expression of NHba. This would allow for inference that most of the bactericidal antibody was directed at FHbp.

Regarding data on ≥4-fold increases in serum bactericidal antibody titer to MenB-4C, the titer one month post-dose 2 is divided by the pre-titer. So, if the subject had a titer of 16 one month after 2 doses and a titer of 4 before, that would be a 4-fold increase. Data from two studies conducted by the manufacturer for vaccine licensure that are included in the FDA package insert, were compared to results from Study 1 for the three reference strains. The Study 1 data are very comparable to the data provided in the package insert. Of the subjects, 95% to 100% are achieving 4-fold increases to the FHbp strain and NadA strain, and about 70% to the PorA strain. This is very similar to Study 2 and is higher than the manufacturer.

In real life, there is a lot of sequence variability as illustrated by this image:



Each of the FHbp variants can be given a different identification number (ID). The MenB-4C vaccine contains ID 1. The closer a variant is in the tree to the MenB-4C vaccine variant (ID 1) indicates the variant has a similar sequence to the vaccine variant. But they all are within the same FHbp family and predicted to be covered by the vaccine.

Serum bactericidal antibody responses to a number of strains were assessed that were largely from outbreaks of disease on college campuses in the US (UC Santa Barbara, Providence College, Ohio University, Santa Clara University, and Princeton University) and two strains from Quebec where there has been hyperendemic disease for a number of years. First, serum bactericidal antibody responses of healthy adults immunized with 2 doses of MenB-4C were presented for FHbp sub-family B containing strains. Dr. Granoff noted that the strains also had other antigens in the vaccine present. Although all strains had at least 2 antigens and some had 3, the 4-fold increases were very similar to the reference strain, which had an FHbp that was an exact match with ID 1 that is contained in the MenB-4C vaccine. The 4-fold increases were much lower with strains that had other FHbp variants [Giuntini et al, *Clin Vac Immunol* 2016, in press]. Dr. Granoff emphasized that a 4-fold response is a measure of a robust response; however, it does not indicate whether the individual is protected. He indicated that he would show some data from the Quebec strain where there was 35% 4-fold rise, and most of the persons at 1 month post-dose 2 actually had protective titers. So, there are really two different measures. His working model is that the portion with 1:4 or greater is a good measure of short-term protection; whereas, the 4-fold response gives a sense of the magnitude of the response and is likely to correlate with duration of protection. Again, this is a model.

In terms of the data for the same sera looking at a group of strains from FHbp sub-family A, the FHbp was mismatched and depended on the other antigens in the MenB-4C vaccine (NHba and NadA). The serum bactericidal antibody responses of adults immunized with 2 doses of MenB-4C were pretty uniform, even for the strain that was mismatched for all 4 antigens, with around 30% to 40% 4-fold increases in bactericidal titer.

Study 2 was of MenB-FHbp (Trumenba®) to assess immunogenicity in adults. There were two study sites: UCSF Benioff Children's Hospital Oakland (N=12) and University of Massachusetts Medical Center (N=5). The median age was 40. Of the subjects, 100% (N=17) were healthcare or laboratory workers. Three doses were used at the recommended schedule (0, 2, 6). There are two FHbp antigens in this vaccine, sub-family A and B. The Pfizer nomenclature is BO1, which is ID 55 and AO5 for the sub-family A, which is ID 45. There is a relationship to a number of the other variants, which were contained in the strains that were tested.

In terms of the serum bactericidal antibody responses of adults immunized with MenB-FHbp on a 2-dose (0,2) schedule, for many of the sub-family A strains more than 70% of subjects had ≥4-fold increases in hSBA titers [Lujan et al, *IPNC* 2016]. With the MenB-4C vaccine, 40% of subjects had ≥4-fold increases in hSBA titers for sub-family A strains. Dr. Granoff noted that they do not actually have the Pfizer reference strains in their laboratory to test, and that he was showing the data from the package insert. He has found similar responses for the 2 doses of this vaccine to the two sub-family A strains that were used by Pfizer.

With MenB-FHbp, a third dose is given at 6 months. In terms of the data showing the 4-fold responses after 2 doses and 3 doses, the 3-dose data is one month post-dose 3 compared to the pre-titer. With the third dose, there was a significant increase for many of the subjects and strains, with most having 80% to 90% 4-fold increases [Lujan et al, *IPNC* 2016]. Again, Dr. Granoff's data are similar to what were reported for sub-family A.

For sub-family B, Dr. Granoff showed data for 2 doses at the 0, 2 schedule. There was quite a lot of variability. A mutant strain, H4476, was included. This is a low expressing mutant, with about 50% lower expression than in a wild type. Having lower expression affects the ability of the antibodies elicited by the vaccine to result in a robust bactericidal response. The results with the two doses of MenB-FHbp vaccine administered at 0,2 months were within in the same

range as the MenB-4C vaccine. The Pfizer data were very similar to what were reported for the sub-family B strains. Giving a third dose of MenB-FHbp vaccine at 6 months results in significant increases for many of the strains, with almost all being over 70% 4-fold [Lujan et al, *IPNC* 2016]. Again, the data are quite similar to what was reported.

Turning to comparative bactericidal titers for a representative strain from Quebec, Dr. Granoff pointed out that persons who are likely to benefit most from vaccination are those who have titers of <1:4 before vaccination with MenB-4C. Out of a group of 20 subjects, 14 had titers <4. Although most of them did not achieve 4-fold response, 11 of 13 had protective titers after dose 2. A small number of subjects had samples obtained 4 months post-dose 2, and they tended to decline. Individuals with low titers tend to decline to below 1:4. The results were very similar for MenB-FHbp. After 2 doses, 13 of 16 had titers of 1:4 or greater and then there was a decline in titers. After a third dose of MenB-FHbp, 11 of 12 subjects had a boost in protective titers. There are no follow-up sera on these at this point [Quebec 2013, Hyperendemic].

Study 3 assessed immunogenicity among students from Santa Clara University who received MenB-4C. Between January 31 through February 3, 2016, there were 3 cases (2 culture-confirmed and 1 suspect) at Santa Clara University caused by a strain that was in the ST 32 clonal complex. Within a few days, MenB-4C vaccination clinics were organized at the university. From February 4-8, the first dose of vaccine was administered to 4921 persons. The vaccine was administered on March 18 and April 6-8 to 4731 persons, most of whom were receiving a second dose. Sera were collected May 23-25 from 246 students (0 dose, N=52; 1 dose, N=91; and 2 doses, N=101).

Serum bactericidal was measured against the three college outbreak strains from Santa Clara, Princeton, and Ohio Universities. Santa Clara University students were immunized with MenB-4C; that strain was positive for three MenB-4C antigens: FHbp subfamily B (ID 510), NadA, and NHba. Protective titers of ≥1:4 were 92% post-dose 2 and 66% post-dose 1. Interestingly against this strain, about 40% already had protective titers before vaccination and 20% had high titers [Interim analysis of results on 160 sera by Dr. Qin Liu, Wistar Institute, Philadelphia].

The investigators also evaluated the strain causing the outbreak at Princeton University where there were 9 cases and 1 death. This strain expressed two MenB-4C antigens: FHbp subfamily B and NHba. A previous study showed that 66% of the students immunized with 2 doses of MenB-4C had developed protective serum bactericidal titers ≥1:4 [Basta et al, *NEJM* 2016].

Looking at the Santa Clara University sera against the Princeton strain, the prevalence of background antibody was much lower with almost nobody having a titer of ≥1:16. There was a significant increase in serum bactericidal activity after 1 dose. After 2 doses, 69% had titers of 1:4 or greater. So the investigators actually replicated the data from Basta at Princeton University, indicating that the strain is relatively resistant, especially when compared to the 92% protective titers against the Santa Clara University strain.

Finally, they looked at an outbreak strain from Ohio University where there had been 13 cases and 1 death for the outbreak strain that expressed of three MenB-4C antigens: FHbp subfamily B (ID 15), NadA, and NHba. Looking at the data again from the interim results, the background level of antibody was very low in the Santa Clara students against this strain. After 2 doses, approximately 52% had titers of 1:4 or greater and about 10% had titers of greater than 1:16 despite the fact that there was a match in the antigen and expression of MenB-4C FHbp, NadA, and NHba.

To conclude about these vaccines, first of all, they are complex. At least 4 antigens are capable of eliciting serum bactericidal activity. The antigen-specific reference strains that were used for licensure are more susceptible to vaccine-induced bactericidal antibodies than many circulating disease-causing strains. Some strains are relatively resistant to bactericidal activity despite prediction of susceptibility by sequence analysis and antigen expression, such as the Princeton University and Ohio University strains. The great majority of subjects have titers of ≥1:4 at 1 month post-dose 2 against most strains. Titers decline by 4 to 6 months, especially against low FHbp-expressing strains.

For the MenB-FHbp, Dr. Granoff said he thought the 2-injection data were the most interesting because they basically saw very similar or higher ≥4-fold increases in serum bactericidal activity as MenB-4C at 1 month post-dose 2. The great majority of subjects, had titers of ≥1:4 at 1 month post-dose 2 against most strains. Titers decline by 4 months, especially against low FHbp-expressing strains. The recommended third dose of MenB-FHbp at 6 months boosted titers. Additional data on antibody persistence are needed, which should include strains relatively resistant to vaccine-induced bactericidal activity to get a sense of the variability on antibody persistence.

In terms of the limitations, these were independent studies that were not designed to provide comparison data between vaccines, and the populations are different. There are relatively few sera 4 to 6 months post-dose 2. That was added at the end of the protocol and it was not possible to get everybody. The serum bactericidal assays used research assays and were not the type that would be FDA-validated, although the assays are robust. The data on the Santa Clara University study are on antibody prevalence. They do not have pre-vaccination sera, but it is possible to compare the 0 dose to the 1 doses and 2 doses. Dr. Granoff emphasized that this is an interim analysis that requires much more work.

Discussion Points

Rino Rappuoli (GSK) commented that it is important to keep in mind that Bexsero® has 4 different components targeting completely different antigens, and each of them can kill the same bacteria. He noticed that in the Trumenba® between 2 and 3 doses, there was a pretty good increase in immunogenicity and coverage. That is more or less what has been observed with Bexsero® between 1 and 2 doses. Bexsero® was licensed as a 2-dose vaccine after multiple studies. In one case during the Phase 3 trials, they also did 3 doses and did not see that kind of increase. So, it looks like Bexsero® increases between 1 and 2 and Trumenba® increases between 2 and 3 doses. Also important to remember is that while the 4-fold increase is a way to look at the longevity of protection, that may underestimate the number of protected people because many people may have a protective titer above 1:4 by bacterial assay and still not have a 4-fold increase. Obviously, all of the serological findings are important, but they are always a surrogate for real data in the field. That is what has been missing during the development of vaccines for so long. In the case of Bexsero®, there are two types of data. One comes from multiple uses in outbreaks in the US and Canada where 2 doses have been used in many instances. There have not been breakthrough cases, which is very important to remember. Second, are the data from the UK where Bexsero® is being used in infants to vaccinate all of the newborns beginning September 2015. Two doses were used in infants. Infants are completely naïve to meningococcus, so they are more difficult to protect than adolescents. With 2 doses, Public Health England (PHE) reported effectiveness of 83% a month ago in a meeting in Manchester. Basically with Bexsero®, there is extremely high effectiveness in the field in a very difficult population.

Dr. Walter said he noticed from Dr. Soeters' presentation that the coverage for vaccination declined from 94% for the first dose to about 80% to 77% for the second and third doses respectively in the campaign. He asked whether there was any sense for why that was, in terms of whether it was that people were concerned at the start of the campaign about disease, or if it was due to concern about side effects.

Dr. Soeters responded that overall, a drop-off has been observed in MenB vaccine campaigns at a lot of the colleges that have had outbreaks. In this particular case, the school did something unusual, which was that they required all students to come to the vaccination clinics and they could sign declination forms that they did not want a vaccine. That is how they achieved high coverage during the first round. They did continue to require it, but students seem to have caught on that if they did not appear, nothing happened to them. A lot of the students experienced and mentioned sore arms, but she did not hear students saying that that was a reason they did not return for vaccination. Other surveys are being conducted to gather more information about students' opinions about the vaccine and what was influencing their decision to get vaccinated or not.

Dr. Friedland (GSK) congratulated the Rhode Island meningococcal carriage group for undertaking such an important study. Certainly, the evaluation of the impact of the meningococcal B vaccines Trumenba® and Bexsero® on carriage is very important. GSK is committed to continue to evaluate the impact of Bexsero® on carriage, and is in the final stages of finalizing the protocol to evaluate the impact of Bexsero® on carriage in over 30,000 individuals that will be powered to detect even small differences in carriage. GSK thinks this is very important, and looks forward to sharing these data with ACIP as they become available.

Dr. Belongia requested clarification about the titer of 1:4 as a protective titer and the basis for using that as a correlate of protection.

Dr. Granoff responded that it went back to a Goldschneider study in the 1960s published in the *Journal of Experimental Medicine* (*JEM*) in which they looked at military recruits. They collected serum samples at the time recruits began training. There was a serogroup C outbreak, and quite a few cases occurred over the next few months. Then they retrospectively collected sera from the people who got disease and had a sample of about 500 sera for people who did not get disease. A titer of 1:4 or greater essentially offered about 90% to 95% protection against developing serogroup C disease. Almost all of the cases were among people who lacked titers. There also was a carriage study going on, and they detected about 30 carriers. About a third of those actually went on to get disease. This was serogroup C, and this was natural antibody. It was not vaccine. Having a titer of 1:4 really correlated with protection. Suffice it to say that collectively, the data are pretty convincing that a titer of 1:4 does predict protection. A titer of less than 4 does not necessarily mean that someone is susceptible, but was associated with all of those cases. This has been accepted by regulatory authorities all over the world, including the FDA as the basis of licensure. These vaccines were not tested in efficacy studies. They used the 1:4 and the 4-fold composite to look at the immune responses, and that was the basis of deciding vaccination schedules and inferring efficacy for the vaccine.

Dr. Paradiso (Paradiso Biologics Consulting) pointed out that when looking at bacterial carriage in the nasopharynx, it is generally considered that clearing bacteria is totally different than affecting acquisition of new bacteria. Often in carriage studies, it is looking at blocking the acquisition of new bacteria. He noted that those were separated out in the carriage study, but the numbers were very small. Of these subjects aged through 20 years of age, 20% or more had carriage that they had gained somewhere along the way probably based on the epidemiology when they were 14, 15, or 16 years old. He wondered whether there was an opportunity or a plan to back up in the age group to see if acquisition could be stopped in a younger age group before it builds up to the 15 or 16 year olds, or if that is even feasible to do. He also thought it was interesting that these two vaccines are not really group-specific completely, because they are protein antigens. For all of the strains for which a group could not be assigned, there was little impact.

Dr. Soeters replied that there are no current plans to look at carriage in adolescents, but they are beginning to examine the within-individual dynamics in carriage over time in this particular population to determine if they are carrying the same strain or if it changes. It seems like some of the students can carry for a couple weeks, while some can carry for a couple of months. It is not clear whether they are acquiring some of these strains in adolescence and then bringing them to college with them, or if there is just a lot of circulation and transient carriage occurring. Incoming freshman entering campus the year after the outbreak were seen their first week on campus and then again 6 months later, and an increase in carriage was seen in those incoming freshman.

Dr. Maldenado (AAP) asked whether there was a possibility of comparing current data to the nicely done natural history colonization studies from the 1950s looking at some of the Army studies done in California and other places in terms of baseline colonization and what happened and the impact of antibiotic prophylaxis and resistance. Obviously, there are better genetic data now. There seem to be many parallels in terms of what happens to these people and, more importantly, if someone is known to be carrying, what should be done with that patient. What was shown in the Army studies was that it did not have a huge impact if there was a lot of rifampin resistance.

Dr. Soeters replied that while this has not been done, it can be.

Dr. Messonnier added that there is a variety of literature on this, including studies that Dr. Stephens and she tried to conduct in adolescents and high school students 10 years ago, getting really low carriage. This is a complicated field, and CDC is very much looking forward to the data from pharmaceutical companies with much higher enrollment rates. The prospective studies CDC has tried to conduct have had sample size power problems. When they have tried to do it in convenience around outbreaks, there have been numerous problems. The large study being planned may help.

Dr. Stephens added that one of the issues is that there is now a lot better typing systems and understanding very specifically, for example, in the study only one individual was carrying the outbreak strain. That is quite a difference from what was known in the old military studies.

MenB-FHbp (Trumenba®) Vaccine Update

Dr. Laura York
Medical Development
Scientific and Clinical Affairs
Pfizer

Dr. York presented an update on Trumenba®, which was licensed in October 2014 and received FDA approval through the accelerated approval regulations to be used in a 3-dose series of 0, 2, and 6 months for prevention of meningococcal B disease in individuals 10 through 25 years of age. This was in response to the unmet need with the outbreaks occurring in the US. Pfizer continued to discuss the schedules with the FDA, and the FDA approved a label change under the same regulations on April 14, 2016. The schedules now include a flexible 3-dose schedule (0, 1-2 months and 6 months) and a 2-dose schedule (0, 6 months). Both schedules were determined by the FDA to be safe and effective. With the two different schedules in the labeling, ACIP guidance is needed in reference to the existing recommendations for providers as they move forward with use of these vaccines. Dr. York briefly reviewed the data that supported the change in the label, and provided some new data on persistence and immune responses following a booster in terms of both schedules.

Pfizer's MenB vaccine, Trumenba®, is based on a surface-exposed factor H binding protein (FHbp), which functions as an important immune evasion mechanism. It actually downregulates the complement cascade and limits the bactericidal activity of complement in that membrane attack system. This protein is expressed in over 97% of the invasive MenB strains that Pfizer has examined, and there has been a comprehensive evaluation survey of invasive meningococcal isolates from 2000 on from the US, several countries in Europe, and Canada. The FHbp sequences segregate into two genetically and immunologically distinct subfamilies referred to as A and B. Trumenba® is composed of two lipidated proteins, A05 and B01, one from each subfamily. The lipidation of that protein is important and really contributes to the breadth of protection observed in terms of the ability to elicit antibodies that could recognize across the diversity of this particular antigen; that is, recognizing across that subfamily and the variance within that subfamily. The vaccine-elicited protective responses are actually demonstrated not through efficacy studies because of the disease incidence of meningococcal, but through the correlate used to predict protection which is the serum bactericidal assay using human complement (hSBA). Pfizer uses 4 invasive MenB strains that are representative of prevalent strains in the US and Europe. The 4 strains express fHBP variants that are different from what is in Pfizer's vaccine (A22, A56, B24, B44). The approach was designed to demonstrate the breadth of coverage. Where those 4 strains are representative, they would be expected to predict the activity against other strains.

The data that contributed to being able to have two schedules and the change in the dosing and administration was from a study (B1971012) that was done in Europe that included individuals 11 through 18 years of age who were randomized into 5 groups to examine two 3-dose schedules and three 2-dose schedules. The participants were enrolled into an additional study, or a follow-on study, with a different number (B1971033) to evaluate the antibody persistence annually and the response to a booster dose at approximately 4 years. The choice of that timing was not to determine when to give a booster dose, but to look at the ability to boost the response—to look for memory. Pfizer knew that these data would be important to ACIP in their considerations of use of the vaccine, so the timing for Pfizer to have these data was based on being able to provide additional information for ACIP's consideration.

The immune response was evaluated on the 4 representative strains, and the proportion of individuals who have a 4-fold response are assessed. As Dr. Granoff said, this is really looking at the vaccine response and the robustness of the response. The minimum titer that a person has to achieve is 1:16 to be recognized as a responder with a 4-fold response. A composite response also was assessed, which is looking at the ability of the antibody generated in an individual to recognize each of the 4 strains all together. This shows the ability of the antibody to recognize across a diversity of the antigens. Dr. York reminded everyone that she had already shown data on 10 additional strains to highlight how these data demonstrate the immune response that is elicited by Trumenba®.

Looking at the immune response in terms of 2-dose schedules at different intervals (0,1 / 0,2 / 0,4 / 0, 6), 0,1 comes from the 3-dose schedule looking post-dose 2 on a 0, 1, 6 interval. In terms of 4-fold and the composite response, as the interval between vaccine doses is increased, there is an improvement on the immune response acquired from receiving the vaccine. This is very important in terms of the 0,6 interval providing robust responses and substantial protective responses in terms of the 4-fold response, and also in terms of composite response with a point estimate of 73.5%. This is a nice, robust, substantial protective immune response with a 2-dose interval that is 6 months.

In terms of 3-dose schedules, there are circumstances in which it is desirable to give 2 doses in close interval. In an outbreak, for example, the goal is to achieve an immune response as quickly as possible in as high a number of individuals as possible. It is known from the 3-dose schedule that a 0,1 or 0, 2 schedule can be used to quickly achieve a comparable type of response. But, in fact, there is an improvement in terms of the percent of responders observed with the third dose in the 3-dose schedules. Dr. Granoff's data show very clearly in terms of a 2-dose schedule at 0,2 or 0,1 that there is a very effective immune response. But, in order to have a high proportion of individuals who are going to respond and have a broadly protective response, the third dose will provide it in the 3-dose series.

This trend also is observed when looking at the response in terms of the percent of subjects who have an hSBA titer of greater than 1:8 and 1:16 on one of Pfizer's test strains. Again, this is higher than the protective correlate of 1:4 that is accepted from the studies conducted very early in the military in terms of the effect of that interval, the range of response anticipated to provide a short interval versus a longer interval of a 2-dose series, and the 3-dose series also giving a robust response, a high percentage of individuals, and a high range of response that would be predicted to be seen against other diverse strains. This also is seen in the GMT with the 6-month interval resulting in slightly higher responses in terms of GMT that are, in fact, more comparable to the 3-dose series. For some of these responses in terms of the percent of individuals with a titer greater than 1:8 or on the GMT that there are overlapping confidence intervals, the two schedules are expected to be effective, and that is why Pfizer has these two schedules in its label. There is no differentiation in terms of safety between the second or the third dose, so consequently there was FDA approval in terms of safety and efficacy of this vaccine on a 2-dose schedule at 0,6 or a 3-dose schedule of 0, 1-2, or 6 months.

Regarding the persistence data following either a 0,6 or 0, 2, 6 schedule of Trumenba® in terms of the percent of subjects with an hSBA titer of greater than 1:4 among two cohorts against the 4 representative strains. As found in a previous study and presented to ACIP, a plateau is established after a waning of the persistence in terms of the percent responders. There seems to be a consistent plateau over the 48 months for Trumenba®. There is a divergence with two of the strains, but the confidence intervals do overlap, which suggests that the response after a 2-dose schedule or a 3-dose schedule will provide persistence in terms of the protective

response. There is a lowering of the response in terms of the percent or the range observed against diverse strains, but clearly in terms of the population, there still is a protective response against MenB.

It was interesting for Pfizer to look at the hSBA responses following a booster about 4 years out of individuals having either a 2-dose schedule at 0,6 or a 3-dose primary schedule at 0,2,6. For simplicity, Dr. York showed a graphic reflecting the response in terms of the pre- and post-primary series and then 48 months post-primary series.

These are the data shown previously but without all of the additional time points from 12 months through to 48 to make a point in terms of the booster response that is observed against these 4 representative strains showing a significant percentage of individuals who are responding to a single booster dose. The composite of this is now well over 90%. Clearly, there has been induction of memory at approximately the same level of memory with either a primary series of the 0,6 or a primary series of 0,2,6.

The memory response is also well-defined in terms of the hSBA GMT responses to the booster dose, with significant responses shown in terms of GMT after a primary series of the 2-dose or the 3-dose schedule, maintaining the plateau in terms of the persistence above the protective level of 1:4. There is a significant increase in the GMT post-booster, which demonstrates the memory response. Regarding the safety of a booster dose, a difference is not observed in terms of the safety profile. Therefore, there is nothing untoward in terms of receiving a booster for approximately 4 years post-primary series.

In summary, Trumenba® (MenB-FHbp) was granted FDA approval under Accelerated Approval regulations in April 2016 resulting in a flexible schedule for use in a 3-dose series at 0,2,6 months or a 2-dose schedule at 0,6. Either schedule can be used to provide protection against invasive meningococcal disease caused by serogroup B in individuals 10 years through 25 years. These data demonstrate that both schedules provide a significant benefit in terms of the breadth of coverage against the diverse MenB strains causing disease. There is flexibility within the 3-dose schedule that may be beneficial when an individual is at significant risk of disease (e.g., outbreak). A 2-dose schedule may improve compliance in an age group where completion of a multi-dose series is challenging. Based on the data, there is similar persistence of the hSBA response. Clearly, after either series the immunological memory is established and a booster dose elicits a response that is actually higher than the response after the primary series.

Discussion Points

In terms of receiving the FDA labeling and both schedules were determined to be safe and effective, Dr. Lee asked at what time point the effectiveness was assessed. In addition, she asked whether there were any long-term follow-up studies that go beyond what Dr. York showed.

Dr. York replied that it was always one month after the primary series. All of the vaccines are licensed on that. No long-term follow-up studies are planned. However, there will be another blood draw after the booster dose, so they will be able to present data to ACIP about a year out from that booster dose. This will show whether the waning is less and plateauing within that.

Considerations for Use of 2- and 3-Dose Schedules of MenB-FHbp

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

Ms. MacNeil presented a summary of the WG's considerations for the use of 2- and 3-dose schedules of MenB-FHbp or Trumenba®. As a reminder, there are two serogroup B MenB vaccines licensed for use in the US in persons 10 through 25 years of age. MenB-FHbp (Trumenba®) contains two components (fHbp subfamily A/v2,3; subfamily B/v1) and originally was licensed by the FDA in October 2014 for administration as a 3-dose series. MenB-4C (Bexsero®) contains four components (fHbp subfamily B/v1; NhbA; NadA; Por A1.4) and was licensed by FDA in January 2015 for administration as a 2-dose series. MenB-4C also is licensed in a number of other countries for use in persons 2 months of age and older.

Current ACIP Recommendations for the use of serogroup B MenB vaccines are:

- Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (Category A)[1]

- A MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease (Category B)[2]

In both of the MenB Policy Notes, the following additional guidance is provided that is consistent with the original licensure:

- MenB vaccine should either be administered as a 3-dose series of MenB-FHbp (Trumenba®) or a 2-dose series of MenB-4C (Bexsero®)[1,2]

[[1]Folaranmi T., et al. Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR*; June 12, 2015; Vol. 64, No. 22, p 608-612; [2]MacNeil JR, et al. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2014. *MMWR*; October 23, 2015, Vol. 64, No. 41, p 1171-1176].

The FDA approved updates on April 14, 2016 to the dosage and administration section for MenB-FHbp. The original and updated language follows, with the changes underlined:

Original Language:

- Three doses according to a 0, 2, and 6 month schedule

Updated Language:

- Three-dose schedule: Administer a dose at 0, <u>1-2</u>, and 6 months

- <u>Two-dose schedule: Administer a dose at 0 and 6 months</u>

The choice and dosing schedule may depend on the risk of exposure and the patient's susceptibility to meningococcal serogroup B disease

Ms. MacNeil discussed the WG's interpretation of the MenB-FHbp data pertaining to short-term immunogenicity, antibody persistence, safety, the proposed policy options for 2- and 3-dose schedules of MenB-FHbp, and the WG's discussions. As a reminder, several dosing schedules were evaluated for MenB-FHbp, including two 3-dose schedules and four 2-dose schedules. For this presentation, Ms. MacNeil focused on the data presented for the 2-dose schedule at 0,6 months and two 3-dose schedules.

Regarding the short-term immunogenicity data one month following the last dose, among the 2-dose schedules evaluated, the 0, 6 month schedule had the highest proportion of responders and GMTs and is most similar to a 3-dose schedule. However, the proportion of subjects demonstrating a composite response to all four primary strains is slightly lower with a 2-dose schedule at 0, 6 months compared to either 3-dose schedule. Similarly, for most strains, the GMTs are lower with a 2-dose schedule at 0, 6 months compared to either 3-dose schedule. For some strains, the 95% confidence interval around the GMTs do not overlap.

Antibody persistence to the four primary strains is shown here for participants who received 2 doses at 0,6 months or 3 doses at 0,2,6 months. The percent of subjects with hSBA titers ≥1:4 to the four primary strains is similar through 48 months for adolescents who received either 2 or 3 doses of MenB-FHbp.

In addition, the GMT responses to a single booster dose 4 years following the receipt of either 2 or 3 doses of MenB-FHbp are similar. As has been presented to ACIP previously, the MenB vaccines are more reactogenic than other vaccines given during adolescence. The most common AE reported is pain at injection site. Overall, the safety and tolerability profiles are similar for the 2-dose and 3-dose schedules of MenB-FHbp.

Again, there are two MenB vaccines in the US for persons aged 10 through 25 years of age: MenB-FHbp (Trumenba®, Pfizer) and MenB-4C (Bexsero®, GlaxoSmithKline). ACIP does not express a preference for either vaccine product. The current ACIP recommendations for the use of serogroup B meningococcal vaccines are show here as a reminder, with no changes proposed during this session:

- Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (Category A)

- A MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease (Category B)

However, because of the recent change in licensure for MenB-FHbp during the remainder of this discussion, the focus was specifically on MenB-FHbp in order to provide guidance from ACIP on when the 2- and 3-dose schedules of MenB-FHbp (Trumenba®) should be used. After reviewing the data, the WG discussed several different policy options. First, for persons at increased risk and for use during outbreaks, a preference for 3-dose schedule of MenB-FHbp was proposed. For healthy adolescents, three possible policy options were proposed: 1) A preference for 2-dose schedule (0, 6 months); 2) An option for either the 2- (0, 6 months) or 3-dose (0, 1-2, 6 months) schedule; or 3) A preference for 3-dose schedule (0, 1-2, 6 months).

Based on the discussions of the WG, there was agreement that ACIP guidance for which schedule to use in each population is needed. There was strong consensus in the WG to express a preference for the 3-dose schedule for persons at increased risk, including during outbreaks, to provide early protection and to maximize immune response. For healthy adolescents, the WG's considerations included the following:

Preference for 2-dose schedule *OR* option for 2- and 3-dose schedules the key considerations were as follows:	When considering a preference for the 3-dose schedule, the key considerations were as follows:
❑ Persistence of the hSBA responses for the 2-dose (0, 6 m) schedule is similar to the 3-dose (0, 2, 6 m) schedule ❑ hSBA GMT responses following a booster dose are also similar for 2-dose. ❑ However, the WG noted that providing an option for either the 2- or 3- dose schedule does not provide explicit guidance to the physician on which schedule to use in healthy adolescents	❑ For people who want to maximize short- term protection, 3 doses is preferred ❑ Both the 2- and 3-dose schedules take 6 months to complete ❑ ACIP could provide guidance that if someone receives their second dose of MenB-FHbp 6 months or more after the first dose, no additional doses would be needed

Based on these considerations, the strong consensus of the WG was to express a preference for 2- and 3-dose schedules as follows:

1. For persons at increased risk for meningococcal disease and for use during serogroup B outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1-2, 6 months

2. When given to healthy adolescents who are not at increased risk for meningococcal disease, 2 doses of MenB-FHbp should be administered at 0 and 6 months

Discussion Points

Dr. Walter asked whether the WG discussed harmonization of the schedule to 0,6 months for both vaccines when given to healthy adolescents.

Dr. MacNeil responded that the WG did not discuss that.

Dr. Atmar pointed out that the data shown reflected clear differences at 7 months, but in terms of the early protection, he wondered whether there were data about immunogenicity or serum antibody levels at earlier time points. That is, other than the benefit at 7 months, what is the benefit of receiving an extra dose at 1 to 2 months or 2 to 3 months compared to not getting that dose.

Ms. MacNeil replied that the data show that the longer the interval between the doses, the better the response is.

Dr. Atmar clarified that his question pertained to the early protection implying that within several months as opposed to at the 7-month time point, there were clear-cut differences. Usually in these studies, blood is drawn in each vaccination time point. He wondered whether this information was available to the WG and, if so, just was not presented to ACIP.

Dr. Cohn clarified that with the 0,6 schedule, data show that there is a similar response after the second dose. If doing the 0, 1-2, 6 schedule, there will be some protection earlier than if using the 0, 6 schedule. That is why the preference was for people at increased risk or at an immediate risk to use the 3-dose schedule.

Dr. Maldonado (AAP) asked whether consideration was given to the scenario of a fully vaccinated high-risk person who is past the point of antibody titers dropping off being placed in a high-risk situation.

Ms. MacNeil replied that the next topic the WG will discuss is boosters for people at increased risk, and whether someone would need to be re-boosted if placed at increased risk.

Dr. Zucker (New York City Department of Health and Mental Hygiene (DOHMH)) pointed out that from a programmatic point of view, for registries this will mean that they will schedule the MenB series at 0, 6. There is a challenge translating the ACIP guidance into what registries will tell providers to do. Most often, providers will listen to the registry and they may not think about whether someone is at increased risk. As long as that is the intent, that is fine. They could translate that into guidance for the pediatric community.

Dr. Moore recalled that Dr. Hunter had mentioned whether immunization registries could key the forecasting based off of the brand of initial vaccine given, so that it would be keyed at a different interval if it were Bexsero® given first versus Trumenba® given first. She wondered whether Dr. Zucker could speak to this issue.

Dr. Zucker (New York City Department of Health and Mental Hygiene (DOHMH)) replied that most registries can do this, but it depends upon whether they receive a lot number and whether it has been reported as a particular product. It could come in as a MenB such that the product is not specified for them.

Dr. Moore emphasized that this created its own complications, because this is one vaccine for which the brands are not supposed to be mixed. That is, 2 or 3 doses should be given of the same brand of vaccine.

Dr. Lee asked whether data would be presented at the next meeting about Bexsero® and 0,6 versus 0,1. She agreed with Dr. Walter that this can be done in an incremental way, but it would be helpful to know where they are headed in the long-term. Otherwise, it will not be practical to implement this from a programmatic standpoint.

Dr. Friedland (GSK) indicated that the 3-dose data have been reviewed by the FDA and the ACIP WG in the past. The vast majority of all of the clinical trials with Bexsero® were with 2 doses, and 2 doses were examined on different schedules: 1 month after, 2 months after, or 6 months after the first dose. In this situation, the percentage of subjects who achieved the protective titer of 1:4 was high regardless of the schedule. That is, a very high proportion of subjects achieved seroprotection on the 0,1 schedule and there was no increase in the percentage of subjects getting a seroprotective level when given 6 months later versus 1 month later. This was the rationale for the indication that the second dose of Bexsero® can be given as soon as 1 month after the first dose.

Dr. Lee requested that this be considered more broadly in terms of thinking about whether someone at high risk could receive a 0,1 or 0,1,6 schedule and if doing this for a permissive routine recommendation, that they just do 0,6. From a clinical standpoint, it will be easier not to have confusing recommendations.

Ms. MacNeil replied that the WG certainly can discuss this.

Dr. Friedland (GSK) said that when they speak to healthcare providers about the use of Bexsero® in clinical practice, they hear that the flexibility of giving the second dose as soon as 1 month after the first dose can be very important. For example, if a student presents to their practice during the summer months, the family can complete the full series of both doses over the summer before they go to college. They are hearing that having flexibility is quite important to and valued by healthcare providers.

Dr. Middleman (SAHM) asked for clarity regarding the statement "for persons at increased risk and for use during outbreaks" preference for a 3-dose schedule meant that the WG had a preference to only recommend the 3-dose schedule or that the WG would allow for either one, but a preference for the 3-doses. She would like to be able to still have the option for those healthy adolescents who want 3 doses to be able to get 3 doses and not be limited to 2 doses.

Ms. MacNeil clarified that the intent is for people who are at increased risk or during outbreaks to receive 3 doses so that they would have the early protection.

Dr. Messonnier clarified that the WG does not make recommendations and was just expressing their preferences for ACIP to make recommendations. The vaccine licensure allows for clinician flexibility. CDC has received feedback that it is already incredibly confusing to have the A versus B recommendation and the two different vaccines. There is a value placed on ACIP trying to make a recommendation that is as simple as possible in this area in a space that is already very complicated.

Dr. Stephens added that the WG spent a lot of time on this question and trying to wrestle with the question in terms of whether they preferred a specific 0,6 or an option. They came to the conclusion that it would create more confusion with a mixed signal in terms of being able to do either one. In the view of the majority of the WG, the data would support the 0,6 schedule for healthy adolescents not at risk in a routine administration setting.

Dr. Kempe emphasized that insurance companies will or will not cover 3 doses for healthy adolescents, which is an implementation issue. She asked whether this was the ACIP saying that either is okay, but they have a preference for one. It did not sound like the objective was to make a recommendation for one.

Dr. Messonnier reminded everyone that there are two places in which decisions are made about coverage. One of them is a VFC vote, which ACIP has the power to make. However, the VFC vote's purpose is separate from the ACIP recommendation because it is meant to be a second step. Then there is the ACA, which is set up to be driven by what is on the immunization schedule. That is different, separate, and a discussion that would occur the next day during the schedule session. It does not have to be in the colored bars on the schedule. It can be in one of the footnotes.

Dr. Stephens made a motion to approve the option reflecting the WG's stated preference.

Dr. Bennett indicated that they have had the issue regarding preferences previously, and it is very difficult in the implementation phase when stated as a preference. She requested additional guidance.

Dr. Messonnier pointed out that a preference implies that the WG would be okay with any of the groups receiving any schedule. They have been concerned about the language of preference due to implementation difficulties. If ACIP considered either schedule to be acceptable for either high-risk or healthy adolescents, but express a preference, they certainly could say that. The issue regarded how a clinician should interpret that. It already is difficult to articulate what ACIP meant by a Category B recommendation. Adding another layer of complexity on top of two different vaccines would make this harder.

Dr. Lee said she thought the problem was the specificity for the vaccine product, and she was not used to thinking of it that way. She proposed that the vote be: 1) for persons at increased risk and for use during outbreaks, a preference for a 3-dose schedule of one product or a 2-dose schedule of another product, but with the intent of it being in a shorter timeframe; and 2) when given to healthy adolescents, a preference for a 2-dose schedule of either product.

Dr. Kempe said that alternatively, she thought it should be a recommendation because it already is problematic and this compounds the degree of complexity. She thought that particular statement should be a recommendation.

Dr. Lee clarified that she meant “recommendation” and just wanted to flip it around in terms of the framing.

Dr. Belongia emphasized that there is a difference between “preference” and “recommendation.” He thought it would be most clear for clinicians if stated that ACIP “recommends a 2-dose schedule for healthy adolescents.”

Dr. Messonnier suggested that the members spend time during the break crafting revised language to pose for a vote.

Dr. Moore said that operationally, while she appreciated the scheduling idea of bringing things together, since these are two products that cannot be interchanged unlike all of the other products that can, it would not be that much more complicated to make a specific FHbp recommendation in this case, because the other stands alone. While she recognized in terms of the schedule it is nice to work on the timing, but here she thought the recommendation could be narrower.

Dr. Middleman (SAHM) requested that if there was a vote for a healthy adolescent to have a 2-dose series, it could still be on the immunization schedule that a 3-dose series would be okay and would, therefore, be covered if there were a healthy adolescent who would like a 3-dose series.

Dr. Messonnier indicated that the discussion for the next day regarding the schedule would allow for flexibility about what to put in the footnotes.

Dr. Cohn added that there is always language in all of the statements that if someone receives a dose at the wrong time or received the second dose at 1 to 2 months, the third dose should be received to complete the schedule because the dose was not given at the right time. That is a

back-up safety net for people to complete to be fully protected if they did not receive the second dose after 6 months.

Dr. Middleman (SAHM) expressed concern that this may penalize the provider in some cases in terms of coverage.

Dr. Bennett suggested taking a half hour break to craft some specific language for the motion and vote. Upon returning, the new language was displayed for a revised motion:

1. For persons at increased risk for meningococcal disease and for use during serogroup B outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1-2, 6 months

2. When given to healthy adolescents who are not at increased risk for meningococcal disease, 2 doses of MenB-FHbp should be administered at 0 and 6 months

    * If the second dose is given at an interval of <6 months a third dose should be given at least 6 months after the first dose

Ms. MacNeil indicated that context would appear before the actual language in the Policy Note stating that there are two vaccines that are licensed for people aged 10 through 25 years in the US, and there is no vaccine preference. This also could include information about the current ACIP recommendation so that it is clear that there is a Category A recommendation for one and a Category B for the other.

Regarding the footnote, Dr. Atmar asked whether there would be a minimal interval. For example, what if the second dose was given at 5.5 months.

Ms. MacNeil replied that they could work on that language.

Dr. Kempe wondered about the need for Bullet 2 since it was a Category B individual recommendation anyway. Bullet 1 was clear and was related to a Category A, so a firm recommendation made sense to her.

Dr. Bennett said at first she suggested stating something such as “when a physician chooses to give to a healthy adolescent,” but she thought “when given to healthy adolescents” summed that up and implied that it would not be given to every healthy adolescent because it is a Category B recommendation and it would be in the context of the statement.

Dr. Moore said that the WG would like to have further conversations about a booster dose for otherwise healthy adolescents immunized during a low-risk period of time who later find themselves involved in an outbreak setting or at high-risk.

Ms. Stinchfield (NAPNAP) pointed out that one issue that seemed complicated was that risks were being lumped. There should be clarity about a person with an innate risk such as an immunodeficiency or a complement deficiency versus the immediate risk of a college outbreak. Those are two different risks that could have two different products and two different schedules. It would be helpful to keep those separated for clinicians. It might be that a clinic setting has one product, while a college and public health might have a different product.

Dr. Bennett said her understanding was that this would be covered in the statement by creating the context.

Ms. MacNeil confirmed this and indicated that each group at risk would be listed in the statement.

Dr. Hunter asked whether there would be CDC guidance regarding how to handle persons who receive the 2-dose series when healthy, but then are exposed to an outbreak situation.

Ms. MacNeil replied that this is something that can be discussed in the future. The next topic the WG wants to discuss is booster doses for people at increased risk, and this would fit into that category.

Dr. Weber emphasized that increased risk could be increased risk of exposure or increased risk due to an immunodeficiency. His particular interest is in microbiologists in hospitals who are at increased risk of exposure, but who are normal immunologically. This would be long-term risk versus immediate risk, so he thought some clarification was needed regarding whether the 2- or 3-dose schedule is recommended for those individuals.

Ms. MacNeil replied that this would depend upon when the exposure would occur, but the 3-dose schedule maximizes immune response, so if they are at increased risk, it may make sense for them to receive a 3-dose schedule.

Dr. Kimberlain (AAP) said he thought he was satisfied with what Dr. Kempe was asking about it being a Category B for the second portion of the second sentence. He asked for confirmation that for the first sentence, this was not a recommendation for Trumenba® over the other product. It simply was the part of the statement that dealt with Trumenba®.

Ms. MacNeil confirmed that this was correct and that they would be very clear that there is no product preference.

Public Comments

Christina Hildebrand
A Voice For Choice Advocacy

I have three comments. The first is that you're recommending this—I know you're not saying it should be given to all healthy adolescents, but you're recommending it for healthy adolescents. Yet, the efficacy of it that was shown in the slides showed that it had severe wear-off after 12 months. It is not efficacious, or that efficacious after 12 months, I wonder why you are recommending it at that point, especially when you look at the number of side effects and deaths that come from the actual vaccine versus the number of deaths from meningococcal, which if you look at those numbers, the number of deaths from the vaccine are higher than the number of deaths that we've had from meningococcal. The other thing that I wanted to say is that as a public person and as a statistician, it really surprises me the data that you use. So, the base sizes of 12, 25, 60, 71 that were up on the screen earlier, you know, I don't know if the WG uses different numbers or sees more information, but to me, those numbers are extremely small for studies that you are projecting onto the general population, even if it's the general population of adolescents. Similarly you have—the largest study that you showed was Pfizer data, which is one of the companies that makes the vaccine. Of course, they're going to say good stuff about it. You know, we've got ethics issues in the CDC. We know that. So sitting here and watching this data just really surprises me that this is the data that you're working off to make vaccine recommendations. Thank you.

Dr. Bennett thanked Ms. Hildebrand for her comments and referred her to CDC's SMEs for clarification.

Vote: 2-Dose and 3-Dose Recommended Schedules for MenB-FHbp

Dr. Stephens motioned to approve the language as revised. Dr. Romero seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution

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

Dr. Santoli indicated that the purpose of this revision was to update the recommended vaccination schedule and intervals for serogroup B meningococcal vaccine. The resolution has two parts, and there are no proposed changes to the meningococcal conjugate vaccine section of the resolution. In the serogroup B meningococcal resolution, there is no change to the eligible groups.

Eligible groups include:

- 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
- Children aged 16 through18 years without high risk conditions may also be vaccinated

The recommended schedule and intervals are shown in the following table, summarizing the recommendation that was just approved:

Age Group	Vaccine[1]	Dosing Schedule
10–18 years	MenB (Bexsero®, GSK)	Two doses, at least one month apart (0 and 1-6 month schedule)
10–18 years	MenB (Trumenba®, Pfizer)	Persons at increased risk for meningococcal disease and for use during serogroup B outbreaks: Three doses (0, 1-2, and 6 month schedule) Healthy adolescents who are not at increased risk for meningococcal disease: Two doses (0, 6 months)[2]

1. Use of brand names is not meant to preclude the use of other serogroup B meningococcal vaccines where appropriate.
2. If the second dose is given at an interval of <6 months a third dose should be given at least 6 months after the first dose

For the recommended dosage and contraindications and precautions, the reader is referred to the product package inserts.

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 Hepatitis B 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.]

Vote: VFC Resolution for 2-Dose and 3-Dose Recommended Schedules for MenB-FHbp

Dr. Stephens motioned to approve the VFC Resolution for the 2-Dose and 3-Dose Recommended Schedules of MenB-FHbp. Dr. Belongia seconded the motion. The motion carried unanimously with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Herpes Zoster Vaccines

Introduction

Edward Belongia, MD
Chair, Herpes Zoster Work Group

Dr. Belongia updated ACIP on the Herpes Zoster (HZ) WG activities, reporting that there currently are two investigational vaccines:

- HZ subunit vaccine (HZ/su) from GSK, which has been evaluated in non-immunocompromised populations and is currently being evaluated in immunocompromised populations
- Inactivated vaccine (V212) from Merck that is being assessed in immunocompromised populations.

Recently, the WG has received updates on the currently licensed vaccine, ZOSTAVAX™, as well as presentations from manufacturers of the pre-licensure vaccines just mentioned regarding their current status and future plans.

ACIP received a presentation during the June 2015 meeting on HZ epidemiology and interim Phase 3 efficacy studies on the HZ/su vaccine in adults ≥ 50 years old. Within the past month, results were published for the HZ/su vaccine in adults ≥ 70 years old. During this session, updates will be provided on HZ epidemiology and vaccine coverage and the final Phase 3 efficacy study of HZ/su vaccine. In the coming year, the WG will be considering the policy options in anticipation of future licensed products.

Herpes Zoster Background

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

Dr. Dooling indicated that the objective of this presentation was to provide background on HZ disease and the current vaccine program for the purpose of information and discussion. She presented information on the clinical manifestations, evolving epidemiology, and prevention of HZ. There is a licensed vaccine for the prevention of HZ in adults, and two investigational vaccines are in development for the prevention of this disease.

Varicella Zoster Virus (VZV) can cause two distinct forms of disease, primary infection that leads to chicken pox or varicella. Following primary infection, the virus establishes latent infection in the dorsal root ganglia near the spinal cord. Reactivation of the virus leads to shingles or HZ. The reactivated virus travels up the nerve root to discrete dermatomes to produce the characteristic shingles rash. Reactivation of virus may affect any dermatome of the body to produce the vesicular rash. The rash usually is unilateral and may involve as many as 3 adjacent dermatomes. It typically arises over a 5 to 7day period, with resolution in 5 to 25 days. Occasional consequences of the rash may include secondary bacterial infections or transmission of VZV to susceptible individuals, resulting in chicken pox.
About 90% of HZ episodes are associated with pain or discomfort. The pain is variable in character and intensity, and precedes rash onset in about 84% of cases. Pain without rash

typically lasts from 1 to 5 days, but it can be weeks. Localized pain in the absence of rash can lead to diagnostic dilemmas, such as unnecessary investigation, treatment, or even surgery. Another severe manifestation of HZ is involvement of the ophthalmic division of the trigeminal nerve. This occurs in approximately 15% of HZ cases. Ophthalmic involvement can cause chronic complications and in some cases loss of vision.

Many people think of HZ as a self-limited illness. On the contrary, post-herpetic neuralgia (PHN), which is a common complication of HZ, can be a devastating illness and may persist for years. PHN is prolonged pain that lasts for at least 90 days following the resolution of rash. Approximately 10% to 18% of HZ patients will go on to have PHN. This pain may persist for months to years, and may be incapacitating. In terms of PHN prevention, antivirals and steroids have been shown to shorten duration of HZ, but do not conclusively reduce risk of PHN. Multiple modalities have been used for PHN treatment with partial or inconsistent efficacy, and have many side effects, especially in the elderly.

The following quote is from an email recently received by CDC from a patient with PHN:

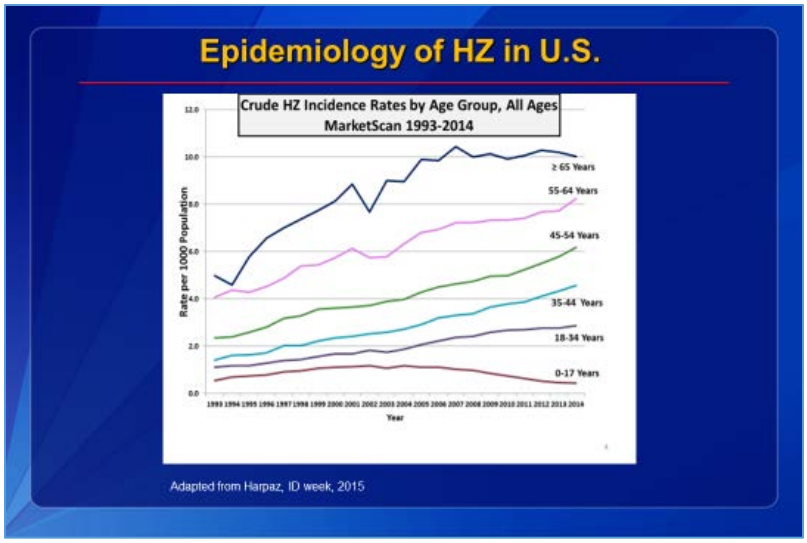
> *"My shingles post herpetic neuralgia is still painful seven years after my shingles episode. My PHN is worse than my cancer and chemotherapy… [it] has made me depressed and suicidal in the past."*

Regarding the epidemiology, HZ has an annual rate of approximately 4 cases per 1000 population. That translates into about 1 million cases of disease in the US annually. The lifetime risk of developing HZ is about 1 in 3 and the age-adjusted rates appear to be increasing. Age appears to be the dominant factor driving incidence, with incidence in 80 year olds being about 10 times more than the incidence in children. Immunosuppression also is a risk factor. Blood malignancies, bone marrow transplant, and HIV all have been shown to increase the risk of HZ by up to 50-fold. In addition to being more common, HZ is more severe in the immunocompromised population, resulting in more disseminated disease and more hospitalizations. Ultimately, the underlying mechanism appears to be related to reduced cell-mediated immunity, which allows VZV to reactivate or progress to HZ.

Data derived from MarketScan, a large healthcare administrative database, demonstrate how the incidence of HZ increases with age. MarketScan contains records for hundreds of thousands of insured people. In the youngest age group, 0 through 14 years of age, the rate of HZ is about 1 case per 1000 population. The incidence increases with age sharply after age 50 [Insinga et al., J Gen Intern Med. 2005, 20:748-53 (MarketScan administrative data].

Similarly, the incidence of PHN increases with age. In this case, data were derived from a population-based cohort in Olmstead County, Minnesota. Recall that only a fraction of individuals with HZ will go on to get PHN. In fact, PHN is rare in individuals younger than 50 years of age, but risk increases steeply after age 60. An 80 year old is approximately 10 times more likely to get PHN than a 50 year old [Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9 (Olmsted County, MN)].

Over time, the incidence of HZ has increased for almost all age groups. This graph shows the increasing incidence by year from 1993 to 2014:



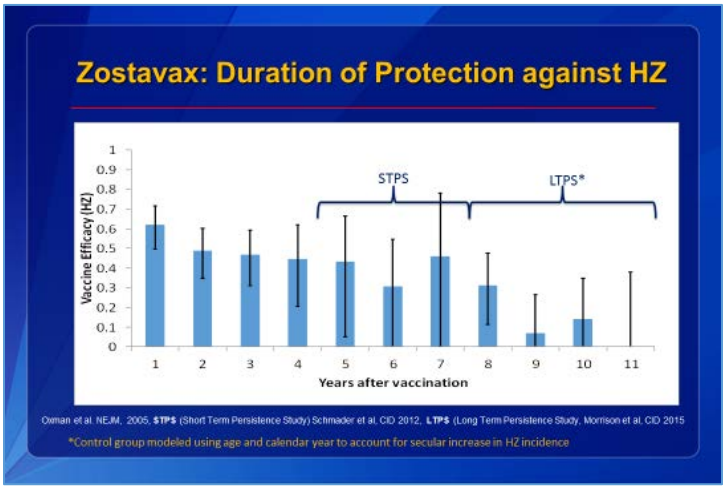
For adults 65 years of age and older, which is the top line on the graph, the incidence plateaued around 2007. For all other adults, the incidence seems to be increasing. For children, displayed on the bottom, there has been a downward trend since about 2005. The reasons for this increasing or plateauing incidence in adults are unknown, but it has been confirmed by numerous data sources. Looking specifically in children, precipitous drops of HZ incidence have occurred during the same time period, which is likely due to the direct effects of vaccination with VARIVAX®, as well as a decrease in circulating VZV, which has resulted in some children not ever having had a primary infection. Thus, they are not at risk for HZ [Adapted from Harpaz, ID week, 2015].

Regarding prevention, ZOSTAVAX™ was licensed by the FDA in 2006. Phase 3 clinical trials involved 38,500 non-immunocompromised adults ≥60 years old with a median follow-up of 3.1 years. This vaccine consists of a live-attenuated Oka-strain VZV, which is about 14 times the concentration in VARIVAX®. Vaccine efficacy (VE) was 51% against HZ and 67% against PHN. SAEs were not more common in the vaccinated group; however, local reactions were more common.

In terms of the results for vaccine efficacy in the Phase 3 clinical trial, overall, the vaccine was 51% effective for the prevention of HZ and 67% effective for the prevention of PHN. The efficacy decreases with increasing age. The protection against HZ ranges from 64% for recipients in their 60s down to 18% for recipients 80 years of age and older. From the same Phase 3 clinical trial, efficacy against PHN was maintained against disease of longer duration. PHN was categorized according to how long the episode lasted, ranging from 30 days to 180 days. ZOSTAVAX™ provided over 70% protection against PHN that lasted for 180 days [Oxman et al. Shingles Prevention Study, 2005].

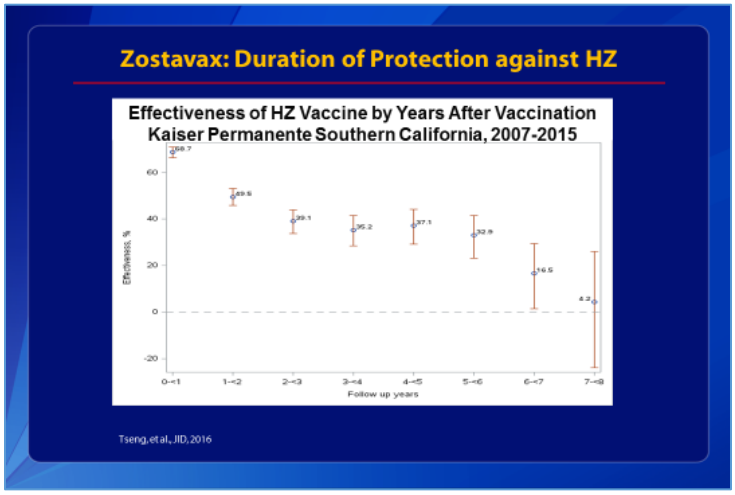
In 2008, ZOSTAVAX™ was recommended by ACIP to be given as 1 dose in adults ≥60 years. As a live vaccine, it is contraindicated in immunocompromised persons. In 2011, there was no change to the ACIP recommendation following an FDA age expansion of the license to 50 through 59 years of age. There were several reasons for this decision. First, there were vaccine shortages at the time that left people in the recommended group without access to the vaccine. This, combined with the fact that that the burden of HZ increases in people ≥60 years of age and over, resulted in maintaining the recommendation as it stood. After vaccine supply

issues were resolved, ACIP revisited the issue in 2013 and affirmed the recommendation for adults 60 years and older. This was based on data that showed waning of immunity. This graph shows the duration of protection provided by ZOSTAVAX™:



VE is shown by year following administration. The first four years of data were contributed by the Phase 3 efficacy trial previously discussed. Years 5 through 7 are contributed by a follow-on study, and years 8 through 11 by following a subset of the vaccinated cohort and a modeled control group. As shown in the above graph, efficacy decreases every year in the 5 years following vaccine receipt. The vaccine may not provide any significant protection after 8 years. As the risk of HZ and PHN increase with age, a higher burden of disease can be prevented with administration after 60 years of age and above [Tseng, et al., JID, 2016].

This graph also shows waning of immunity protection of ZOSTAVAX™, but the data come from an observational study in a large health maintenance organization (HMO), Kaiser Permanente:



In the Kaiser Permanente study, protection among all vaccinees started at 69%. However, by years 7 to 8 post-vaccination, vaccine protection decreased to 4% and it was not statistically significant [Tseng, et al., JID, 2016].

ZOSTAVAX™ uptake has shown slow and steady progress since 2007. By 2014, 28% of adults 60 years of age and older in the US reported prior ZOSTAVAX™ receipt [2007: National Immunization Survey (Lu et al, Vaccine 27:882-7); 2008-13: NHIS (Am J Prev Med 40:e1-6 & MMWR February 5, 2016 / 65(1);1–36)]. In terms of why uptake has been sluggish, the price is high and there may be significant co-pays. In addition, the storage and handling of the vaccine requires freezing and reconstitution. This may dissuade some providers from carrying the vaccine. Also, supply shortages were a problem in the early years. However, this has since been resolved. For Medicare recipients, the vaccine is covered only by Part D and reimbursement can be complicated. Finally, the lower prioritization of adult vaccines as compared to the pediatric program and the general fragmentation of preventive care for seniors may contribute to low uptake. The first three factors described are vaccine-specific and may be ameliorated by modification of the existing vaccine or introduction of a new vaccine. The second three factors are system-related and must be addressed on a broader scale if there are to be meaningful increases in ZOSTAVAX™ vaccination.

There are new vaccines on the horizon. The HZ/su vaccine developed by GSK is a vaccine consisting of VZV glycoprotein E as well as an adjuvant system. It is administered in 2 doses, 2 months apart and it is refrigerator-stable. It was tested in a Phase 3 clinical trial in over 30,000 non-immunocompromised adults 50 years of age and older. The primary endpoint was prevention of HZ, and the secondary endpoints were prevention of PHN, safety, and reactogenicity. In those Phase 3 clinical trials, VE for the prevention of HZ ranged from 97% for 50 through 59 years olds to 91% for recipients 80 years and older. VE of at least 85% was maintained for all 4 years after administration in all age groups. This vaccine was found to be highly reactogenic. In study participants 70 years of age and older, 79% of vaccine recipients reported local symptoms compared to 30% of placebo recipients, and 12% of vaccine recipients reported Grade 3 reactions (e.g., symptoms that interfered with their daily lives) compared to 2% of placebo recipients.

Prevention of HZ in the immunocompromised population remains an unmet need. Two vaccines are in development for just this purpose. V212 developed by Merck is an inactivated formulation of ZOSTAVAX™. It is a 4-dose series in persons 18 years of age and older. There is an ongoing Phase 3 efficacy trial of V212. HZ/su developed by GSK consists of a formulation of VZV glycoprotein E as well as an adjuvant system. It is administered as a 2-dose series in persons 18 years of age and older. There is an ongoing Phase 3 efficacy trial of HZ/su as well. Thus, there are exciting developments in the prevention of HZ. The WG anticipates deliberating on policy issues for non-immunocompromised and immunocompromised persons for several years to come.

In conclusion, the epidemiology of HZ is changing. However, the reason for this is not fully understood. Approximately 28% of adults 60 years of age and older have been vaccinated with ZOSTAVAX™ in the US. Vaccines to prevent varicella and HZ are reducing the amount of circulating VZV in the US population. The two new vaccines for the prevention of HZ that have been developed and are being evaluated may further reduce the disease burden.

Update: Herpes Zoster Subunit (HZ/su) Vaccine

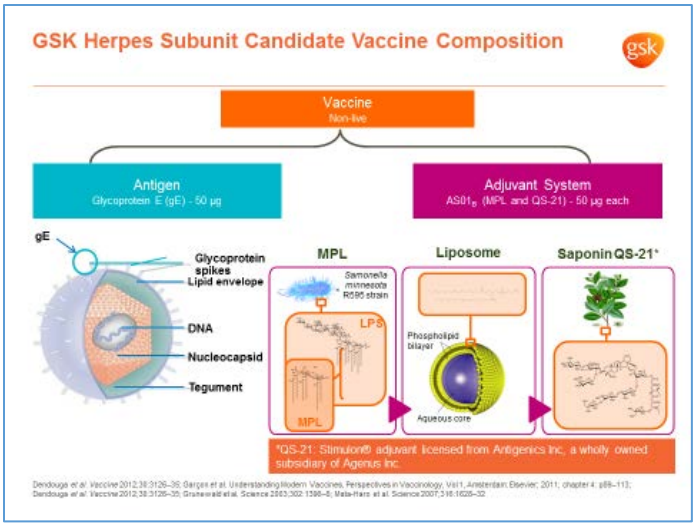
Romulo Colindres, MD, MPH
Global Medical Affairs Lead, Zoster
GlaxoSmithKline

Before beginning, Dr. Colindres indicated that he is a former EIS Officer and was really enjoying being back in Atlanta and connecting with old colleagues and friends, and being back on the CDC campus. He noted that he would be presenting on behalf of a very large team at GSK and many study investigators across the world on GSK's HZ adjuvanted subunit vaccine, HZ/su, specifically with regard to recent trial results in people 70 years of age and older.

Dr. Colindres highlighted the burden of disease of HZ, with approximately 1 million cases of disease being reported annually in the US[1]. Per CDC statistics, everyone has a 32% estimated lifetime risk of HZ[1]. With such a high percentage, it is not difficult to find someone who has been impacted by this disease. In his case, his 72 year old mother suffered from a very serious case of shingles 5 years ago, which included facial nerve involvement. Given her painful experience, he was sure she would be happy to learn about the new advances being made to prevent this disease. The risk of shingles also increases with age, such that above 85 years of age, the risk is 50%[1]. The most important risk factor is increasing age due to a natural decline in immune system function, immunosenescence, and also immunosuppression either because of disease or immunosuppressive therapy. HZ is generally not life-threatening. However, there can be some very serious complications, the most common being PHN with pain lasting greater than 3 months. Also, HZ opthalmicus can cause dangerous eye involvement, and there also can be cranial nerve palsies [[1]CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. 2015].

The development of the HZ/su vaccine began at GSK 16 years ago at which time two target populations were chosen, adults ≥50 years of age and immunocompromised adults ≥18 years of age. From early in the development program and also specifically as Phase 3 clinical studies were being designed, several key aspirations were considered. The first was to achieve high vaccine coverage in persons ≥50 years of age. Because GSK did not think that was sufficient, they also wanted to increase VE in the older age groups ≥70 years and above. Again, these groups are the most susceptible and are at the highest risk for shingles and shingles complications. At the core of the aspirations was having a safe vaccine for all persons. This includes safety / efficacy in all persons at increased risk for HZ, including immunocompromised populations. The fourth aspiration was to have prolonged duration of protection. The final aspiration was ease of manufacture and reliability of supply. Many of these aspirations have been met.

The following illustrates the composition of the non-live, adjuvanted subunit vaccine:



On the left in turquoise is the antigen, which is 50 µg of recombinant glycoprotein E. This is the most abundant protein found on the envelope of VZV, which elicits a specific cellular and humoral immune response. On the right is the adjuvant system, which is $ASO1_B$. $ASO1_B$ is a liposome-based adjuvant system that contains immunostimulants MPL and QS-21. MPL enhances cellular and humoral immunity, while QS-21 stimulates Th1 cell-mediated immunity as well as cytotoxic T- lymphocyte activity. Synergistically, when MPL and QS-21 are combined, there is an enhanced proinflammatory response or innate immunity, as well as cellular and humoral response increases. Overall, this results in a faster, stronger, and longer lasting immune response [Dendouga *et al. Vaccine* 2012;30:3126–35; Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam: Elsevier; 2011; chapter 4: p89–113; Dendouga *et al. Vaccine* 2012;30:3126–35; Grunewald et al. Science 2003;302:1396–8; Mata-Haro et al. Science 2007;316:1628–32].

In terms of background conclusions from the early phase studies, early phase safety and immunogenicity studies determined the combination of adjuvant and antigen and the dosing scheme. That led to the composition just described to be given as a 2-dose regimen. With regard to long-term immunogenicity in people 60 years of age and older, two doses of HZ/su induced a strong cell-mediated immune response of 19-fold higher than baseline at 1 month after dose 2. The immune response was maintained with age, including in adults ≥70 years of age. While a decline is observed in immune response after the first few years, this plateaus by year 4 and still remains 4 times above baseline 6 years post-vaccination [Chilbek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults 2015; *Vaccine*, Volume 34, Issue 6, Pages 863-868].

Three Phase 3 efficacy studies make up the HZ/su development program. ZOE-50 (006)[1] and ZOE-70 (022)[2] are studies that evaluate HZ efficacy safety and immunogenicity in populations 50 years and older and 70 years and older, respectively. These studies were begun in 2010 and were recently completed. ZOE-50 results were presented to ACIP in 2015 and were published in the *New England Journal of Medicine* (*NEJM*). As a reminder, the primary results of ZOE-70 as well as pooled results from ZOE-50 and ZOE-70 were published in the *NEJM* in September 2016 [[1]Lal H. *NEJM* 2015;372:2087-96; [2]Cunningham AL. *NEJM* 2016;375:1019-1032]. Study 002 is evaluating HZ efficacy, safety, and immunogenicity in adults ≥18 years of age receiving an autologous hematopoietic stem cell transplant (aHCST).

In terms of the general study design and objectives for ZOE-50 and ZOE-70, both studies were randomized, placebo-controlled, multi-center studies running parallel in 18 countries across North America, Europe, Latin America, and Asia-Pacific. The primary objectives were HZ efficacy in persons ≥50 years of age or ≥70, respectively. Since the studies were conducted at the same sites, individuals who were 70 years or older were randomly assigned to either ZOE-50 or ZOE-70. There also were pre-specified primary objectives for a pooled analysis, which included all subjects 70 years of age and older from both studies. These objectives were PHN efficacy and HZ efficacy. There were 16,160 subjects enrolled in ZOE-50 and approximately 14,800 enrolled in ZOE-70. Subjects were randomized 1:1 in two groups. The vaccine group received 2 doses of HZ/su at 2-month intervals and the placebo group received 2 doses of 0.9% saline solution at 2-month intervals. There were 3 exclusion criteria: 1) having a previous episode of HZ disease, 2) having previous varicella or HZ vaccination, and 3) having an immunocompromising condition.

In terms of the results in ZOE-50, for the primary objective, 6 cases were detected in the vaccine group versus 210 in the placebo group for a VE of 97% in individuals 50 years of age and older. That 97% was maintained independent of age, even in subjects 70 years of age and older with quite tight confidence intervals. The primary objective for ZOE-70 was to evaluate VE in the prevention of HZ, with secondary objectives to evaluate VE in the prevention of PHN and evaluate vaccine safety and reactogenicity. The pooled analyses has 2 pre-specified primary objectives, which were to evaluate VE in the prevention of PHN in subjects ≥70 years of age across both Phase 3 studies, and evaluate VE in the prevention of HZ in subjects ≥70 year of age across both Phase 3 studies.

It is important to have a good understanding of the cohorts that were used for each of the analyses. The total vaccine cohort (TVC) included 13,900 subjects who all received at least 1 dose of HZ/su. The follow-up time was 4 years. This was the primary cohort used for the safety analysis. The modified total vaccinated cohort (mTVC), excluded subjects not receiving dose 2 or those who developed HZ within 1 month after dose 2. There were 13,163 subjects in this cohort. The mean follow-up time was 3.7 years. This was the primary cohort used for the efficacy analyses. The diary card cohort was a subset of TVC of approximately 1000 subjects, which was used for the reactogenicity analyses. Here are the ZOE-70 demographics results:

ZOE-70

Results – Demography

TVC – Total Vaccinated Cohort

ZOE-70

Characteristics	HZ/su N=6950	Placebo N=6950
Age (mean age at dose 1, years ± SD)	75.6 ± 4.7	75.6 ± 4.7
Age, years (%)		
70-79	78	78
≥ 80	22	22
Gender (%)		
Female	54	55
Male	46	45
Region (%)		
Australasia	19	19
Europe	54	54
Latin America	8	8
North America	19	19
Race (%)		
White	77	77
Black	1	1
Asian	18	18
Other	4	5

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age and Older. NEJM 2016;375:1019-32

The mean age at dose 1 was 75.6 years, 54% of subjects were female, and there were virtually no differences between the vaccine and placebo groups for age, gender, region, or race. Approximately 20% of subjects were recruited from North America.

In terms of VE against HZ overall and by age group as derived from the mTVC for ZOE-70, 23 shingles cases were detected in the vaccine group compared to 223 cases in the placebo group for a VE of approximately 90%. This VE was maintained even in the older age group of 80 years of age and older. The pooled ZOE-70 and ZOE-50 analyses include all subjects 70 years of age and older from both studies, the primary objective. These results are considered the most robust as there were approximately 3400 additional subjects who came from the ZOE-50 study. With respect to the primary objective, 25 shingles cases were seen in the vaccine group versus 284 cases in the placebo group for a VE of 91%. Even among those individuals 80 years of age and older, the VE of 91% was maintained with consistent and narrow confidence intervals.

Another important aspect to look at is VE by year post-vaccination. From the pooled analysis, including all subjects 70 years of age and older, only 2 cases were detected in year 1 in the vaccine group versus 83 cases in the placebo group for a VE of approximately 98%. This year seems to be an outlier. In year 4, 4 years post-vaccination, VE was stilled maintained at 88%. Although these VE estimates are a snapshot, there is some consistency between years as can be seen by the overlapping confidence intervals. In terms of the pooled results of VE against PHN, the most important complication of shingles, there were 4 PHN cases in the vaccine group compared to 36 in the placebo group for a VE of 89% in individuals 70 years of age and older. Looking across all age groups, in general, VE is maintained with the exception of those 80 years of age and older in which there were too few cases to have statistical significance. This differs from what was observed in the ≥80 group for HZ where there was quite robust significance and quite high VE.

Turning to safety and reactogenicity as observed in ZOE-50 and ZOE-70, one observation as might be expected due to comorbidities and older age is that there were more SAEs and deaths reported from ZOE-70 than from ZOE-50. However, the important take-home message is that independent of coming from ZOE-50 or ZOE-70, there were no imbalances between vaccine recipients and placebo recipients for any of the endpoints (SAEs, pIMDs, or deaths). ZOE-50 and ZOE-70 also provided some interesting information regarding reactogencity. In terms of solicited local symptoms reported 7 days post-vaccination of any grade comparing the vaccinated to the placebo group, as may be expected with an adjuvanted vaccine, injection site reactions were common and were more common in vaccine recipients than in placebo recipients. The median duration of these symptoms was 2 to 3 days, and most were mild to moderate in intensity.

Looking specifically at reactogencity for Grade 3 reactions (greater than 100 mm for redness and swelling and impeding normal activities for pain) for local symptoms, 8% or less of Grade 3 reactions were reported. However, these were reported more often in vaccine recipients than in placebo recipients. The mean duration for these symptoms was 1 to 2 days. Looking at solicited systemic symptoms reported 7 days post-vaccination of any grade, the 3 most common systemic symptoms were fatigue, headache, and myalgia. These were more commonly reported in the vaccine recipients compared to placebo recipients. Most were mild to moderate in intensity, and the median duration was 1 to 2 days. Regarding the Grade 3 systemic symptoms reported, 6% or less were reported across the study. They were more frequent in vaccine recipients compared to placebo recipients specifically for fatigue, headache, myalgia, and shivering. The median duration was 1 to 2 days.

Regarding compliance with the second dose, for ZOE-50 compliance with the second dose was 96% for both vaccine and placebo groups. For ZOE-70, it was 95% or 96% for vaccine and placebo groups. Essentially across the board, there was very high second dose compliance.

In summary of safety and reactogenicity for ZOE-70 and ZOE-50 / ZOE-70, no safety signal has been detected. There was no imbalance in the incidence of safety endpoints (SAEs, pIMDs, deaths) were observed between the HZ/su and placebo groups. Additionally, AEs and safety endpoints were as expected in this patient population. Local and systemic reactions to HZ/su were common in the first 7 days after vaccination. The large majority were of mild-moderate intensity and of short duration.

In summary of efficacy for ZOE-70 and ZOE-50 / ZOE-70, ZOE-70 VE in adults 70 years and older was >90% for the prevention of HZ. These results are fairly consistent with the previous 97% VE in this age group from ZOE-50 trial. In the pooled analyses, considered to be the most robust analysis, VE for the prevention of HZ in adults 80 years and older was 91%. HZ/su VE of 88% was demonstrated through year 4, and exhibited similarly high efficacy of 89% in the prevention of PHN in individuals 70 years and older.

With respect to upcoming evidence generation, GSK has quite a bit of ongoing evidence generation activity. There is a revaccination study that is evaluating the immunogenicity, safety, and reactogenicity in individuals with a history of ZOSTAVAX™ immunization at least 5 years prior who were subsequently vaccinated with HZ/su. There are a series of co-administration studies to evaluate the immunogenicity, safety, and reactogenicity of the vaccine when co-administered with quadrivalent influenza, pneumococcal polysaccharide vaccine 23 (PPSV23), and Tdap. There also is a duration of protection study in which efficacy, safety, and immunogenicity persistence are being assessed over a long period of time up to 10 years post-vaccination as an extension of the ZOE-50 and ZOE-70 studies.

The other exciting news is that GSK plans to submit a BLA for Center for Biologics Evaluation and Research (CBER) review of the candidate HZ/su vaccine before the end of 2016, with the expected indication of prevention of HZ in adults 50 years of age and older. GSK is very proud of HZ/su and believes this vaccine not only has the real potential to improve the prevention of shingles and its complications, but also could shed light on the way future vaccines are developed to overcome the challenges of decreasing immunity in older adults and the elderly.

Discussion Points

An inquiry was posed regarding whether GSK planned to assess the use of HZ/su vaccine in individuals who have a previous history of HZ. In addition, there was a low number of Black participants in the study of only 1%.

Dr. Colindres replied that GSK has conducted a study looking at vaccinating individuals who had a previous episode of HZ disease, which should be published soon. The results were that the vaccine was immunogenic and safe. With regard to the percentage of Black participants in the study, there are two considerations. The first is that this study was conducted worldwide in a lot of countries throughout the world including Europe, Asia-Pacific, and Latin America. Looking at that number for North America in the US, it would be approximately 4%. It is still less than the percentage of African Americans in the US population, but it is slightly higher.

Regarding ZOE-50, Dr. Middleman (SAHM) pointed out that slide 9 showed that the efficacy among those ≥70 is 97.9% with a pretty nice confidence interval. In ZOE-70, the efficacy for 70 through 79 years was 90% with still a pretty tight confidence interval. She asked whether there had been any thought about why the two studies would have different VE findings.

Dr. Colindres responded that he did not have a magic answer to that, other than it was what came out in the clinical study. There was some degree of overlap in the confidence intervals, which accounts for some of it.

Dr. Kimberlain (AAP) noted that on the pooled analysis for HZ, the sample sizes were in the 8200 to 8300 range. However, the PHN pooled analyses that increased to 13,000 for the sample sizes. He asked whether Dr. Colindres could explain why.

Dr. Colindres replied that this essentially was because the 50 year old group also was included. For the pooled analyses, which would include the primary objective, the other sample size of 8000 or so is correct. This sample size included those 50 years and above, which included all subjects including the 50.

Dr. Atmar noted that the frequency of PHN in persons over 80 years of age was remarkably lower in the placebo group compared to younger age groups where it was about 50% to 60% of people who develop HZ. He asked whether there was an explanation for that.

Dr. Colindres replied that he did not have an explanation of why it was lower in those 80 years of age and above, although they did observe that as well. The prevention of PHN was clearly associated with decreased incidence of HZ disease, so clearly one was linked to the other.

Dr. Walter requested clarification regarding whether the efficacy analyses included only the period following 1 month after the second dose, and if he had any information on the distribution of cases that occurred following the first dose in that time period.

Dr. Colindres responded that the efficacy analyses included after 30 days essentially, and there were under 20 cases during that time period following the first dose.

Dr. Messonnier asked whether Dr. Colindres to provide some sense of the timing of when data would be available from the upcoming evidence generation, and Dr. Bennett asked about vaccination of people who have previously received HZ vaccine.

Dr. Colindres replied that they are actively working on the revaccination study and should have results by about April or May of 2017. They are working closely with the ACIP HZ WG to have that information reviewed as soon as possible. The co-administration studies are completed and in the analysis phase. An abstract of the influenza co-administration study will be presented during IDWeek and showed quite good results. The duration of protection study is still a way off. The study of people who previously have had HZ has been completed, and GSK is in the process of writing the manuscript.

Dr. Hahn (CSTE) asked whether Dr. Colindres had data on AEs from first dose compared to second dose, and if a person had an AE the first time, did they had a worse reaction from the second dose.

Dr. Colindres indicated that there does seem to be some correlation, but GSK is still in the process of analyzing these data. They will share it as soon as it is available.

Dr. Whitley-Williams (NMA) noted that in addition to under-representation of Blacks in the study, she did not see Hispanics in the US population. While she recognized how difficult it can be to conduct studies in the US, she emphasized that studies should reflect the population as it is represented in the US, particularly regarding immunogenicity and AEs. If this was rolled out and for whatever reason there was an increase in AEs in a particular ethnic group, this could negatively impact an already challenging adult immunization system.

Dr. Friedland (GSK) indicated that GSK works extremely diligently to identify investigators and patients who are representative of the US population in its clinical trials. These results are not different from other clinical trials with other vaccines. It is very difficult to identify patients and investigators who can enroll in these clinical studies in order to have representative populations. GSK is not giving up and will continue to work on this.

Yellow Fever Vaccine

Mark Gershman, MD
Travelers' Health Branch
Division of Global Migration and Quarantine
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Gershman reminded everyone that Yellow Fever (YF) is caused by the YF virus, which is in the genus flavivirus. This virus is transmitted predominantly by *Aedes* mosquitoes. YF disease is endemic in sub-Saharan Africa and tropical South America. Asymptomatic infection occurs in most people. When clinical disease occurs, it ranges from mild febrile illness to severe disease with jaundice and hemorrhage, and can be fatal. Outbreaks occurred in 2016 in areas of Africa where cases had not been reported for decades, with the most notable being a large outbreak in Angola that is now subsiding.

YF vaccine is a live-attenuated viral vaccine produced in chick embryos. There are 4 WHO-prequalified vaccines available globally. Vaccine Prequalification is a process established by WHO to ensure the quality and safety of vaccines provided through the United Nations (UN) for use in national immunization programs. There is only one YF vaccine licensed for use in the US, which is YF-VAX® that is manufactured by Sanofi Pasteur. YF-VAX® is not WHO-prequalified and is, therefore, not part of the global supply. YF vaccine is the only one for which proof of vaccination can be required by countries from arriving travelers under International Health Regulations (IHR) of 2005.

Regarding the global YF vaccine supply in 2016, 6 million doses of YF vaccine are placed in a global emergency stockpile annually. This stockpile is managed by the International Coordinating Group (ICG) on Yellow Fever Vaccine Provision (WHO, UNICEF, MSF, Red Cross/Red Crescent). The emergency response to large outbreaks in Africa this year depleted this stockpile several times. Consequently, YF vaccine doses allotted for childhood and prevention campaigns were rerouted for response efforts. Also, as a dose-sparing measure in the face of global shortages, fractional doses of YF vaccine were used in Democratic Republic of the Congo (DRC) for preemptive vaccination of residents of Kinshasa.

In the US, YF vaccine is used to vaccinate people travelling internationally, including the military. This is for travel to countries where there is risk of YF virus transmission, and for travel to countries that have entry requirements for proof of YF vaccination as allowed under IHR 2005. Also, YF vaccine is used to vaccinate laboratory workers potentially exposed to YF virus in their line of work. Regarding the YF vaccine supply in the US, historically, intermittent manufacturing issues have led to temporary supply shortages. Since the end of 2015, there has been an ongoing YF vaccine shortage in the US, with ordering restrictions in place this entire time. This was compounded by the anticipation of additional demands on the vaccine supply for travel to the Brazil Olympics this past summer by athletes, official delegations, and tourists.

In conjunction with the large YF outbreak in Africa and global supply issues, concerns about the US YF vaccine supply led to the initiation of stakeholder discussions in spring 2016. The focus of these discussions was how to assure a stable YF vaccine supply for travelers, military, and response personnel in the US. Participants included CDC, Sanofi Pasteur, FDA, and the Department of Defense (DoD). The options to assure the US YF vaccine supply reviewed in these discussions included the following:

- ❑ Maintaining the status quo by relying on the release of new YF-VAX® lots currently in production

- ❑ Implementing an Expanded Access Investigational New Drug (IND) application to allow for importation and use of YF vaccine licensed outside the US

    - This vaccine would be STAMARIL®, which is manufactured in France by Sanofi Pasteur and is licensed and marketed in more than 70 countries

- ❑ Using fractional dosing of YF vaccine as was done in the DRC

At present, the status of these options for the US YF vaccine supply is that YF-VAX® lots currently being produced are scheduled to be released before the current inventory is exhausted. Notably, the current inventory is lasting longer than anticipated because the level of increased demand for the Olympics did not occur. Current ordering restrictions for YF-VAX® would remain in place to help modulate the future depletion of current inventory. A contingency plan is being developed with submission of an IND application to import and use STAMARIL®, the YF vaccine licensed outside the US. The IND application is presently under a 30-day review by the FDA. The IND protocol, including training of clinicians, would be implemented should there not be an adequate US supply of YF vaccine. Fractional dosing was not considered to be a viable option based on limited data and many uncertainties.

In conclusion, in 2016, limitations occurred in both the global and the US YF vaccine supply. Contingency plans are being developed for the US YF vaccine supply. These plans will be enacted as needed based on demand and supply.

Discussion Points

Dr. Belongia asked for additional explanation about how the IND works with a vaccine licensed in another country, and what the protocol is.

Dr. Gershman replied that the protocol is basically the plan regarding how to get the vaccine distributed to the clinicians who will use it, the conditions of distribution, the conditions of monitoring safety, et cetera. It is not an experimental protocol. Expanded access is a clinical

protocol, similar to that for an orphan drug, to supply a vaccine or drug that otherwise would not be available and is deemed to be absolutely necessary. He deferred to Dr. Sun from the FDA or representatives from Sanofi Pasteur to offer further information, given that Sanofi Pasteur wrote the protocol.

Dr. Greenburg (Medical Affairs, Sanofi Pasteur) agreed with Dr. Gershman's summation. This is a clinical protocol as opposed to a study per se, such as a clinical trial with hypotheses and specific statistical questions being asked. Instead, it is a mechanism that is reviewed and approved by the FDA to import STAMARIL® as an unlicensed product into the US and distribute it to clinicians throughout the US at specific sites that use a lot of YF vaccine. These will be clinicians who are used to administering YF vaccine, who would administer the vaccine as they normally would with YF-VAX® and monitor / report safety issues to Sanofi Pasteur as the manufacturer and to the FDA. Otherwise, use of the vaccine is fairly routine with some additional safety follow-up.

Dr. Gershman added that the challenge with this is that it is a unique vaccine and a unique situation. Over 5000 civilian clinics administer YF vaccine, so it would not be practical or achievable to distribute STAMARIL® to all of those clinics. It would be virtually impossible. Part of the protocol involves how site selection is accomplished. What seems to be a reasonable situation has been worked out to distribute to those clinics that appear to be the top users by volume, and such that geographical access is maintained for people in all states. It is a delicate balance, because the amount of work involved is quite a lot. However, the vaccine needs to be accessible in order to prevent the importation of a potentially fatal disease.

Dr. Hunter asked whether the current situation with the US supply being separate from the global supply was a conscious policy decision, or if it developed historically for market reasons.

Dr. Gershman replied that he thought it had developed historically for market reasons because in general, YF vaccine is used for two main purposes: 1) for international travelers, in which case it is used only in the country in which it is produced, which is a very circumscribed market; and 2) for vaccines provided through the UN for use in national immunization programs, which go through the rigorous WHO Vaccine Prequalification process to ensure the quality and safety of those vaccines for mass vaccination campaigns. Sanofi Pasteur did not pursue WHO prequalification for the US-manufactured vaccine YF-VAX®, but justifiably so. Why would it need to be done? It is a lengthy and expensive process. STAMARIL® is produced in France and is one of the WHO prequalified vaccines used globally, including in routine infant immunization programs and in mass vaccination campaigns - preemptively, and in response to outbreaks.

Dr. Plotkin (Vaccine Consultant) apologized at this late hour, but wanted to make a specific request since he did not know when YF would come up again. He requested that CDC reconvene the YF WG to reconsider its recommendation regarding YF vaccine boosters, and indicated that he had data. In February 2016, the YF WG recommended that revaccination is unnecessary for YF. They stated and printed that 92% of vaccinees are seropositive at 10 years, that there is a paucity of vaccine failures, and evidence of seropositivity. Recently, an article was published by Amanna and Slifka in which they reviewed the literature and concluded that immunity is lost in 20% to 33% at 10 years, and that children are at greater risk for losing their seropositivity. He quoted from their article, "An extensive study examining cases of yellow fever in Brazil has provided much needed insight. In this study, patients were not only queried about their vaccination status, but also asked whether they had been vaccinated within 10 years prior to contracting yellow fever. There were 831 cases of yellow fever identified between 1973

and 2008. Vaccination status was unavailable for 372 of the patients, but the remaining 459 cases had received prior yellow fever vaccination, and yet still contracted yellow fever. Since all of the cases of yellow fever were virologically confirmed, we believe that this is likely to be a more accurate representation of vaccine failures than the previous estimate of only 23 worldwide vaccine failures." Then the comment that "52% of those had been vaccinated more than 10 years previously" [Ian J. Amanna & Mark K. Slifka, *Questions regarding the safety and duration of immunity following live yellow fever vaccination,* Pages 1519-1533 | Received 01 Mar 2016, Accepted 02 Jun 2016, Accepted author version posted online: 08 Jun 2016, Published online: 20 Jun 2016]. Dr. Plotkin recommended that the WG read this paper. There also is a study from Brazil specifically in children, which shows seroconversion rates after the first vaccination of only about between 80% and 85%. Michael Tauraso reviewed the situation. It is true in the abstract he says that duration of immunity is good, but looking at his table, for those studies in which there were more than 100 people involved, the persistence was 76% at 17 years, 81% at 30 years, 75% at 10 years, 69% at 4 years, and 65% at 10 years. There was no study of Africa where YF is epidemic, so the duration of immunity is unknown in an African population. He thinks that duration of immunity of the YF vaccine has been exaggerated. He thought this should be reevaluated in light of all of the data available, not simply those that apparently were used by the initial group.

Dr. Bennett thanked Dr. Plotkin for his comments and said she thought the issue would be taken into consideration by the WG.

Ms. Pellegrini asked whether there was any explanation for why YF has reemerged so suddenly and so aggressively in parts of Africa. Over the last couple of years, there seem to have been a number of cases where flaviviruses have done this, or left continents and wreaked havoc. She wondered whether they should be worried about YF perhaps spreading to additional areas.

Dr. Gershman replied that while he did not think anyone knew for sure, he thought it was partially a result of a combination of global climate change, and El Niño cycles that are periodic and normal. This can lead to an increase in the density of mosquito vectors, which has occurred during a time of growing populations in urban areas in Africa. This is an urban cycle YF outbreak that has been so severe in Africa. In general, there are several different cycles of YF virus transmission. The urban cycle has as its vector the *Aedes aegypti mosquito*, and involves person-to-mosquito to person transmission of the YF virus. The sylvatic cycle is jungle YF where people wander into the jungle and are bitten randomly by mosquitos that usually prefer to bite monkeys. As more roads are being built, more access is created to people from areas where they might be exposed to YF virus by the jungle transmission cycle, to urban areas, where they can then introduce it to heavily populated areas with dense levels of *Aedes* aegypti mosquitos. He thinks it is a host of all of these factors.

In the context of the events that occurred, Dr. Thompson (NVAC) requested further information about what occurred to cause the supply disruption and whether anything is being done to increase the safety stock to address this.

Dr. Gershman replied that it is a manufacturing issue, and deferred to the Sanofi Pasteur representative to provide more details.

Julian Ritchey (Sanofi Pasteur) confirmed that it is a manufacturing issue and for some time, Sanofi Pasteur has been looking to move to a new manufacturing facility. The current manufacturing facility is older, and they are in the process of making that transition and making it seamless.

Regarding Ms. Pellegrini's question, Dr. Sun (FDA) added that YF cases from the recent outbreak in Africa were imported to China. Even though the mosquito that transmits YF has been endemic in Asia, Asia has not had YF. This is an enigma for flavivirology. Travel-associated YF that is imported from areas of outbreak is of great concern. Regarding IND, Dr. Sun explained that the Expanded Access IND is a mechanism by which unapproved products can be made available for use, and in this case, for wider use. The same mechanism was used for Bexsero® for MenB in university outbreaks. There are various versions of the Expanded Access IND. There is one for products that are to be licensed, and one for products that are not headed for licensure. They are dealt with somewhat differently, but the basic principle is that it is still considered an unapproved product and, therefore, the transport across state lines has to be under IND. In addition, there has to be a streamlined approach to collection of AEs.

Day 1: Public Comment

Dr. Stanley Plotkin
Vaccine Consultant

Once again I apologize for keeping the committee, but I just don't have any choice in the matter so to speak. What I am now urging on the committee is to form a Lyme Disease Vaccine WG. That a Lyme disease vaccine is sorely needed I think is without question. The CDC itself estimates 300,000 annual cases, and there are another 20,000 estimated in Europe. Carditis, neurological complications, and rare deaths occur. I have spoken to this committee before and mentioned that one of my own sons had a life-threatening case of Lyme carditis. At any rate, the original vaccine that was licensed in the late 90s worked quite well in terms of its efficacy, although boosters were needed because of the mechanism of the OspA (outer surface protein A) antigen that was in the vaccine. Unfortunately, and I say this carefully but clearly, that CDC did not support the original Lyme disease vaccine. That was one of the reasons why it was taken off of the market. Another reason was that the manufacturer did not do a pediatric study until it was too late. Then there was a questionable safety signal, which was never supported by VAERS analysis, was never supported by laboratory analysis, but was enough to decrease sales and the manufacturer took it off. I should mentions as far as the pediatrics is concerned, the study that was done late in the game shows that if anything, children responded about 10 times better to the vaccine than did adults. So, the question now is can we have a new vaccine? I've been working with potential Lyme vaccine manufacturers, and I should say clearly that I have no financial interests in this whatsoever. But, they do not know if ACIP is interested and will make a positive recommendation. Clearly, ACIP cannot make a recommendation without having an actual vaccine. But, it could indicate interest in having one. I think a Lyme Disease WG to consider the target product profile and to meet with potential new vaccine manufacturers, and there are candidate vaccines, would be very desirable. The situation I think is similar to the rotavirus situation. If you recall, the original rotavirus vaccine was taken off of the market because of intussusception. Then the issue for the manufacturers, and I was personally involved in this, was will a new vaccine be recommended? It was clear at the time that ACIP wanted to prevent rotavirus disease and, therefore, two manufacturers undertook to

make new vaccines, which ultimately were licensed. Again, and lastly, I hope that the ACIP will consider forming a Lyme Disease Vaccine WG to indicate that they have an interest in an eventual vaccine. In 2000, the IOM did an analysis of what vaccines—that is, what diseases for which we need vaccines, what are the first priorities for developing vaccines? That was a very important document. That had a major effect on the manufacturers in terms of choosing targets. That sort of analysis is really needed. NVAC should do it, but they won't. The ACIP could do it by various mechanisms, but again, has not undertaken to do that. Thank you.

Dr. Bennett responded that Dr. Plotkin posed an interesting problem, but that it probably was beyond the purview of the ACIP to develop a WG to advocate for the development of a vaccine. However, it is not beyond the purview of the CDC or the SMEs at the CDC. This is an overarching problem in the US. How do we decide which vaccines we advocate for the development of? There is not a very good systematic approach to this.

In response to whether this would fall under NVAC's purview, Dr. Birkhead (NVPO) said he thought that the NVPO addresses the development of new vaccines. However, he was not aware of a formal mechanism by which recommendations are made for vaccines that are of interest for further development.

Dr. Thompson (NVAC) indicated that NVAC has been very interested in recent meetings in the area of vaccine innovation. She thought this would fall into that category as it would be a new vaccine. NVAC certainly is assessing all of the incentives that the whole system faces with respect to innovation in the vaccine area, so she thought this was something NVAC could take up as a question, but in the context of the broader theme. One issue that Dr. Plotkin raised that has been raised by others to NVAC is the fact that manufacturers or developers in general would like some assurance that there would be a market for a product. That is very hard for any advisory committee to give. The concept of target profiles is interesting and is worthy of exploration, and certainly is something that NVAC could consider. Perhaps ACIP could in some way consider that as well at some point.

Christina Hildebrand
A Voice For Choice Advocacy

To finish off the evening, I wanted to come back to a few comments that I made earlier and just expand on them. The first one is, you know, looking at all of the data that was presented today, it was either really small base sizes or it was by the pharmaceutical companies, which is not independent research by any means. I really urge the CDC to do independent research that is not the CDC or the pharmaceutical companies doing research, because both of you get money out of this, and so we need an independent research body doing research. We've got 12 CDC researchers who came out today questioning the ethics of the CDC, and the infiltration of money into the CDC and into our government. We know that pharmaceutical companies are the largest lobbying force out there. We also have one CDC whistleblower, Dr. William Thompson, who has shown that there's been fraud at the CDC. He's shown that there has been fraud on the MMR studies. There's also, you know, efficacy research on the MMR. There's a lawsuit right now questioning the efficacy of the MMR. I just, you know, I look at this data and I look at what you're doing here at the ACIP and at the CDC and I just ask that independent research is done or that you use the independent research that is out there, because using paid for research or your own research just isn't good enough. Thank you.

Zika Virus Update

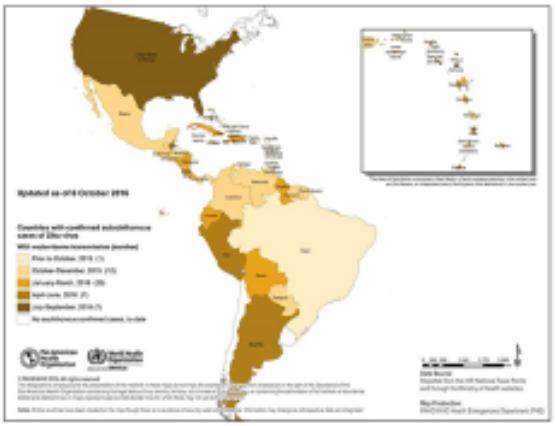
Ms. Stacey Martin
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Ms. Martin explained that Zika virus is an ribonucleic acid (RNA) flavivirus related to dengue, YF, Japanese Encephalitis (JE), and West Nile Virus (WNV). Transmission to humans is primarily by *Aedes* (Stegomyia) species mosquitoes. Infection is typically asymptomatic or causes mild dengue-like illness. However, recent outbreaks have identified new modes of transmission and clinical manifestations.

Zika virus was first isolated from a sentinel rhesus macaque monkey in Uganda in 1947. Before 2007, only sporadic human disease cases were reported from Africa and Southeast Asia. In 2007, the first Zika outbreak was reported on Yap Island, Federated States of Micronesia. In 2013–2015, more than 30,000 suspected cases were reported from French Polynesia and other Pacific islands. Local transmission was first identified in the Americas in May 2015 and subsequently spread across the region.

As of October 13, there are 47 countries and territories in the Americas that have confirmed mosquito-borne transmission of Zika virus. The map below provides a timeline of the first reports of local transmission with Brazil confirming its first case prior to October 2015 and the US confirming its first case this summer. The table on the right reflects the number of locally transmitted Zika virus disease cases reported to the Pan American Health Organization (PAHO) by country in the Americas, now in excess of 660,000:

Locally transmitted Zika virus disease cases reported to PAHO by country in the Americas, 2015–2016 (as of Oct 13)



Country/Territory (N=47)	(N=661,183)*	
Brazil	298,827	(45%)
Colombia	104,465	(16%)
Venezuela	60,176	(9%)
Martinique	36,467	(6%)
Honduras	31,799	(5%)
Guadeloupe	30,969	(5%)
Puerto Rico	26,701	(4%)
El Salvador	11,285	(2%)
Other	60,494	(9%)

*23% of cases are lab-confirmed

http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=36555&lang=en

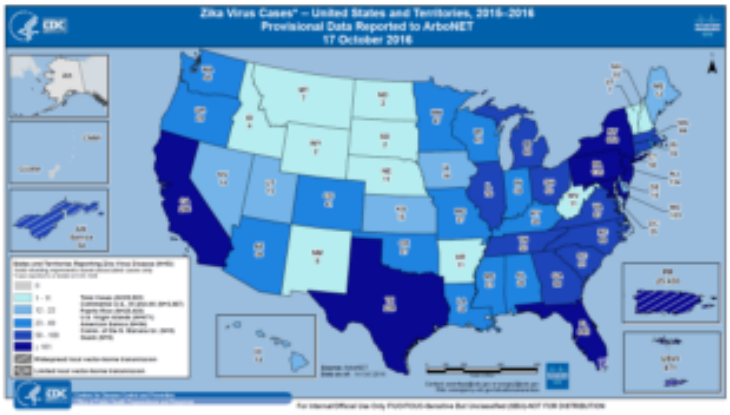
Approximately 60% of the total cases were reported from two countries, Brazil and Colombia. Of note, most of the reported cases are suspect cases and only 23% of cases are laboratory-confirmed. Most suspected and confirmed locally transmitted cases reported to PAHO, as of October 2016, were reported from South America (73%), followed by the Caribbean (18%), and then Central America (8%).

Zika virus disease was made a notifiable condition in Brazil in February 2016. For this reason, temporal trends of cases are only available in 2016. There was an increasing trend starting in January that peaked in February. Since then, there has been a steady decline in both confirmed and suspected reported cases. Zika became a reportable condition in Columbia in October 2015. Reported cases began to increase in August 2015 and continued until early February 2016. Reported cases have declined since the peak. In Mexico, the first confirmed case was reported in late 2015. In 2016, Mexico reported an increase in cases that peaked in August. As of epidemiology week 42, and given the expected lag in reporting, it was too soon to say whether they are experiencing a decline in cases. CDC also has recently learned about cases being identified in communities along the border with Texas.

In the US, a total of 3892 travel-associated cases have been reported to ArboNET as of October 12th. Of these travel-associated cases, 98% were reported from the States. For locally acquired cases, a total of 25,999 cases have been reported, and 98% of these were reported from Puerto Rico. In the States, 128 locally-acquired cases have been reported to ArboNET, all from Florida.

The following map shows laboratory-confirmed Zika virus disease case reported to ArboNET by state or territory, with 49 states having reported cases. The highest reporting states are New York and Florida, each reporting over 20% of the cases, followed by California and Texas. All other states have reported less than 5% of the total cases:

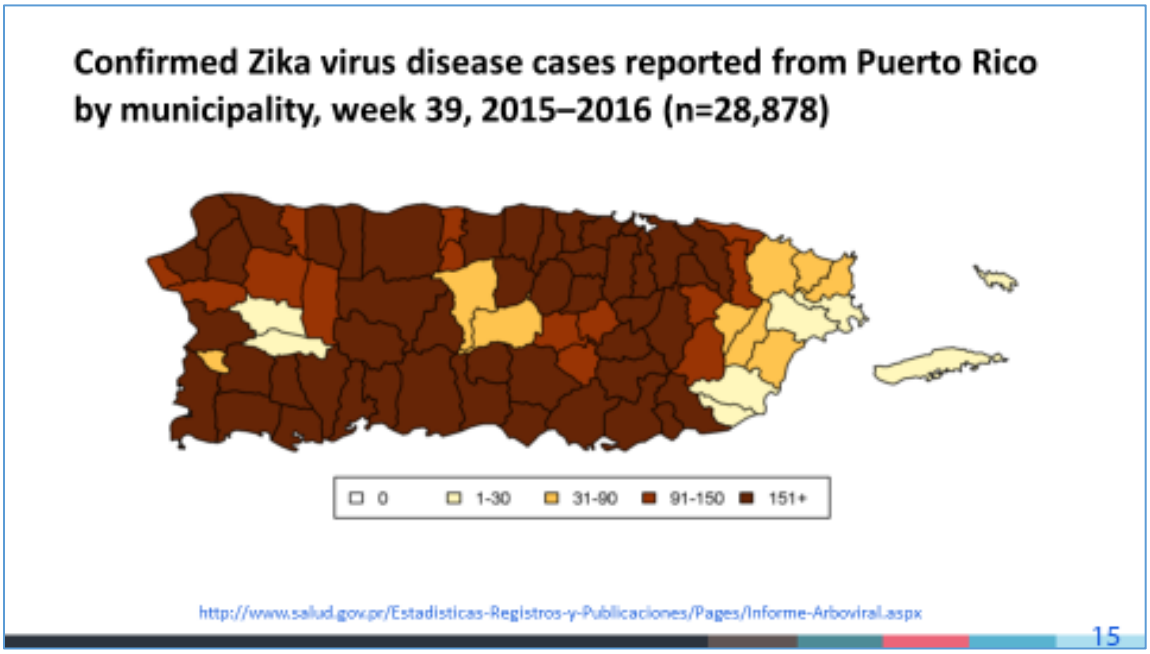
State of residence for reported Zika virus disease cases — U.S. states 2015-2016 (as of Oct 12, 2016)



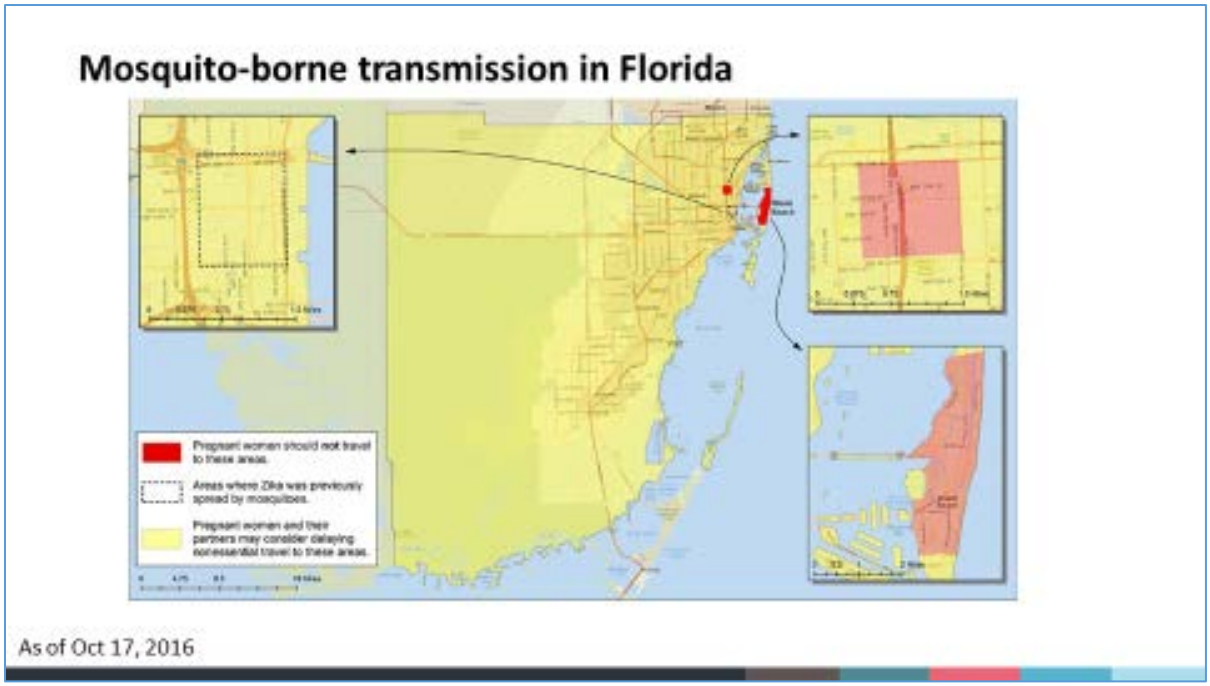
State	(N=3,936)
NY	858 (22%)
FL	836 (21%)
CA	296 (8%)
TX	228 (6%)
PA	135 (3%)
NJ	134 (3%)

Between January and October 2016, there have been a total of 3775 travel-associated cases and 137 locally acquired cases in the US reported to ArboNET. The epi curve suggests the number of reported cases peaked in July, but there is a lag in reporting. Also, the US reported its first locally transmitted case in June from Florida. Florida continues to report locally transmitted cases. The majority of cases occur in adults, with the highest number of cases in 30 through 39 year olds. Travelers returning from the Caribbean represent the highest proportion of travel-associated cases, followed by travelers from Central America, South America, and North America.

Puerto Rico reported its first case at the end of 2015. The number of reported confirmed cases increased from January through August of 2016. Following the peak, the weekly number of reported cases has declined. The Puerto Rico Department of Health has reported over 28,000 cases. As shown in the following map, the cases are distributed throughout the island. This is likely a significant underestimate of the true number of infections, since the clinical presentation of Zika virus infection is typically mild or asymptomatic:



As previously mentioned, Florida has reported over 100 locally acquired Zika cases. The first area to be identified was the Wynwood neighborhood of Miami-Dade County, followed by Miami Beach, and then most recently, Little River, also in Miami-Dade County. To summarize, Florida has experienced sporadic locally acquired cases in multiple counties in Florida. Many of these are believed to be single transmission events without further spread. The three areas highlighted on the following maps were found to have multi-person transmission, which prompted Florida and CDC to recommend that pregnant women avoid travel to those areas:



In Wynwood, state and local officials appear to have successfully ended local transmission after aerial spraying and other mosquito control efforts. As of October 17th, Florida has reported 160 cases of locally transmitted infections. Concerns about low levels of transmission outside of the three designated areas zones prompted Florida and CDC to state that pregnant women and their sex partners may consider postponing nonessential travel to all parts of Miami-Dade County. As of October 19th, CDC began recommending laboratory testing for all pregnant women who have had exposure to all areas of Miami-Dade County after August 1st.

Before ending, Ms. Martin provided a high-level overview of Zika virus vaccine development activities. She indicated that a US government interagency working group that includes members from the Assistant Secretary for Preparedness and Response (ASPR), National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority (BARDA), FDA, CDC, and Walter Reed Army Institute of Research (WRAIR) was established to: 1) evaluate promising candidate vaccines for safety, immunogenicity, and efficacy; 2) ensure availability of one or more candidate vaccines in 2018 for emergency use in US population at high risk of exposure or disease; and 3) work with partners to commercialize vaccines for broad distribution by 2020. Currently, there are many vaccine candidates in preclinical development which will be presented to ACIP at a later date. There are expected to be four vaccines in phase 1 clinical trials by the end of 2016, and phase 2 studies are scheduled to begin in 2017.

Discussion Points

Given that about 80% of Zika cases are asymptomatic, Ms. Pellegrini asked whether CDC thinks it is possible or likely that the 25,000 plus in Puerto Rico could be 20% or possibly even less for people not seeking care at all in terms of the actual number of infections in Puerto Rico.

Ms. Martin stated that it is possible. The only data CDC has that provides a ratio of symptomatic to asymptomatic cases is from Yap Island. It is believed to be about 1:4. The number of reported cases is likely a dramatic underestimate of the true burden of disease on the island.

Once the epidemic curve has run its course in a population, Dr. Hunter asked what the role of vaccination would be in a country that is going to be endemic versus a country that has different areas that are going to be endemic and others that are not.

Ms. Martin replied that there always are likely to be susceptible populations in new cohorts, but the use of vaccines may differ between a country that has had large epidemics versus countries that have endemic disease.

Noting that there is endemic dengue in Puerto Rico, Dr. Sun (FDA) asked whether in the epidemic curve for Zika the dengue cases could be superimposed with Zika cases in order to get a sense of whether Zika is declining is because the rainy season is over and there is less transmission of all types of mosquitos, or if it is just a case of Zika going away.

Ms. Martin responded that it is probably a combination of multiple factors. They have had a large epidemic, and it is likely that the true burden has been underestimated. In addition, most of the island has now been affected, so the number of susceptibles has also probably dropped. She said she did not want to make any comments about the vector side because she is not an arboviral expert, but it is likely multi-factorial.

Dr. Fryhofer (AMA/ACP) requested guidance on what to tell patients when they are traveling to areas like French Polynesia that do not have high levels of active infection right now, but certainly have had peaks in the past.

Ms. Martin replied that CDC is currently considering its guidance for endemic areas. Obviously, pregnant women who are traveling to any areas that may have transmission of Zika should take precautions.

Dr. Bennett reminded everyone that in February 2017, there will be a session on Zika vaccine to update ACIP on the state of the science.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier emphasized that CDC remains very occupied with the Zika response. Dr. Frieden always characterizes it as the most complicated response CDC has ever managed. This is partly due to the fact that so many parts of the agency are engaged, because it is so multifactorial and because the science continues to evolve. Regarding the use of vaccines, as always, CDC will call upon the ACIP for assistance in thinking about US vaccination policy.

On September 29th, CDC and the National Foundation for Infectious Diseases (NFID) held a joint press conference to kick off the 2016-2017 Influenza Vaccination Campaign. For the 2016-2017 season, vaccine manufacturers have estimated that up to 168 million doses of injectable influenza vaccine will be available. More than 93 million doses of influenza vaccine already

have been delivered. This season's vaccines have been updated. Most of the research suggests that they will cover the strains that are more common during 2016-2017. As of this week, overall influenza activity was low in the continental US (CONUS). Adult influenza coverage was low last year, but CDC is working to try to understand that and figure out what to do to improve influenza coverage this year.

The National Immunization Conference (NIC) was held in September in Atlanta, with thousands of immunization enthusiasts in attendance. It was actually the largest number of attendees NIC has ever had. She expressed gratitude for the many individuals and groups in the room for their strong support. The next National Adult and Influenza Immunization Summit (NAIIS) will be held in Atlanta in May 2017.

In terms of the election, CDC is working with HHS and the Office of Management and Budget (OMB) to plan and prepare for any administrative changes to come. The processes will accelerate following the election.

Globally, CDC is consistently reminded of the challenges to building global capacity for public health. Earlier this year, colleagues in CDC's Global Immunization Division (GID) released *CDC's Strategic Framework for Global Immunization 2016-2020*. The framework is built around five interconnected goals: an overarching goal to improve global health impacts; three goals to increase the amount of people reached by strengthening country-owned immunization programs; and CDC's foundational goal of providing evidence for effective policy and program implementation. That framework is available on the CDC website.

International collaboration will continue to be important as CDC looks to enhance new technologies, including for example learning about other countries that are continuing to use the nasal influenza vaccine this year. There is also much that can be learned about vaccine policy from CDC's international partners. CDC is pleased to be able to welcome its partners from China who are here to discuss priority scientific activities, and is glad to have the opportunity to learn from each other.

Centers for Medicare and Medicaid Services (CMS)

CMS recently issued a Medicare Provider notice regarding Medicare payment for the quadrivalent influenza vaccine. This notice instructs Medicare Administrative Contractors to pay for this vaccine using code 90674 with no coinsurance and deductibles. Coverage of the quadrivalent influenza vaccine was effective August 1, 2016. Because claims processing changes will be implemented on January 1, 2017, contractors and providers have been told to hold the claims until after that date.

Department of Defense (DoD)

Dr. Deussing expressed DoD's appreciation for the valuable work of ACIP and the opportunity to participate in this work, which helps protect this country's service members, their families, and all 9.4 million DoD beneficiaries worldwide. He briefly highlighted two current vaccine issues for the DoD. First, the DoD is working with the manufacturer of IMVAMUNE®, the non-replicating smallpox vaccine, to fulfill the final Phase 3 study requirement for licensure. Complete enrollment is expected by December 2016. IMVAMUNE® is projected to meet the US government's preparedness requirement for development of an attenuated smallpox vaccine in sufficient quantity to protect 66 million people, comprising those for whom replicating smallpox vaccine is contraindicated and their household contacts. Second, he reminded everyone that

the previous day they heard an excellent presentation on the current YF vaccine supply challenges. The DoD has worked very hard to mitigate the effects of the YF vaccine shortage through close collaboration with the Defense Logistics Agency (DLA), the military departments, other federal partners, and Sanofi Pasteur. As a result of this concerted effort, the DoD reduced utilization of YF vaccine by 80%, but still vaccinated all service members and beneficiaries deploying to or traveling to a YF endemic area. The DoD looks forward to the availability of the Expanded Access IND for STAMARIL®, and will continue to work with its partners on solutions to this shortage.

Department of Veterans Affairs (DVA)

Dr. Pittman reported that the VA is nearing completion for national release of its latest software patches as part of the Veterans Immunization Enhancement 2.0 Project. These patches improve support for upcoming user-facing enhancements in its EMR and the Enterprise Health Management Platform (eHMP). They also provide multidivisional support for the VA's larger integrated facilities to track immunization inventory more closely. VA has partnered with Walgreen's for the 2016-2017 influenza season and will receive data for veterans who obtain their immunizations at Walgreen's during the influenza season. This information with then be available in the VA's Veterans Information Systems and Technology Architecture (VistA) EHR in any facility where that veteran is registered.

Food and Drug Administration (FDA)

Dr. Sun reported that since the June 2016 ACIP meeting, FDA approved two additional seasonal influenza quadrivalent vaccines, Afluria® and Flublok®. In addition, FDA approved the use of Prevnar13® for ages 18 through 49 and the 9vHPV 2-dose regimen. In addition, recognizing the importance of LAIV for both seasonal and pandemic influenza, FDA has been working very closely with the manufacturer, representatives from the ACIP Influenza WG, and CDC on further evaluation of the root cause of the observation of lower effectiveness in the observational studies. This includes work on many fronts, including manufacturing issues, further analysis of observational data, and virologic studies. FDA will continue to work closely to address these problems.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that the National Vaccine Injury Compensation Program (VICP) has had a very busy year processing claims for Fiscal Year 2016, for which 1116 claims were received. At the end of the Fiscal Year, the VICP awarded approximately $250 million that were paid to petitioners and attorneys for their fees for compensated and dismissed claims, as well as interim fees and costs. More information and data about this program can be found on HRSA's website. HRSA is in the process of updating the Vaccine Injury Table. Comments on the Notice for Proposed Rulemaking proposing changes to the Vaccine Injury Table have been reviewed, and a draft Final Rule is being developed. It is currently going through the clearance process, and HRSA hopes to have that finalized and published in the *Federal Registry* before the end of this calendar year. As of August 2016, HRSA's Countermeasures Injury Compensation Program (CICP) has compensated 39 claims totaling $4.9 million.

Indian Health Services (IHS)

Dr. Groom reminded everyone that IHS developed a policy to require influenza vaccine for its HCP last season, but had not successfully bargained for it with the unions, so they were able to only partially implement it in IHS facilities. Even with only partial implementation, they achieved about a 10% increase and had coverage of approximately 85% for IHS HCP. She said she was very pleased to report that they completed bargaining with two of the largest unions, so 97% of IHS union employees are now covered by this policy, which they expect to implement fully across the IHS. They are hopeful that they might achieve the Healthy People 2020 goal this season. IHS is pleased to join a number of private and public institutions on the IAC's honor roll and have their federal mandate there along with the DoD colleagues. Regarding maternal immunizations, IHS is partnering with Johns Hopkins to develop a performance measure for the IHS to assess influenza and Tdap vaccination among pregnant women, and a reminder in the IHS EHR for its providers.

National Institutes of Health (NIH)

Dr. Gorman reported that with regard to revision of the Common Rule, the comment period is now closed. Approximately 1500 public comments were received during the comment period. Some comments contained over 150 signatures. The agencies involved are now reviewing these comments and making decisions on how to respond. The multiple agencies involved are presently driving toward consensus. They have heard that there may be an announcement soon.

NIH is now requiring a single IRB for all clinical trials that include multiple sites. *Policy Announcement NOT-OD-16-094: Final NIH Policy on the Use of a Single Institutional IRB for Multiple Site Studies* was published on June 21, 2016. This policy describes the rational for this policy and exemption criteria during the transition period.

In terms of personnel, NIH has two new institute Directors. The National Institute of Mental Health (NIMH) has appointed Dr. Joshua Gordon as its new Director: https://www.nih.gov/news-events/news-releases/nih-names-dr-joshua-gordon-director-national-institute-mental-health The National Institute of Child Health and Development (NICHD) has appointed Dr. Diana Bianchi as its new Director: https://www.nih.gov/news-events/news-releases/nih-names-dr-diana-bianchi-director-national-institute-child-health-human-development.

In terms of the National Institute of Allergy and Infectious Diseases (NIAID), NIAID researchers in influenza have advanced the understanding of how influenza protection can facilitate the development of a universal or broadly protective influenza vaccine. A nanoparticle vaccine based on an H1N1 stem, rather than the HA head, offered protection against a lethal dose of H5N1 challenge. This protection was antibody based, but did not develop neutralizing titers, which will present an issue in terms of attempting to license the new vaccines: http://www.niaid.nih.gov/diseases-conditions/niaid-researchers-advance-development-universal-flu-vaccine.

In terms of personnel at NIAID, Dr. Stephen Holland was named the Director of the Division of Intramural Research (DIR): https://www.niaid.nih.gov/news-events/niaid-selects-director-division-intramural-research. NIH continues to search for a new Division Director for Division of Microbiology and Infectious Diseases (DMID). Dr. Fred Cassels, Branch Chief of the Enteric and Hepatic Diseases Branch (EHDB) retired from government service on September 30, 2016. He will be continuing his career with a new position at PATH.

NIAID is working on a new YF vaccine. A phase 1 trial is underway for safety and immunogenicity: https://www.nih.gov/news-events/nih-launches-early-stage-yellow-fever-vaccine-trial. While it will not answer Dr. Plotkin's question about Lyme Disease vaccine, NIAID is in the early planning phases for a clinical trial to evaluate the effectiveness of prophylaxis of tick bites to prevent Lyme Disease. In terms of the Zika virus, NIAID is actively pursuing multiple vaccine candidates to prevent Zika virus infections, including the following strategies:

- A DNA-based vaccine that uses a strategy similar to an investigational flavivirus vaccine for West Nile virus infection, which entered an early-stage trial in August 2016 and the dosing of those individuals is now complete

- A live-attenuated investigational Zika vaccine building on a similar vaccine approach for the closely-related dengue virus

- An investigational Zika vaccine that uses a genetically engineered version of vesicular stomatitis virus (VSV), with plans underway to evaluate this candidate in tissue culture and animal models

- A whole-particle inactivated Zika vaccine based on a similar vaccine approach used by the Walter Reed Army Institute of Research (WRAIR) to develop vaccines against the related Japanese Encephalitis (JE) and dengue viruses; information regarding NIAID-supported Zika research may be found here: https://www.niaid.nih.gov/diseases-conditions/zika-virus

NIH and Fundacao Oswaldo Cruz-Fiocruz (Fiocruz), a national scientific research organization linked to the Brazilian Ministry of Health, have begun a multi-country study to evaluate the magnitude of health risks that Zika virus infection poses to pregnant women and their developing fetuses and infants. The study is also opening in Puerto Rico and will expand to several locations in Brazil, Colombia, and other areas that are experiencing active local transmission of the virus. The Zika in Infants and Pregnancy (ZIP) study plans to enroll as many as 10,000 pregnant women ages 15 years and older at up to 15 sites. The participants will be in their first trimester of pregnancy and will be followed throughout their pregnancies to determine if they become infected with Zika virus and if so, what outcomes result for both mother and child. The participants' infants will be carefully followed for at least one year after birth. Here is a link to the NIH press release from June 21, 2016: https://www.nih.gov/news-events/news-releases/nih-launches-large-study-pregnant-women-areas-affected-zika-virus.

Some suggested publications include:

- Gonorrhea Vaccine: LM Wetzler*et al.* Summary and recommendations from the National Institute of Allergy and Infectious Diseases (NIAID) workshop "Gonorrhea Vaccines: the Way Forward."*ClinVaccine Immunol*(2016 Aug 5)

- Zika Vaccines: Nature: Vaccine protection against Zika virus from Brazil, http://www.nature.com/nature/journal/v536/n7617/full/nature18952.html

- Zika Vaccines: Science: Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys, http://science.sciencemag.org/content/early/2016/08/03/science.aah6157

National Vaccine Program Office (NVPO) / NVAC

Dr. Birkhead reported for both NVPO and NVAC. First, as a companion to the National Adult Immunization Plan (NAIP) released last February, NVPO plans to release a *Pathway to Implementation of Adult Immunization Report* in the near future to facilitate action on the goals of the original plan. The report suggests 8 priorities and potential activities to focus on, down from the 78 strategies in the original plan, and include:

- Addressing technical and legal and administrative and practical barriers to greater use of EHRs and immunization registries to track adult immunization data
- Evaluating the impact of current healthcare quality measures for adult vaccination and the feasibility of developing composite measures
- Assessing the impact of financial barriers such as co-pays on adult vaccination uptake
- Identifying legal, practical, and policy barriers impeding expansion of adult immunization
- Encouraging all providers to implement the NVAC *Standards for Adult Immunization Practice*
- Engaging community leaders in promoting the importance of adult vaccination to the public
- Examining the total costs of adult vaccination to adult vaccine providers for providing vaccine services such as vaccine ordering, handling, storage, administration, patient recall and reminders, counseling, et cetera

NVPO recently awarded two contracts that may be of interest. The first contract addresses the last point about the cost to providers of adult immunization by looking in detail at the business case for providers of adult immunizations, taking into account both the costs and the reimbursement by provider type and geographic region. The second contract is for the development and testing of a composite healthcare quality measure for maternal immunizations with the National Committee for Quality Assurance (NCQA), incorporating both Tdap and influenza vaccinations. This was referenced the previous day by Dr. Carol Hayes in the context of the Adult Vaccine Summit Quality Performance Measure WG led by LCDR Angela Shen at NVPO.

NVPO and CDC are collaborating to put on a webinar entitled *Vaccines During Pregnancy: A Strong Record of Safety* to help providers address patient concerns around maternal immunization. The webinar will be on November 9th from 12:00 PM to 1:30 PM Eastern Time and will cover the effectiveness of influenza and Tdap vaccines in pregnant women, their safety profile and common mild AEs, a review of the vaccine safety surveillance efforts and research activities specific to maternal immunizations, and strategies and resources to address patient concerns around maternal immunizations. To view the webinar, register at the NVPO home page at hhs.gov/nvpo.

The last NVAC meeting was on September 20th and included presentations / discussions on *CDC's Strategic Framework for Global Immunization 2016-2020*, the mid-course review of the 2010 NVP, NVPO's *Pathway to Implementation of Adult Immunization Report*, and a review of the process of developing healthcare quality measures. That discussion kicked off the process to develop consolidated quality measures, both for adult and maternal immunizations. During the meeting, NVAC also voted on and unanimously adopted a Maternal Immunization WG (MIWG) report called *Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations*. That report is available on the NVPO website and will be published in *Public Health Reports* (*PHR*). The next NVAC meeting is February 7-8, 2017 at the Humphrey Building and will be available by webcast.

Child and Adolescent Immunization Schedule

Introduction

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

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

Dr. Romero indicated that for the remainder of this presentation, Dr. Robinson would discuss proposed edits to some specific vaccine footnotes as well as Figure 1, and would introduce a proposed child/adolescent high-risk figure which, if adopted, would become figure 3. This year, a few vaccines' schedules required attention. ACIP members were provided with these slides in their binders, as well as on the meeting background materials' website. The slides presented during this session were updated to include footnote and figure edits that incorporate the results of the previous day's votes. The changes to the footnotes include edits to the HepB, Hib, pneumococcal, influenza, meningococcal, and HPV footnotes.

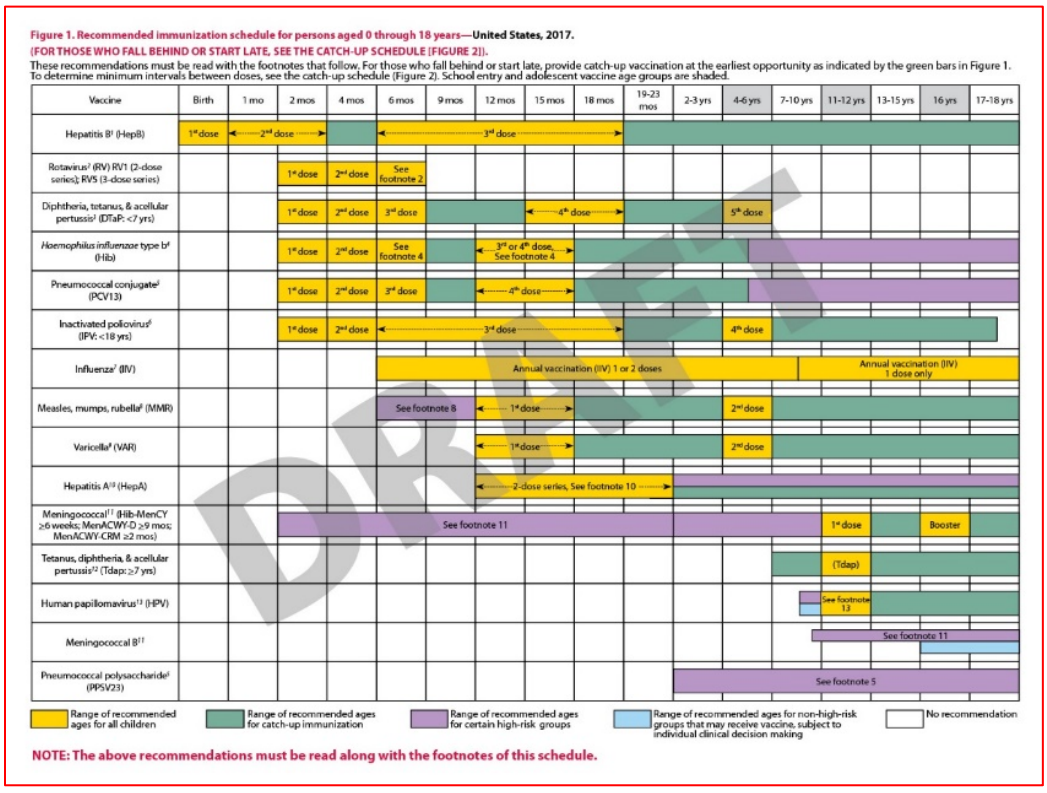
Child and Adolescent Immunization Schedule 2015

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

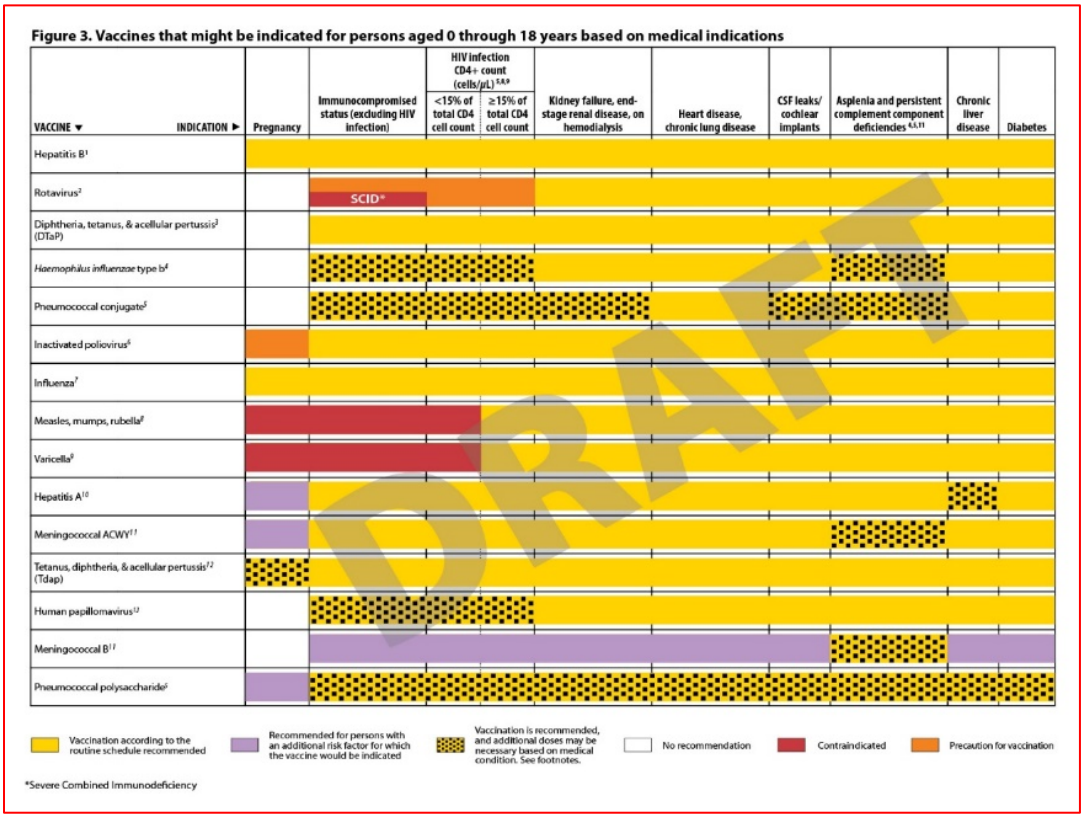
Dr. Robinson indicated that on the title page, the title was changed to "Recommended Immunization for Children Aged 18 Years or Younger." This new title harmonizes with the new adult immunization title to be presented later in the morning. The year was updated to 2017. There are no proposed changes for Figure 2, the catch-up schedule.

In the 2016 version of the schedule, the text beneath Figure 1 was largely a repeat of the text that already appeared on the title page of the schedule. In the proposed 2017 version, this text has been removed. There are a number of proposed additions to Figure 1 for the 2017 schedule. The age 16 years has been separated from the ages 17 through 18 years, and the 16-year column has been shaded. The WG felt that this change would highlight the need for the meningococcal conjugate vaccine booster dose at this age. This also may provide an opportunity for catch-up vaccination if other adolescent vaccinations have not yet been administered or the series has not yet been completed.

Within the influenza row, live attenuated influenza vaccine (LAIV) has been removed as a recommended vaccine given the ACIP recommendation to not use LAIV during the 2016-2017 influenza season. Last year, a purple bar was added within the HPV row at age 9 through 10 years to represent the recommendation to begin the HPV series at age 9 years in children with a history of sexual abuse or assault. Feedback was received from providers who indicated that this bar did not reflect the recommendation that HPV may be started at 9 years of age for those without a history of sexual abuse or assault. A blue bar was added at age 9 to 10 years to indicate that vaccination may begin at 9 years of age, even if there is no history of sexual abuse or assault. Here is the revised schedule:



The proposed high-risk figure pictured below demonstrates that most children with medical conditions can, and should, be vaccinated according to the routine child/adolescent immunization schedule. It indicates when a medical condition is a precaution or contraindication to vaccination. It also indicates when additional doses of vaccines may be necessary secondary to the child's/adolescent's medical condition:



On the high-risk figure, the yellow color indicates "Vaccination according to the routine schedule recommended." The purple color indicates "Recommended for persons with an additional risk factor for which the vaccine would be indicated." The black and yellow stippled pattern indicates "Vaccination is recommended and additional doses may be necessary based on medical conditions. See footnotes." The white color indicates "No recommendation." The red indicates vaccination is "Contraindicated." The orange color indicates "Precaution for vaccination."

Within the Additional Information section of the footnotes, providers are referred to the ACIP general recommendations on immunization and the relevant vaccine specific ACIP statement for additional contraindications and precautions information. The following additional changes were made to the footnotes:

- A bullet was added on the National VICP. This addition was made to harmonize with the adult schedule, which already contains information regarding the program and the vaccines covered.

- The HepB footnote was updated to reflect the recommendation for HepB administration within 24 hours of birth. For infants born to HBsAg-positive mothers, the post-vaccination testing window was updated to reflect the new recommendation of testing at age 9 through 12 months.

- Within the *Haemophilus influenzae* type B (Hib) footnotes, HIBERIX® was added to the list of vaccines that may be administered for the primary Hib series. Additionally, COMVAX™ was removed from the list of available vaccines, as this vaccine is no longer produced and all doses of the vaccine have now expired. Language regarding the restricted use of HIBERIX® has been removed. The Catch-Up Vaccination section has been clarified to reflect that unvaccinated children 15 through 59 months of age should receive 1 dose of Hib vaccine.

- Throughout the pneumococcal footnotes, mention of PCV7 vaccine has been removed as the last doses of PCV7 vaccine expired in 2010. Thus, children who received PCV7 as part of a primary pneumococcal series have since aged out of the routine pneumococcal recommendation.

- Within the influenza footnotes, information regarding LAIV has been removed and the following statement has been added, "For the 2016-17 season, use of live attenuated influenza vaccine (LAIV) is not recommended." The *MMWR* reference has been updated to reflect the 2016-2017 influenza recommendations publication.

- In the meningococcal footnotes, the Clinical Discretion section outlines the MenB category B recommendations. This section has been updated to read, "Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) may be vaccinated with a 2-dose series of either Bexsero® (0, ≥1 month) or Trumenba® (0, 6 months) vaccine to provide short-term protection against most strains of serogroup B meningococcal disease." This reflects the recommendations made during the previous day's vote. Within the Meningococcal Conjugate Vaccine section, children with HIV infection have been added to the section regarding vaccination of persons with high-risk conditions. The footnote regarding use of MenB among persons with high-risk conditions will remain unchanged, recommending a 2-dose series of Bexsero® at least 1 month apart, or a 3-dose series of Trumenba® with the second dose at least 1-2 months after the first and the third dose at least 6 months after the first dose. The reference and website for the meningococcal and HIV-infected persons *MMWR* will be added once the citation is available.

- Within the Tdap footnote, language was added regarding vaccination among pregnant women. The footnote states, "Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy, preferably early during gestational weeks 27 through 36 weeks gestation, regardless of the time since prior Td or Tdap vaccination." Additionally, the Catch-Up Vaccination section has been updated to indicate that persons who receive a dose of Tdap at age 7 through 10 years as part of a catch-up series, may receive a Tdap at 11 through 12 years of age.

- The HPV footnote was re-written to reflect the recommendations approved during the previous day's vote. Routine vaccination now reads, "Administer a 2-dose series of HPV vaccine on a schedule of 0, 6-12 months to all adolescents aged 11 or 12 years. The vaccination series can start at age 9 years. Administer HPV vaccine to all adolescents through age 18 years who were not previously adequately vaccinated. The number of recommended doses is based on age at administration of the first dose. For persons

initiating vaccination before age 15, the recommended immunization schedule is 2 doses of HPV vaccine at 0, 6-12 months. For persons initiating vaccination at age 15 years or older, the recommended immunization schedule is 3 doses of HPV vaccine at 0, 1–2, 6 months. A vaccine dose administered at a shorter interval should be re-administered at the recommended interval." For special populations the language reads, "For children with a history of sexual abuse or assault, administer HPV vaccine beginning at age 9 years. Immunocompromised persons* including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series at 0, 1–2, and 6 months regardless of age at vaccine initiation. Note: HPV vaccination is not recommended during pregnancy, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remaining vaccine doses should be delayed until after the pregnancy. Pregnancy testing is not needed before HPV vaccination."

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

- ❑ Does ACIP approve of the edits to the pre-existing portions of the child/adolescent schedule?

- ❑ Does ACIP approve of the proposed high-risk figure for inclusion in the 2017 schedule?

Discussion Points

Dr. Bennett requested that the discussion be limited to conceptual issues, and that any edits to the wording be submitted to Dr. Robinson to be taken into consideration.

As a primary care pediatrician, Dr. Szilagyi said he thought the high risk figure could be incredibly helpful. The next burden will be on partner organizations, AAP and AAFP, for how to translate that into very practical methods such as prompts or alerts in the EMR or codes so that high risk patients can be flagged.

Dr. Moore agreed that the high risk figure would be very helpful for those caring for children. Focusing on the two vaccines being used now that have a 2-dose or 3-dose schedule, MenB-FHbp and HPV vaccine, she requested that someone look carefully at the math on recommended intervals. For example, if someone is using a 2-dose schedule and gives the dose too early at less than 6 months, the recommendation for MenB-FHbp is if it is 0 and less than 6 months, repeat the dose 6 months later. That actually is much longer than the interval that could be used for an ordinary 3-dose schedule of that vaccine, which is 0, 1-2, and 6 months. This issue is also true for the HPV vaccine. She emphasized that a minimum schedule for administration of 3 doses should not vary based on one's intention to try a 2-dose schedule versus a 3-dose schedule. There should just be one minimum schedule regardless of what is intended for those 3 doses. Operationally, that is really important. She said she would feel silly telling someone they would have to wait longer than they would if they were using a 3-dose schedule.

Dr. Robinson replied that the Policy Note for HPV vaccine has some draft language about what to do if a dose is administered early in a 2-dose schedule versus administering a dose early in a 3-dose schedule. Portions of that Policy Note draft can be added to make it clear to providers what to do based on what schedule they were attempting initially.

Dr. Cohn added that they could speak with the SMEs for those two vaccines as well to ensure that the Policy Notes math is right as well.

Dr. Middleman (SAHM) expressed gratitude for the great schedules. She pointed out that the title still uses the word "children" instead of "persons." All of the figures state "persons." From a developmental perspective in terms of what constitutes a child, adolescent, or adult, those are developmental terms. The preference would be to use ages, because they do not talk about a toddler schedule. It is a developmental stage. SAHM appreciates the highlighting of places in the schedule with 4-6, 11-12, and 16 where there is a new place to have a vaccine.

Dr. Robinsons said they could change it to "persons" or "children and adolescents." She thought they did this because the other schedule uses "adults."

Dr. Belongia expressed gratitude for a really great figure for practitioners. He asked about any plans for translating this for clinical decision support systems, which will become increasingly important going forward, and development of rules to translate these categories into analytical quantitative measures.

Dr. Wharton responded that the challenges of translating the ACIP recommendations into clinical decision support is something CDC recognizes as well and is continuing to think about how to incorporate this into WG work. This cannot be undertaken within the schedule process. It needs to be addressed with individual recommendations. CDC is open to suggestions for how to proceed with that. This is an ongoing challenge that they are trying to take on.

Dr. Kempe said she knew of a number of different systems that already have done this. She suggested beginning with people who have already done this to avoid duplication.

Dr. Lee said that she loved the figures. She recalled that the previous day, there was discussion about standardizing terminology or perhaps providing examples of what constitutes CLD. Similarly, this should be done for all of the categories. Some of them are very binary and others are more challenging. For example, "level of immunocompromise" is difficult to assess. It might be helpful to offer categories of guidance, depending on the level of immunocompromise.

Dr. Cohn indicated that there are plans to address this issue over the next year more completely throughout all of the language and recommendations. Making sure these schedules are clear can be included in that process.

Vote: Child and Adolescent Immunization Schedule

Dr. Belongia made a motion to approve the Child and Adolescent Immunization Schedule and the High-Risk Figure. Dr. Kempe seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Adult Immunization Schedule

Introduction

Laura E. Riley, MD
Chair, Adult Immunization Work Group
Advisory Committee on Immunization Practices

Dr. Riley began by thanking Dr. Kathleen Harriman for her leadership as Chair of the Adult Immunization WG for many years, recognizing her remarkable ability to cut through the forest of footnotes and succinctly get them to where they needed to be. She will remain on the WG as a consultant. She also welcomed new member Dr. Paul Hunter, who brings his public health and clinical perspective to the WG.

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

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

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

There will be several updates to the schedule, which are derived from the ACIP recommendations and include the following:

- ❑ Influenza vaccination (June 2016)
  - ➢ Do not use LAIV in 2016–2017, modified language on egg allergy
- ❑ Tdap vaccination (October 2016)
  - ➢ Guidance for use during pregnancy
- ❑ HPV vaccination (October 2016)
  - ➢ Updated dosing schedule
- ❑ Hepatitis B vaccination (October 2016)
  - ➢ Updated at risk populations
- ❑ Meningococcal vaccination (June and October 2016)
  - ➢ Use MenACWY vaccine for adults with HIV, updated schedule for MenB-FHbp

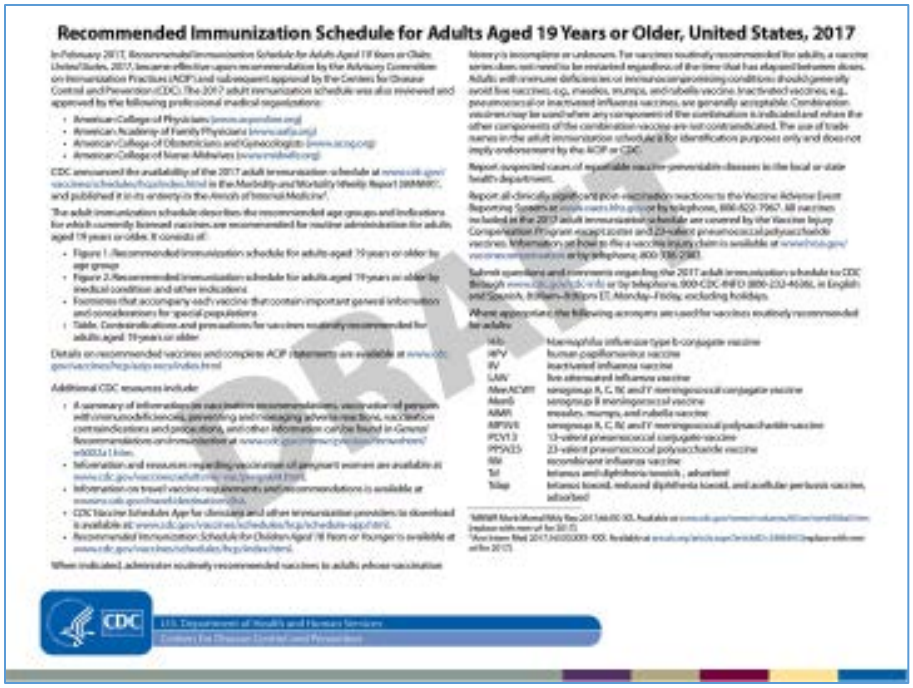
- Format changes
  - *Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017*
  - Unified cover page, figures, footnotes, table – 6 panels
  - Considered human factors and ergonomics for figures
  - Modified footnotes for simplicity and consistency

Adult Immunization Schedule

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

In this presentation, Dr. Kim described the proposed changes to the 2017 Adult Immunization Schedule. The 2017 schedule is now a 6-panel document with a cover page of introduction and general information, two figures with accompanying footnotes, and a table of contraindications and precautions.

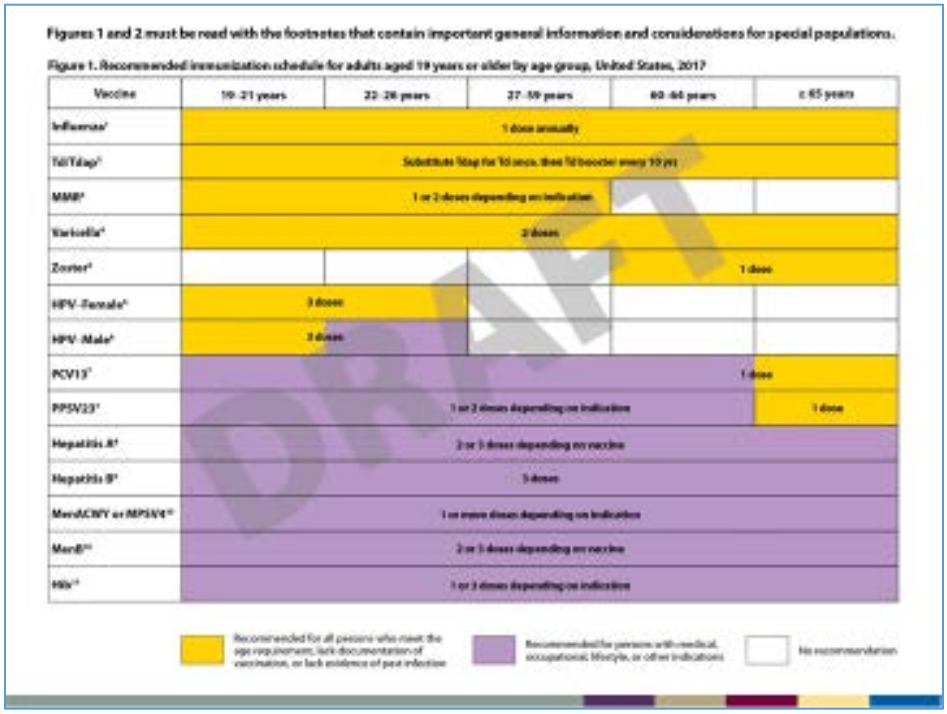
On the updated cover page, the title has been changed to "Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017." It is now consistent with the Child and Adolescent Schedule. The text that was in the periphery of Figures 1 and 2 in the 2016 schedule has been moved to the cover page. The revised cover page introduces a list of acronyms used for vaccines routinely recommended for adults. When these changes are incorporated, the cover page for the proposed 2017 schedule contains more information and looks like this:


Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017

The changes proposed for Figure 1 for 2017 include the following:

- ❑ Revise the title and instruction to the reader
- ❑ Combine age groups 27 through 49 and 50 through 59 to create the new age group 27 through 59
- ❑ Use the acronyms introduced in the cover page in the vaccine column
- ❑ Lump the live vaccines (MMR, varicella, zoster) together to consolidate information and to simplify graphics
- ❑ Use colored blocks instead of colored bars for indication
- ❑ Move the footnote on the VICP to the cover page
- ❑ Remove the clause “zoster vaccine is recommended regardless of past episode of zoster” in the legend, because the information is contained in the footnote for zoster vaccination
- ❑ Move the text to the cover page.

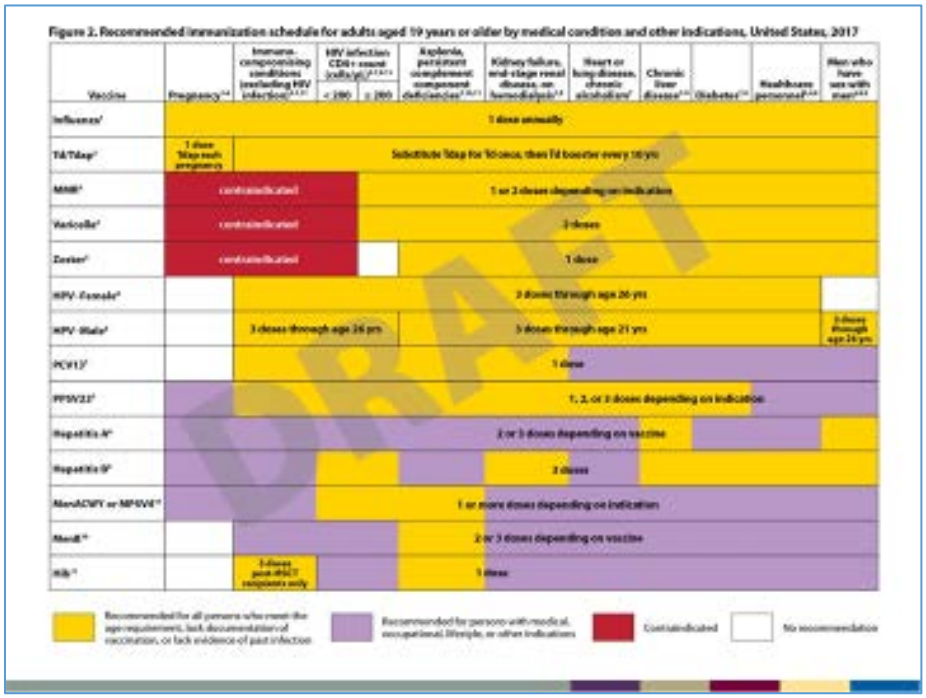
After incorporating the proposed changes, this is what the proposed Figure 1 would look like:



The changes proposed for Figure 2 for 2017 include the following:

- ❑ Make the changes already described for Figure 1
- ❑ Move the column for MSM to the right of healthcare personnel to lump at-risk populations
- ❑ Update the footnotes to link them with the information specified by medical conditions and other indications
- ❑ To reflect the recommendation made by ACIP in June to routinely vaccinate adults with HIV infection with serogroups A, C, W, and Y meningococcal vaccine, change the color of this indication bar for this group from purple to yellow

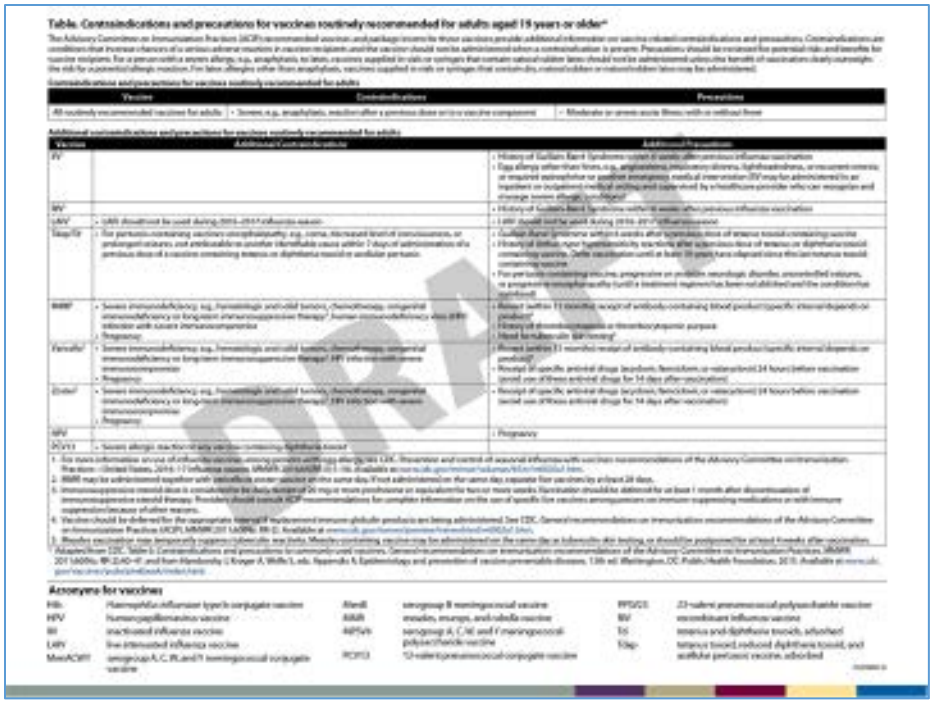
After incorporating the proposed changes, this is what the proposed Figure 2 would look like:



Proposed changes to the Table of Contraindications and Precautions include the following:

- ❑ Add general information to explain the significance of contraindications and precautions for vaccination
- ❑ As in Figures 1 and 2, use acronyms for the vaccine column and list the acronyms at the bottom of the new page
- ❑ Consolidate contraindications and precautions that are applicable to all routinely recommended vaccines
- ❑ List additional contraindications and precautions for applicable vaccines
- ❑ Revise precaution for IIV in egg allergy per June 2016 update
- ❑ State that LAIV should not be used during the 2016-2017 influenza season

Currently, this table is available through the ACIP website and is a standalone document that is not integrated into the schedule. However, it will become a part of the schedule in 2017. Here is what the Table of Contraindications and Precautions will look like based on these changes:



The footnotes went through a substantial makeover. The proposed footnote revisions for Figures 1 and 2 include the following:

- ❑ The footnotes are limited to information about vaccines:
  - ➢ The footnote on *General information* was moved to the cover page
  - ➢ The footnote on *Immunocompromising conditions* was removed, with applicable information added to specific vaccination sections

- ❑ To standardize the structure, each footnote has been formatted to include the following:
  - ➢ A general information section that describes routine recommendations
  - ➢ A special populations section that describes recommendations for groups identified in Figure 2

- ❑ To standardize the content, each footnote has been reviewed and revised to ensure the following:
  - ➢ Consistent sentence structure, flow of information, use of mathematical symbols and acronyms
  - ➢ Trade names are included for identification purposes only (hepatitis B and meningococcal vaccines)

Changes to the content of specific footnotes follow, with the changes shown as strikethroughs (deletions) and / or underlines (additions):

Footnote 1. Influenza Vaccination

- General information
  - All persons aged 6 months or older…
  - Adults aged 65 years or older may receive high-dose IIV or adjuvanted IIV
  - ~~Healthcare personnel who care for severely immunocompromised persons… should receive IIV or RIV; [those] who receive LAIV should avoid providing care for severely immunocompromised…~~
  - LAIV should not be used during the 2016–2017 influenza season
- Special populations
  - Adults with a history of egg allergy who have only hives after exposure to egg should receive age-appropriate IIV or RIV
  - Adults with history of egg allergy other than hives may receive age-appropriate IIV or RIV. IIV should be administered in… medical setting and supervised by a healthcare provider…
  - Pregnant women and women who might become pregnant in the upcoming influenza season should receive IIV

Footnote 2. Td/Tdap Vaccination

- General information
  - Adults who have not received Tdap or for whom pertussis vaccination status is unknown should receive 1 dose of Tdap followed by a Td booster dose every 10 years
- Special populations
  - Pregnant women should receive 1 dose of Tdap during each pregnancy, preferably early during gestational weeks 27–36, regardless of her prior history of receiving Tdap

Footnote 4. Varicella Vaccination

- General information
  - Adults without evidence of immunity to varicella should receive…
- Special populations
  - Pregnant women should be assessed for evidence of varicella immunity… Birth before 1980 is not considered evidence of immunity
  - Healthcare institutions should assess and ensure that all healthcare personnel have evidence of immunity to varicella. Birth before 1980 is not considered evidence of immunity…
  - Adults with a malignant condition, including those affecting the bone marrow or lymphatic system, or systemic immunosuppressive therapy should not receive varicella vaccine
  - Adults with HIV infection and CD4+ count ≥200 may be considered for a 2-dose series of varicella vaccine… CD4+ count <200 should not receive varicella vaccine

Footnote 5. Zoster Vaccination

- General information
  - Adults aged 60 years or older should receive 1 dose of zoster vaccine, regardless of whether they had a prior episode of herpes zoster
  - ~~Although… licensed by the U.S. Food and Drug Administration for… persons aged ≥50 years… ACIP recommends… begin at age 60 years~~
- Special populations
  - Adults aged 60 years or older with chronic medical conditions may be vaccinated unless they have a medical contraindication…
  - Adults with a malignant condition affecting the bone marrow or lymphatic system or who receive systemic immunosuppressive therapy should not receive zoster vaccine
  - Adults with HIV infection and CD4+ count ≥200 have no zoster vaccine recommendation because there is a lack of evidence available for or against zoster vaccination… CD4+ count <200 should not receive zoster vaccine

Footnote 6. HPV Vaccination

- General information
  - Adult females through age 26 years and adult males through age 21 years who have not received any HPV should receive a 3-dose series of HPV at 0, 1-2 and 6 months. Males aged 22 through 26 years may be vaccinated
  - Adult females through age 26 years and adult males through age 21 years (and males aged 22 through 26 years) who initiated HPV series before age 15 years and received 2 doses at least 5 months apart are considered adequately vaccinated and do not need an additional dose of HPV
  - Adult females and males… who initiated HPV series before age 15 years and received 1 dose or 2 doses at least 5 months apart are not… adequately vaccinated… and should receive 1 additional dose of HPV
  - Note: HPV is routinely recommended… at age 11 or 12 years. For adults who initiated but did not complete HPV series, consider their age at first HPV vaccination and other factors to determine… adequately vaccinated
- Special populations
  - MSM through age 26 years, if not previously vaccinated, should…
  - Adults through age 26 years with immunocompromising conditions (described below), including HIV, should receive…
  - Pregnant women are not recommended to receive HPV…

Footnote 9. Hepatitis B Vaccination

- General information
  - Adults who seek protection from HBV infection may receive a 3-dose series of… hepatitis B vaccine at 0, 1, and 6 months
- Special populations
  - Adults with chronic liver disease, hepatitis C virus infection, HIV infection, age <60 years with diabetes… should receive…
  - Adult patients receiving hemodialysis ~~or with other immunocompromosing conditions~~ should receive a 3-dose series of 40 mcg/mL Recombivax HB at 0, 1, and 6 months or a 4-dose series of 40 mcg/mL Engerix-B at 0, 1, 2, and 6 months

Footnote 10. Meningococcal Vaccination

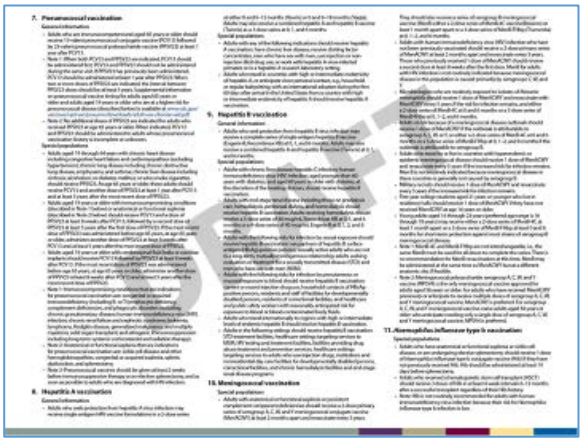
As a reminder, the ACIP recommendations made October 19, 2016 were:

- For persons at increased risk and for use during outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1–2, and 6 months
- For healthy adolescents who are not at increased risk for meningococcal disease, 2 doses of MenB-FHbp should be administered at 0 and 6 months
- If second dose is given at an interval less than 6 months, a third dose should be given at least 6 months after the first dose

This footnote reflects these recommendations and the recommendation made during the June 2016 meeting that persons with HIV should receive MenACWY as shown below.

- Special populations
  - Adults with… asplenia or… complement component deficiencies should receive… MenACWY… and either a 2-dose series of MenB-4C at least 1 month apart or a 3-dose series of MenB-FHbp administered at 0, 1–2, and 6 months
  - Adults with HIV infection… should receive a 2-dose primary series of MenACWY at least 2 months apart... Revaccinate with MenACWY every 5 years… MenB for adults with HIV infection is not routinely indicated…
  - Microbiologists… should receive… MenACWY… and either a 2-dose series of MenB-4C… or a 3-dose series of MenB-FHbp…
  - Adults at risk because of… outbreak… should receive… either a 2-dose series of MenB-4C… or a 3-dose series of MenB-FHbp… if the outbreak is attributable to serogroup B
  - Young adults aged 16 through 23 years may be vaccinated with either a 2-dose series of MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0 and 6 months…

When incorporated, the footnotes in the 2017 schedule would look like this:



Based on ACIP comments and suggestions during this session, the draft 2017 adult immunization schedule will be revised and reviewed again by the WG and SMEs. Concurrence will then be obtained by the ACP, AAFP, ACOG, and ACNM. The revised adult immunization schedule, including figures and footnotes, will be submitted to CDC for clearance by January 2017. The cleared adult immunization schedule will be submitted to the *MMWR* as a Notice to the Reader referring the reader to the CDC website to access the updated schedule, and the *Annals of Internal Medicine* for publication in February 2017. With help from its partners, CDC will work to disseminate the schedule widely to help promote adult immunization.

The 2017 Adult Immunization Schedule has gone through a lot of changes. The graphics were evaluated for usability and simplicity, the text in footnotes and elsewhere were overhauled for readability, completeness, and consistency. However, there is more work to do to improve the schedule as a useful tool for healthcare providers. Toward that end, CDC will kick off the Adult Immunization Schedule Evaluation Project in November 2016. Over the next year, CDC will conduct in-depth interviews of healthcare providers who use the adult immunization schedule to learn what their needs are, continue the efforts to improve the graphics and content of the schedule, and continue to work on improving the implementation of ACIP recommendations for immunizing adults.

Discussion Points

Dr. Messonnier explained that typically the schedule has been presented on the first day of the ACIP meeting. However, there would then be votes that impacted the schedule. This seemed out of order, so the decision was made to purposely change the schedule presentation to the second day of this meeting. She thanked Dr. Kim for incorporating all of the changes from the first day, and apologized for the copies provided to the members with incredibly small font. She assured everyone that they would keep working to give the members better access to ensure that they have adequate time to think about substantive changes.

Dr. Bennett requested that everyone focus on the content versus the wording, given that there will be additional time to submit comments to Dr. Kim and his team to have some impact on the wording.

Dr. Kempe said she thought they had done an incredibly good job of simplifying the schedule and that it was a great improvement. While the footnotes are still voluminous, she found them to be very well-organized.

Dr. Lee said she liked having the presentation on the second day and thought the schedule was great. In many ways, it reinforced the intent of the recommendations, which came across in the wording of the schedule. Regarding the zoster vaccine, she wondered whether it should be distinguished that it was referring to the live attenuated vaccine because that will need to be clarified now or later as things change over time. Regarding immunocompromised individuals, the 3 doses of Hib post-stem cell transplant stood out to her, in part because stem cell transplants also are done in young children. That one recommendation seemed out of place to her, in part because she was trying to make it concordant with persons 18 years of age and younger, and she was trying to figure out why not the other vaccines that also would be administered. She suggested that additional thought be given to that detail.

Dr. Kim said that as a general reference, the Adult Immunization Schedule and the Child / Adolescent Immunization Schedule reflect decisions already made by ACIP and approved for publication. The inclusion of select vaccines, such as Hib, is because there are indications for that vaccine for adults. However, there are exceptions to routine recommendations. It is these exceptions that drive the volume up on in the footnotes. Where possible, the work group tried to minimize outlining all details but it's a balancing act to have enough detail but not drive up the volume of the footnotes. The goal is to be as comprehensive as possible based on the recommendations already made by ACIP.

Dr. Cohn added that as part of what they are talking about in terms of making some of these definitions consistent throughout the different vaccines over the next year, they also intend to find inconsistencies in the recommendations, but it may just be a different WG proposing different things. The goal is to harmonize in places where it seems reasonable.

Dr. Fryhofer (AMA/ACP) did not think that the blocks instead of bars were practical. If looking at Figure 2 when trying to pick one of the special conditions and follow it down, it is not clear what goes with what. It would be a lot more practical for the busy practicing physician to be able to follow the headings down and figure out what immunizations that particular patient needs. Regarding Footnote 9: Hepatitis B Vaccination, she could not tell from what was shown on the screen if fatty liver disease was included specifically because this is being seen so much in practices and might not be a condition that many clinicians realize is an indication for hepatitis B vaccine.

Referring to Figure 2, the high-risk figure in the pediatric schedule, with lines behind it, Dr. Messonnier asked whether that would solve the issue.

Dr. Fryhofer (AMA/ACP) said that she had specifically compared the two and it would be very helpful.

While she appreciated Figure 2 and the effort to address high-risk, Dr. Groom (IHS) expressed concern about how it will be interpreted. For example, looking down the list for MSM, it appears that MSM should receive PCV13 and PPSV23. For those who do not know that this is just for a certain medical indication, but not that medical indication, clinicians will look at it and think PCV13 must be given to all of their diabetic patients. Perhaps the footnote could be changed to state "may be recommended for patients with the appropriate medical condition," but this is a high risk table and when people see that condition, she is afraid they will assume if it is purple, it means that a high-risk person should get it because they are in that special risk group.

Dr. Thompson (NVAC) applauded the efforts to further develop this table and thought it was a big step forward. She noted that the tables for the younger individuals under 18 years of age did not include an MSM column. There also are some differences between the two tables in the pregnancy columns, which appear in both. Tdap is recommended for each pregnancy, so it is probably unusual that there are many individuals who have pregnancies under the age of 18. But, she wondered what the recommendation would be in that case in terms of the clinician reconciling these two things. Adolescents are "falling through the cracks" still, so reconciling these might be useful. Also, it was not clear to her why the vaccines were listed in the order that they were. It seemed to her that they could be listed alphabetically or at least in the same order on both charts.

Regarding the exclusion of MSM on the child / adolescent schedule, Dr. Robinson pointed out that though vaccines for adults differ by MSM status, they do not differ for children. For instance, adult males 22 through 26 years of age receive HPV if they are MSM. However, all adolescents through 18 years of age are recommended to receive HPV vaccine.

Regarding the order of vaccines presented for Figures 1 and 2, Dr. Kim indicated that these were done with graphics in mind. In years past, an effort was made to use alphabetical order but that simply did not work because of the complexity that it imposed on the eyes to follow. Other attempts were made with different colors, different shades, and hatching of the bars. However, through trial and error, the current listing was made. He invited recommendations to improve on that.

Dr. Romero indicated that the ordering for the childhood / adolescent vaccines was an attempt to reflect how these vaccines are used and the timing in which they are used. There was discussion about putting them in alphabetical order, but it made more sense to the WG to leave them in the order in which they are introduced in children.

Dr. Kempe wondered whether one of the concerns might be addressed by using the same wording for the purple color on the childhood schedule that basically states that one has to have an additional risk factor for which the vaccine would be recommended, or using the hatch marks. Those two wordings were created because of the concern raised that it was difficult to tell whether something was indicated or additional doses were needed.

Dr. Messonnier expressed appreciation for all of the comments. One issue is that it is unknown how the schedule is used, especially by adult providers. It is clear that Pediatricians are using it routinely as part of their normal practice, and that the schedule has been vetted a lot. The issue of the adult schedule and extensive footnotes is that this is the first step toward moving the adult schedule. The questions everyone was asking were the same as the ones CDC is asking and hopes to get at through the testing of the schedule with adults, and asking how many clinicians use the schedule versus clinical support tools or online aids versus a hard, flat copy of the schedule on the wall. More information will be provided about this over the next year. They do not want to make dramatic changes until more information is acquired.

Regarding the footnote under influenza pertaining to pregnant women and women who are planning to become pregnant during the upcoming influenza season, Dr. Wayne Hachey (Protein Science) suggested adding recombinant influenza vaccine (RIV) as it does have a Class B category for pregnancy and does not contain extras in the vaccine that many pregnant women avoid. He also suggested adding RIV for adults 65 years of age or greater. Protein Science submitted data to the WG and ACIP showing that Flublok® had increased effectiveness in the over 50 population to include the over 65 population during the influenza season. Even with the mismatch, Flublok® still provided protection for the over 65 group.

Dr. Bennett replied that the goal was to ensure that the recommendations on the schedule match the influenza recommendations.

Regarding the issue of how schedules are used in clinical practice, Dr. Hunter said that as a clinician and a public health practitioner, he did not think they were talking about the audience who administers vaccination, which is medical assistants and nurses. He suggested including their impressions of how the schedules are being used. Forecasts are printed out from registries or the EHR for a particular patient, but his impression is that clinicians look at the

schedule to double-check it to determine whether it really makes sense and then look at standing orders to determine whether to give the vaccination.

Dr. Hayes (ACNM) registered her objection to using the word “lifestyle” as she does not think it is clinically appropriate. She agreed with Dr. Kempe about using the language for the purple bar from the child / adolescent schedule.

Dr. Kim said he was hesitant to comment on that because it was not a decision made by him. It was a reflection of the content of previous publications on ACIP policy. ACIP could address that, as could the community that deals with these issues in general.

Dr. Moore echoed the encouragement that if it is feasible at all, to use exactly the same wording on the purple bar for both adults and children in order to clean up the question about lifestyle. If using the same color, people who treat children and adults will anticipate that when they see the same color, it means exactly the same thing.

Dr. Messonnier replied that they would review this to determine whether there is a way to make the language more harmonious with the childhood schedule and avoid pitfalls wherever possible.

Dr. Fryhofer (AMA/ACP) said she thought internists are having to grapple with the increased complexity of adult immunization. They must learn from their pediatric colleagues and become more disciplined in looking at the adult schedule. It is totally different from the training many clinicians received in training during residency. It is a wonderful fact of life that there are now wonderful ways to keep people healthy, so the ACP has many efforts underway to help increase internists’ knowledge and use of the schedule. It is a very valuable tool. She expressed great appreciation for all of the work that the WG has put into making the schedule a “go to” source. She also expressed support for changing Figure 2 back to bars.

Dr. Moore suggested that a nice way to deal with 2-dose versus 3-dose based on feedback from her colleagues who work in registry programming is simply for vaccines that may be given on a 2- or 3-dose schedule to state “if the minimum interval for a 2-dose schedule is not met, please complete using the 3-dose schedule.” This avoids dealing with all of the convoluted language about invalid doses.

Dr. Savoy (AAFP) emphasized that the schedules were simply summarizing what had already been decided and voted upon in the actual recommendations, so they could not just make changes as they pleased. For example, the term “lifestyle” must have been used in a recommendation so they could not just edit it in the schedule. She thought they probably would have to find the source recommendation and bring it before the committee for review. While family physicians have been relatively easy to train on the schedule because they see all ages, she is finding that a number of people are using electronic ways of managing the schedule. Although most everyone’s office has the schedule posted on the wall, the vast majority of people are getting their information from some type of electronic version. For example, the schedule has been translated into a variety of apps that people are using. Others are using it directly out of their EMR or their registry for their state pulls and sends them that information. Even though they spend a lot of time on how to make the schedule look pretty or how to make it work, she honestly did not think the vast majority of clinicians are spending as much time looking directly at the child or adult schedule as they are the content of what is behind it. She would be more interested in ACIP being crystal clear about the definitions of what they want and

the start and end points so that the registries are as accurate as possible, than worrying as much about the lines.

Dr. Pittman (DVA) said that DVA eagerly awaits the release of the adult schedule every year, and asks Dr. Kroger to hold a webinar for the people in the field to discuss the changes, and it is very well-received. They do use the schedule to translate into an electronic record, because it is growing increasingly complex.

Regarding the comment about influenza vaccine, Dr. Belongia thought it was a valid point that since ACIP does not make any preferential recommendations for any particular product, the language should state "use any licensed influenza vaccine" or it should list all of them.

Ms. Stinchfield (NAPNAP) underscored the earlier comment about the end users of the schedules, the MAs and RNs. Their schedule WG takes that into consideration and talks about it quite a bit. CDC sent a team to Children's Minnesota clinics to conduct focus groups, speaking to most of their MAs. The agency has done this across the country, and it is a really important point to keep focused on.

Dr. Fryhofer (AMA/ACP) added the importance of eventually establishing a national immunization registry. Because the adult schedule has become so complicated, it is sometimes very difficult for a practicing clinician to know which vaccines to give because they do not know which vaccines patients have received. Some EMRs will report vaccines to the state registry, but people do not always live in one state. Currently, the registries do not speak back to the EMRs. She has patients who are over-vaccinated and others who are under-vaccinated due to this. Children and young adults cannot go to school or college unless they have immunizations. But there is not a similar check-up for adults who go to a new job unless they are in healthcare. A national immunization registry would help with this and improving the interface between registries and EMRs.

Dr. Kempe said she very much supported the prospect of a national registry; however, they recently conducted a national survey of internists, family physicians, and pediatricians across the country. The unfortunate fact is that a very small minority of internal medicine physicians are using their state registries. A national registry is not going to work unless there is much more consistent use of registries by adult providers. She thought that was where they needed to go first.

Vote: Adult Immunization Schedule

Dr. Riley made a motion to approve the Adult Immunization Schedule. Dr. Romero seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Pneumococcal Vaccines

Introduction

Allison Kempe, MD
Pneumococcal Vaccines Work (Arthur Reingold, Chair, unable to be present)
Advisory Committee on Immunization Practices

Dr. Kempe

She reminded everyone that the Pneumococcal Vaccines WG's terms of reference are to:

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

As a reminder, ACIP recommended PCV13 for adults ≥65 years of age in August 2014. The WG conclusions at that time were that in the short-term, such a recommendation for universal PCV13 use in this age group was warranted for the opportunity to prevent disease for the 2014-2015 respiratory seasons and for a number of additional years. However, the WG did realize that in the long-term, continued herd effects could limit the utility of such a universal recommendation. The magnitude of indirect effects were unknown, and there was uncertainty around the burden of vaccine preventable non-bacteremic pneumonia.

Because of the recognition of this being a time-limited recommendation, the following statement was included in the ACIP vote:

> *The recommendations for routine PCV13 use among adults ≥65 years old should be re-evaluated in 2018 and revised as needed.*

ACIP recommended that there should be monitoring of the impact of the new recommendation in the target population of adults ≥65 years old, as well as continued monitoring of disease trends among PCV13-naïve adults 19 through 64 years of age without PCV13 indications, to evaluate the impact of herd effects and the long-term utility of routine PCV13 use among adults. In addition, ACIP is to be updated routinely on the changes in the vaccine-preventable disease burden among adults due to PCV13 direct and indirect effects during the next 3 years, and these data should inform revisions as needed to the proposed adult PCV13 recommendations in 2018.

During this session, updates were provided on the direct and indirect impact of PCV13 use on invasive disease among adults and children in the US; PCV13 impact among adults with chronic medical conditions with and without indications for PCV13 use; and the proposed research agenda to inform potential policy reconsideration in 2018 for PCV13 use among adults.

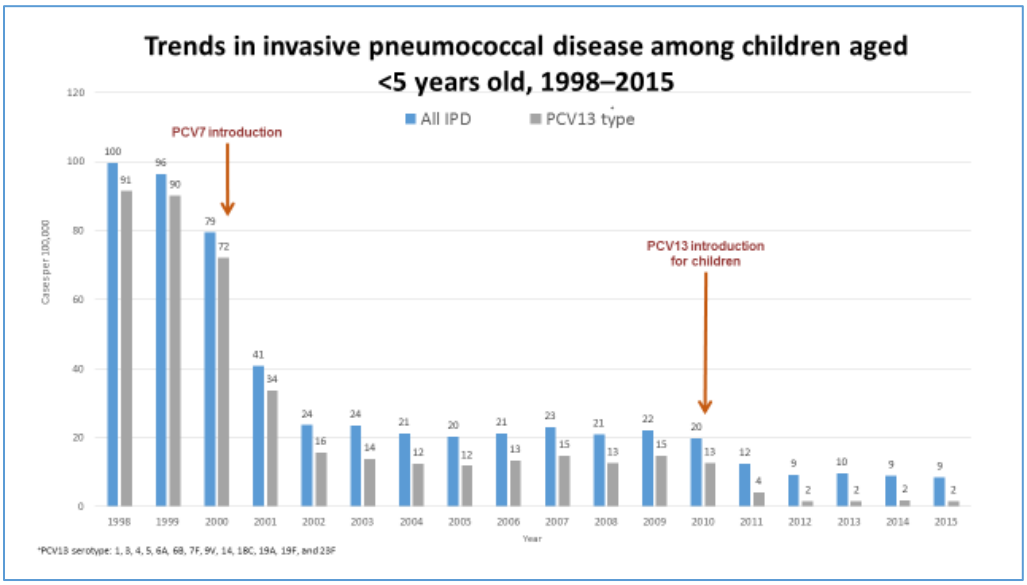
Direct and Indirect Impact of PCV13 on Invasive Disease Among Adults and Children in the US

Tamara Pilishvili, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Pilishvili reminded everyone that in 2010, PCV13 replaced PCV7 in the US infant immunization schedule. In 2014, PCV13 was recommended for use in series with PPSV23 for all adults ≥65 years. The impact of PCV13 on invasive pneumococcal disease (IPD) among adults and children was evaluated. Data were used from the ABCs system to compare incidence as cases/100,000 population before PCV13 was introduced using the time period 2007-2008 to post-PCV13 using the time period 2014-2015.

With regard to trends in IPD incidence by serotype group in children under 5 years of age from 2007–2015, dramatic reductions were observed in invasive infections shortly after 2010. These reductions continued through 2012. All of the reductions observed were driven by PCV13 serotypes. From 2012 through 2015, the rates plateaued at around 2/100,000.

Regarding the changes observed in individual serotypes, the most dramatic reductions in PCV13-type disease were driven by reductions primarily in serotypes 19A and 7F. These also were the only statistically significant reductions observed. Reductions were observed in serotype 3 disease, but they were not statistically significant. Also being monitored is whether any replacement disease is being observed due to non-vaccine serotypes. Thus far, no increases have been observed in non-vaccine serotypes. To put everything in perspective, Ms. Pilishvili showed the following graph of the overall impact of conjugate vaccines, PCV7 introduced in 2000 and PCV13 introduced in 2010:

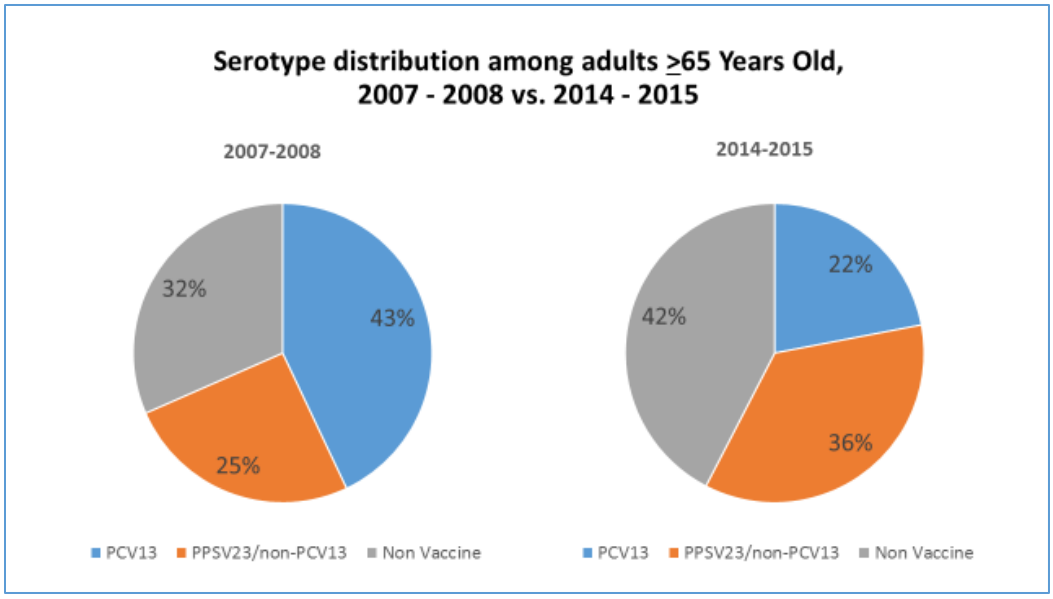


In children under 5 years of age, overall invasive pneumococcal infections have been reduced from approximately 100/100,000 to about 9/100,000. Vaccine-type infections have been reduced to 2/100,000. This is a great success story.

In terms of annual trends in IPD incidence among adults ≥65 years of age from 2007 through 2015, when the pediatric vaccine was introduced, reductions also were observed in adult disease. The incidence among adults decreased from approximately 40/100,000 to about 25/ 100,000 for overall infections. PCV13 types drove these changes with the introduction of the pediatric vaccine. Infections caused by PCV13 types in this age group are down to approximately 5/100,000. Looking at other serotypes that are included only in the polysaccharide vaccine, PPSV23 (11 serotypes not included in PCV13), or serotypes that are not included in any vaccine formulation, no significant changes have been observed at the population level.

Regarding rate differences by serotype among adults ≥65 years from 2007 through 2008 versus 2014 through 2015, PCV13 serotypes 19A and 7F essentially drove the reductions observed. These were statistically significant, but among adults, statistically significant decreases also were observed in serotype 3 infections. In 2014 and 2015, vaccine type IPD has plateaued and a slight increase in serotype 3 disease was observed. So far, the 2014 / 2015 increases observed in serotype 3 infection have not been statistically significant and it is unclear how to interpret this, but monitoring will continue. Very small magnitude increases have been observed in non-vaccine serotypes, with statistically significant increases only for type 23B IPD. With respect to trends in invasive pneumococcal disease among adults aged ≥65 years old from 1998 through 2015, again, there were very dramatic reductions in invasive pneumococcal infections that were driven with the introductions of PCV7 and PCV13 serotypes.

The following pie charts demonstrate how the serotype distribution has changed since introduction of PCV13 in adults:



In 2007-2008, PCV7 serotypes accounted for 43% of invasive infections. In 2014-2015, that decreased to 22% of all invasive infections. In 2014-2015, serotypes that are unique to polysaccharide vaccine accounted for 36% of invasive disease and non-vaccine serotypes account for 42% of invasive disease.

This table shows the picture being observed across the age groups in terms of the impact of PCV13:

Age (years)	Serotype group	% change (95%CI)
<5	PCV13	-86.82 (-90.59, -81.53)*
	Non-PCV13	-10.88 (-28.09, 10.44)
	ALL IPD	-58.24 (-64.67, -50.65)*
5-18	PCV13	-84.78 (-91.04, -74.13)*
	Non-PCV13	-5.77 (-34.63, 35.83)
	ALL IPD	-55.28 (-66.11, -41.00)*
19-64	PCV13	-68.66 (-72.17, -64.72)*
	PPSV11	6.19 (-4.85, 18.52)
	NVT	-10.9 (-21.47, 1.08)
	ALL IPD	-35.11 (-39.23, -30.72)*
≥65	PCV13	-69.29 (-73.73, -64.10)*
	PPSV11	-10.11 (-22.59, 4.39)
	NVT	-12.77 (-23.52, -0.50)*
	ALL IPD	-36.47 (-41.42, -31.1)*

* statistically significant decrease

In summary, significant reductions were observed in PCV13-type IPD following the 5 years of PCV13 use. Reductions were driven by types 19A and 7F. There were significant decreases in overall IPD among children and adults. No significant changes were observed in non-PCV13 types among children and adults. There were increases of a small magnitude of <0.5/100,000 in select non-PCV13 serotypes. In 2010-2015, PCV13 use in children has prevented an estimated 280,000 IPD cases and 20,000 deaths among all ages.

In conclusion, in the 5 years post-PCV13 introduction, significant reductions were observed in IPD caused by the PCV13 serotypes in children and adults, indicating continued direct and indirect effects. There has been no evidence of serotype replacement in children or general population of adults.

Discussion Points

Dr. Schmader (AGS) emphasized that 66 year olds are generally different from 88 years in their vulnerability to problems, and asked whether the data could be categorized in different age groups above 65 such as 70 through 79 and above 80.

Ms. Pilishvili replied that they have stratified it across different age groups. The impact is similar. Obviously, 85 year olds have higher overall incidence of disease. In terms of decreases in PCV13 types and lack of strong replacement observed, it is similar across age groups.

Dr. Bennett requested further information about why plateauing was occurring.

Ms. Pilishvili responded that through 2014, reductions were observed in all PCV13 serotypes. From 2014 through 2015, there were plateaus or slight increases that were driven by serotype 3. At this point, it is not statistically significant and the meaning of it is difficult to interpret. They will continue to monitor this.

Dr. Romero asked how granular Ms. Pilishvili could get with regard to invasive disease. For example, could it be broken out by pneumococcal meningitis? In a consortium of 8 children's hospitals, since the introduction of PCV13, there was not a decrease in the number of cases of pneumococcal pneumonia. There was a decrease in the number of vaccine strains, and there was a slight trend of increasing non-vaccine types.

Ms. Pilishvili indicated that they can look at individual clinical syndromes. Some of those analyses are still ongoing. They did assess pneumococcal meningitis, and the trends they are seeing are similar. Although there seems to be more replacement observed with meningitis in the elderly.

Dr. Gemmill (NACI) asked whether there was any information on coverage rates for children versus those over 65 years of age since the recommendation in 2014, to determine what type of impact that is having.

Ms. Pilishvili indicated that the last presentation would address adult coverage. Pediatric coverage has been pretty stable. After the transition from PCV7 to PCV13, uptake was similar in the pediatric population.

Dr. Whitley-Williams (NMA) asked whether there has been any reduction in the disparity gap between blacks and whites, particularly as it relates to IPD.

Ms. Pilishvili responded that they have not analyzed this with the most recent data, but they have assessed the disparities and how those have changed post-PCV7 and shortly after PCV13 was introduced. The disparities have been eliminated in terms of the PCV13 vaccine-type infections. However, the disparities still exist in terms of overall IPD caused by other serotypes.

Dr. Whitley-Williams (NMA) asked whether that was due to the fact that other serotypes are not contained in the vaccine that are more prevalent in the black population.

Ms. Pilishvili indicated that the distribution is similar overall. In later years, non-vaccine serotypes account for a higher proportion of infections. While the vaccine did prevent cases among various groups and reduced or eliminated those disparities, overall infections are caused by non-vaccine serotypes in every group. However, the disparities still exist in terms of the rates of disease cause by non-vaccine types.

Dr. Sun (FDA) said his understanding was that the recommendation was subject to reevaluation because it depends on the challenges of sorting out the direct and indirect effects of the impact of PCV13 on the elderly. He asked how direct and indirect effects would be sorted out with these observed trends.

Ms. Pilishvili requested that Dr. Sun hold this question until after her next presentation, during which she planned to discuss how direct and indirect effects would be sorted out.

Dr. Stephens asked whether there are specific data on Alaska Natives and / or other susceptible populations among whom pneumococcal disease has been significant.

Ms. Pilishvili responded that ABCs does not have data on the Alaska Natives or other highly susceptible populations. Disparities are typically addressed in terms of racial disparities. There are studies ongoing in Alaska similar to the ABCs surveillance that monitors the trends and impacts of PCV13. She believes they see a similar impact of PCV13 introduction, with somewhat more replacement in the Alaska population than observed in the general US population. She deferred to Dr. Whitney for additional information.

Dr. Whitney (SME) added that Alaska had very good impact quickly with PCV13 serotypes disappearing. They may have experienced a little bump up in the non-vaccine types. It is a population that needs to be observed more closely because they are susceptible to other serotypes, but it also is a population for which the numbers are small so it is hard to draw too much of a conclusion from the early figures. They will check this again and will provide additional information to ACIP.

Ms. Groom (IHS) indicated that Johns Hopkins is continuing to monitor in the Southwest. In some American Indian populations, there is an ongoing disparity similar to what is observed in the African American population that continues to perplex them. They are contemplating ways to continue to tease that out. Great gains have been made with PCV13, but at the same time, they are still observing a disparity of IPD in the American Indian population.

Changes in Invasive Disease Burden Among Adults With and Without Indications for PCV13 Use

Sana Shireen Ahmed, MD
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

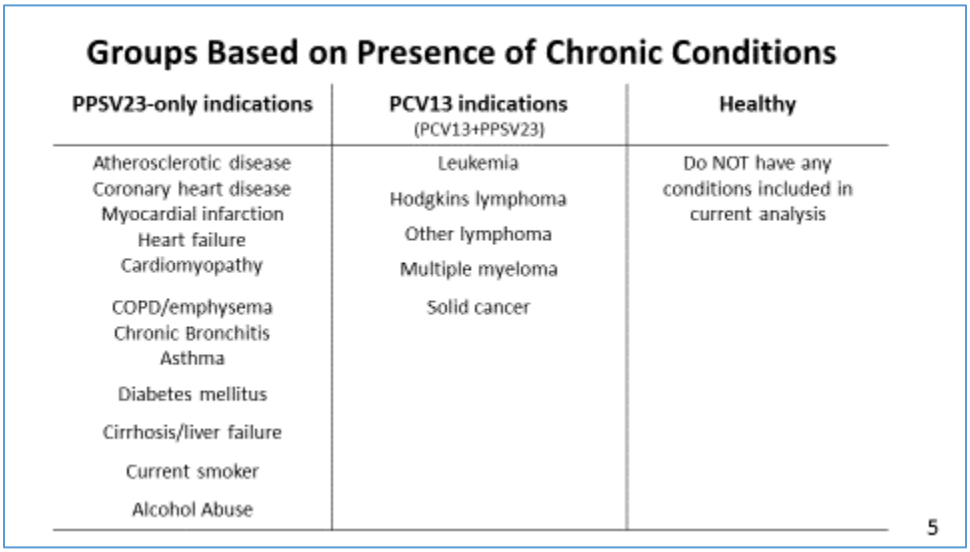
The focus of Dr. Ahmed's presentation was to discuss the impact of PCV13 on invasive disease among various groups of adults, with and without indications for PCV13 use. ACIP has recommended the 13-valent pneumococcal conjugate vaccine (PCV13) in series with 23-valent polysaccharide vaccine (PPSV23) for all adults 65 years and older and for adults 19 through 64 years old with immunocompromising conditions. For immunocompetent adults <65 years of age with chronic conditions, such as heart disease or diabetes, only PPSV23 is recommended currently. Thus, this subgroup of adults with no PCV13 indications is experiencing only indirect PCV13 effects through PCV13 use in children.

The objectives of this study were to: 1) evaluate PCV13 impact in terms of direct and indirect effects on IPD burden among adults 19 through 64 years of age, with and without current indications for PCV13 use; 2) estimate remaining vaccine preventable IPD burden among adults 19 through 64 years old with select medical conditions in 2013–2014, following 4 years of PCV13 use in children.

For the numerators, IPD cases were identified through the ABCs system, a laboratory and population-based surveillance system ongoing at 10 sites. An IPD case was defined as isolation of pneumococcus from a normally sterile site. For the denominators, the National Health Interview Survey (NHIS) was used to estimate the US population of adults. NHIS is a data collection program of the CDC's National Center of Health Statistics (NCHS). It is a cross-sectional survey with interviews administered to households and non-institutional groups throughout the year. The analysis included ABCs IPD cases among adults 19 through 64 years

of age with and without select chronic conditions, and corresponding NHIS population denominators.

Adults with the following conditions were identified within ABCs and NHIS and were placed into three groups:

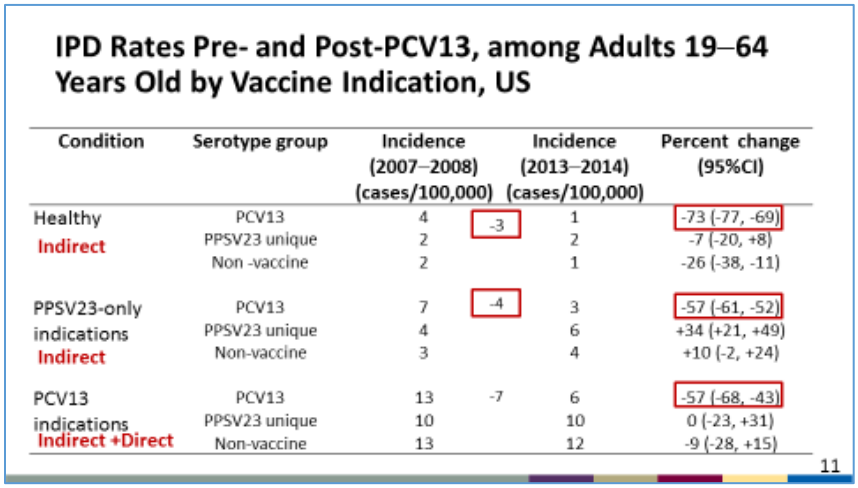


Conditions and risk factors for which there are current indications for PPSV23 vaccination alone will be referred to as “PPSV23-only indications group” shown on the left. Adults with immunocompromising conditions for which PCV13 and PPSV23 are recommended will be referred to as “adults with PCV13 indications.” Please note that HIV and renal failure, both current indications for PCV13 use, were not included in this analysis due to NHIS data limitations. Healthy adults in the same age group who did not have any of the medical conditions listed above will be referred to as the “healthy group.”

In order to compare the effects of PCV13 use on IPD burden among adults 19 through 64 years of age with select conditions, two distinct periods were assessed during the 2007-2014 period. PCV13 replaced PCV7 in 2010 for use among children, so anything prior to 2010 was considered pre-PCV13, the baseline. From 2010-2014, adults were experiencing PCV13 indirect effects. This is considered to be the post-PCV13 era. In 2012, PCV13 was recommended for use among adults with immunocompromising conditions. Since 2012, healthy 19 through 64 year old adults and adults with conditions for which only PPSV23 is recommended continued to experience indirect PCV13 effects. Since 2012, adults with PCV13 indications have been experiencing both direct and indirect vaccine effects. Therefore, in order to evaluate PCV13 effects on burden, a pre-PCV13 baseline for the period 2007-2008 was compared to the post-PCV13 period 2013–2014.

To address the first objective, estimates were calculated for IPD incidence, percent changes in overall and PCV13-type IPD incidence between the 2 periods, and the contribution from direct and indirect effects on overall impact among adults with PCV13 indications. Overall, IPD rates declined among healthy adults from 8/100,000 to 4/100,000 with a 47% decline in overall IPD rates. Among adults with PPSV23-only indications, IPD incidence declined from 15/100,000 to 12/100,000 with a 19% decline. Among the group with PCV13 indications, IPD rates declined from 36/100,000 to 27/100,000 persons with a 24% decline. To further understand the primary

drivers of these declines in IPD rates, the burden was broken down by serotype groups. This table shows IPD incidence pre- and post-PCV13 and percent changes in the last 3 columns by serotype group and presence of vaccine indication:



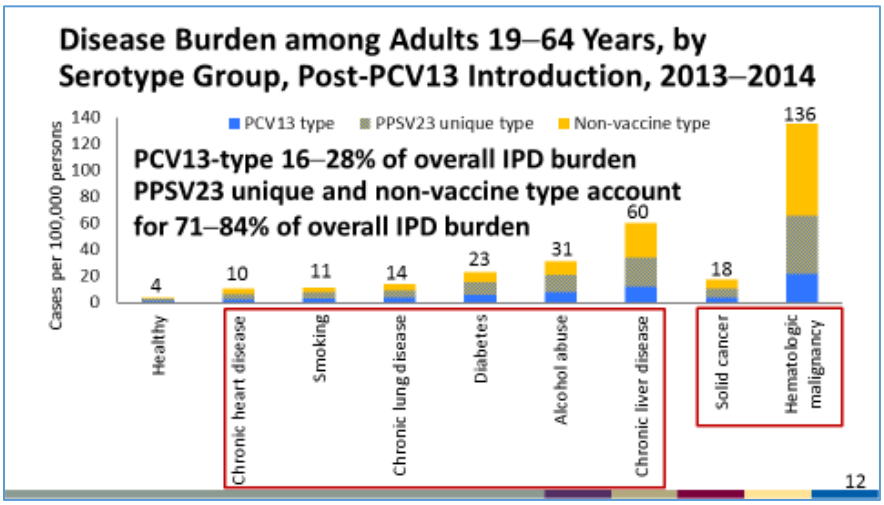
IPD Rates Pre- and Post-PCV13, among Adults 19–64 Years Old by Vaccine Indication, US

Condition	Serotype group	Incidence (2007–2008) (cases/100,000)		Incidence (2013–2014) (cases/100,000)	Percent change (95%CI)
Healthy	PCV13	4	-3	1	-73 (-77, -69)
Indirect	PPSV23 unique	2		2	-7 (-20, +8)
	Non -vaccine	2		1	-26 (-38, -11)
PPSV23-only indications	PCV13	7	-4	3	-57 (-61, -52)
Indirect	PPSV23 unique	4		6	+34 (+21, +49)
	Non-vaccine	3		4	+10 (-2, +24)
PCV13 indications	PCV13	13	-7	6	-57 (-68, -43)
Indirect +Direct	PPSV23 unique	10		10	0 (-23, +31)
	Non-vaccine	13		12	-9 (-28, +15)

11

The serotypes were grouped as PCV13-types, the 11 serotypes unique to PPSV23 labeled as "PPSV23 unique," and non-vaccine types, which includes serotypes not covered by any vaccine. Looking at the rate changes across serotype groups, the reductions in overall IPD rates are driven by declines in PCV13 IPD rates. PCV13 IPD rates declined by 73% in the healthy group and by 57% among adults with and without indications for PCV13 use. Similar absolute changes in rates among healthy adults and adults with PPSV23 indications demonstrate that both groups experience similar indirect effects from child vaccination. Similar percent declines in IPD incidence were seen in adults with and without PCV13 indications, suggesting that the adults with vaccine indications largely experienced indirect effects. In 2013-2014, PCV13-type IPD rates were low across all groups. No reductions or increases were seen in IPD caused by PPSV23 unique serotypes across all condition groups, and no evidence of replacement disease was seen in non-vaccine type IPD across condition groups.

This bar graph demonstrates the disease incidence and underlying conditions among adults 19 through 64 years old by serotype groups 3 to 4 years after PCV13 introduction:



Looking across the different conditions, overall incidence rates were higher among adults with select medical conditions compared to the incidence of 4/100,000 in healthy adults. The rates among those adults with chronic medical conditions ranged from 10/100,000 for adults with heart disease to 136 / 100,000 for adults with hematologic malignancy. In addition, the largest burden of disease for all groups was caused by serotypes not covered by PCV13 as shown in the yellow bars. The incidence of PCV13 type IPD ranged from 2/100,000 to 12/100,000 in adults with PPSV23-only indications to 4/100,000 to 21/100,000 adults with PCV13 indications and accounted for 16% to 28% of all IPD. PPSV23 unique serotypes and non-vaccine type IPD accounted for 71% to 84% of overall IPD burden.

In order to estimate the contribution from direct and indirect effects on observed reductions in IPD among adults with PCV13 indications, adults with hematologic malignancy were chosen as a demonstration example since it is a group for which PCV13 has been recommended since 2012. In this group, a contribution is expected through both the direct and indirect effects of PCV13. An estimated 890 cases of PCV13-type IPD would be expected to be observed among adults with hematologic malignancy in the US with pre-vaccine IPD rates applied to the 2013-2014 population of adults with hematologic malignancy. There were an estimated 260 cases of PCV13-type IPD observed in adults with hematologic malignancy in 2013-2014. For simplicity, it was assumed that the observed burden in the post-PCV13 era was influenced only by PCV13. It was also assumed that there were no PPSV23 effects, and that PCV13 direct and indirect effects had an additive impact on disease burden. With those assumptions, it was inferred that the difference in the number of estimated cases between the time periods is the number of cases prevented by direct plus indirect effects. There were 630 cases prevented by PCV13 effects.

To estimate the contribution from direct effects alone, additional assumptions were made. Vaccine coverage was assumed to be about 5% to 7% based on a recent study estimating cumulative PCV13 uptake through 2014 for adults 19 through 64 years with current PCV13 indications. Also assumed was that vaccine efficacy was 74% against vaccine type IPD based on the results of an efficacy trial in HIV+ adults and similar to IPD efficacy in adults ≥65 years old from the CAP Immunization Trial in Adults (CAPiTA). The number of cases prevented from direct PCV13 effects is the factors of baseline PCV13 type IPD burden, vaccine coverage and vaccine efficacy. Given these assumptions, it was estimated that approximately 33 to 46 cases would be expected to be prevented from direct protection afforded by PCV13 use in adults. The remaining 584 to 597 cases would have been prevented through indirect PCV13 effects. These estimates demonstrate that in a setting of 5% to 7% coverage with PCV13, 93% to 95% of the observed impacts in 2013-2014 is expected to be due to indirect or herd effects from childhood vaccination. If higher PCV13 coverage of 20% is assumed, similar to the current PPSV23 coverage in adults <65 years old with vaccine indications, the number of cases estimated to be prevented directly by PCV13 increases, decreasing the proportion prevented through indirect effects to 79% of observed total PCV13 impact. In a setting of remaining vaccine-preventable disease burden, the relative contribution of direct PCV13 impact increases with increase in vaccine coverage among adults.

There were several limitations to the study. NHIS population estimates and ABCs IPD estimates were obtained using different methodologies. Groups from ABCs and NHIS are subject to misclassification bias. Because of the limitations in the data sources, vaccine impact among adults with HIV and dialysis could not be evaluated and, due to the same data limitations, these groups could not be excluded from the healthy group, so the incidence estimate for this group may be an overestimate. Medical conditions were not mutually exclusive and interactions may exist. However, similar trends in disease burden were seen when certain

groups were restricted to adults with only one condition. The analysis was focused on IPD and did not include community-acquired pneumonia (CAP), which contributes to the largest burden in adults. The burden of vaccine-preventable pneumonia should be considered for estimating overall impact on pneumococcal disease burden.

In summary, the investigators found that that PCV13 introduction among children reduced incidence among healthy 19 through 64 years old adults and those with underlying conditions. Reductions of a similar magnitude were observed in those with and without PCV13 indications in the context of low PCV13 coverage, suggesting that observed benefits to date are largely due to indirect PCV13 effects. Adults with underlying conditions still continue to experience higher IPD rates compared to healthy adults in the post-PCV13 period, but most of the remaining burden of IPD in adults is from non-PCV13 serotypes with little remaining PCV13 disease. There is no evidence of serotype replacement disease among these groups of adults.

Discussion Points

Regarding the risk groups, Dr. Maldonado (AAP) pointed out that for diabetes or smoking, the risk is lower but the population base may be higher. She asked whether Dr. Ahmed thought the indirect impacts may be larger and if she looked at any others besides the immunologic malignancy group for the rough estimation.

Dr. Ahmed responded that for the rough estimation, they looked at that group because PCV13 already was indicated for them. They were able to distinguish between direct and indirect effects.

Dr. Bennett pointed out that so far, PCV13 is not recommended for risk groups other than those who are immunocompromised, in that age group.

Dr. Maldonado (AAP) suggested that they still could look at a larger burden of disease for indirect effects.

Dr. Atmar asked whether instead of subtracting the direct effects from the total cases, they considered coming at it from the other direction and looked at the impact of the indirect effects, assuming they were similar for what was observed in groups for whom PCV13 is not indicated. It looked like the magnitude of decrease was similar, so they might be able to better estimate about the direct effects by taking that approach to get the range.

Dr. Ahmed responded that they did not take that approach in the calculations, but agreed that it was another way they could consider looking at it.

It seemed to Dr. Zahn (NACCHO) that in the past when they assessed indirect effects when PCV7 was introduced, the indirect effects for high risk populations was not as impressive. That is, indirect protection of non-high risk individuals was better than high risk individuals. This seemed somewhat different from that in a better way. He wondered whether it actually was different or if the data they have now is just more robust in terms of teasing out the answer to that question.

Dr. Ahmed said she thought historically looking at PCV7, there were similar effects even for high risk groups at that time.

Dr. Moore observed that this study did not include any assessment of CAP. She asked whether studies were underway or were being planned to assess any impact on CAP.

Dr. Ahmed indicated that Ms. Pilishvili would address this in the next presentation.

Dr. Lee noted that Dr. Ahmed's presentation was very elegant, pointing that it was a lot of complicated data and Dr. Ahmed did a really nice job presenting it visually. Similar to Dr. Atmar's question, she wondered whether Dr. Ahmed could do a sensitivity analysis by flipping it to take an indirect effects perspective since she came up with estimates for the herd protected only groups. She said part of her rationale for thinking about this was because it was easy for her to believe that for the general population, the vaccination rates are 5% to 7%, but it was harder for her to believe that the vaccinations rates are that low for the immunocompromised population. She wondered whether Dr. Ahmed could back into it that way to come up with guesstimates of vaccine delivery in that population to see if that actually quantitatively makes sense. It would at least offer two different bounds.

Dr. Ahmed indicated that in terms of vaccine coverage, what she listed as 5% to 7% was for those 19 through 64 years of age with current PCV13 indications. She agreed that the coverage rates for each condition group might vary, with some higher and lower, so depending on coverage they may be afforded a higher level of protection if they are higher coverage.

Dr. Lee suggested that it might also be helpful to capture mean and median age of the population of those with chronic conditions, in part from the pediatric perspective because she feels like they see a lot of families. If the median age is among families and young children, it might make sense that their exposure is just inherently different than another population that is either much older or much younger.

Dr. Bennett asked whether a sensitivity analysis was performed looking at the immunization rates. That does seem to drive the analysis to a large extent. It was surprising to her even that among people with a hematologic malignancy, the vaccination rates would be only 20%. It seems that they would be higher.

Dr. Hunter said he was not surprised from an implementation point of view based on his experience in the City of Milwaukee. The health department was asked to come to a tertiary care center to provide vaccination services, because they were not able to provide it within the subspecialty clinics. Based on some manuscripts he has seen related to a hematologic malignancy, the vaccination rates for that particular condition were quite low. He was really surprised about that. He wondered why they thought specialists would do any better job than primary care physicians.

Dr. Cohn requested clarification about whether the coverage estimates Dr. Ahmed used were for any pneumococcal vaccine or just for PCV13, and how the question was asked in the survey from which the 5% to 7% was obtained.

Dr. Ahmed replied that that analysis was done by Pfizer which assessed uptake and did modeling, which showed that among those 19 through 64 years of age in high risk groups that included immunocompromised individuals, PCV13 coverage was about 5% to 7%.

Dr. McLaughlin (Pfizer) said the first thing to note about uptake is that it is a very difficult question. The way they addressed it was through a multifactorial approach. The easiest way to do it is to look at IMS Health claims uptake, which are claims for the vaccine. The difficulty is by just looking at the claims, some claims are missed that might have occurred in the pharmacy or a specialty office that are not typically captured by an entity like IMS Health. They also looked at Pfizer's internal sales data. Even though sales data are not split by pediatric and adult, they tried to parse it out by which practices the claims came from. Essentially, they looked at the IMS claims data and then factored that to what they were seeing in the sales data to try to get an overall picture of not just claims from health insurance, but also missed claims that were showing up in their sales. For risk groups, the numbers are probably a slight underestimate because not only is it more difficult to get data from these specialty clinics, but also it is more difficult to know what the underlying health status is of people with these claims. That has to be based on claims rather than a medical record. It is more likely that coverage will be underestimated in the risk groups than in the general population.

Outline of Research Agenda to Inform Potential Policy Change in 2018 for PCV13 Use Among Adults

Tamara Pilishvili, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases

Ms. Pilishvili indicated that lastly during this session, the WG wanted to share with the committee a roadmap of how the WG plans to approach the potential policy consideration in 2018 for PCV13 use among adults. She highlighted some of the key ongoing studies that will help contribute to this evidence that the WG will share with the committee in 2018. The WG thought that in order to address the potential policy reconsideration in 2018, the following basic but key questions need to be answered before the 2018 review:

- Is PCV13 use preventing disease among adults ≥65 years old?
- To what extent are the observed benefits driven by adults PCV13 use (direct effects) versus pediatric PCV13 use (indirect effects)?
- What benefits would be expected from continued PCV13 use among adults versus reconsidering this policy?

For each of these questions, Ms. Pilishvili presented on the types of studies the WG believes will be helpful in answering the questions and highlighted some of the methodologies and objectives for some of the key ongoing studies.

In terms of the first question regarding whether PCV13 use is preventing disease among adults >65 years old, the obvious study and action is to continue monitoring the impact of new recommendations in the vaccine target age group. In order to understand how much of the impact being observed can be attributed to the direct PCV13 effects in adults, it is important to understand changes in the IPD burden before and after PCV13 recommendation; changes in pneumococcal pneumonia burden before and after PCV13 introduction; uptake of vaccine among adults >65 years old; and the effectiveness of PCV13 and PPSV23 against IPD among adults >65 years old. CDC is conducting a PCV13 case-control effectiveness study among adults >65 years of age. The idea is to determine how the new recommendations work in the US population.

With respect to the second question regarding the extent to which the observed benefits are driven by adults PCV13 use versus pediatric PCV13 use, the data shared thus far demonstrate the indirect effects that have been observed to date. That is important for IPD, but it also is important to assess the same data for pneumonia. It is important to continue to monitor the impact of PCV13 use in children on adult disease burden to assess changes in IPD and pneumonia among adults ≥65 years old before and after PCV13 introduction for children and before PCV13 recommendations for adults; and changes in IPD and pneumonia among adults <65 years old without current PCV13 indications. This will allow for assessment of the indirect effects observed to date to determine whether the indirect effects will continue or have plateaued.

Colonization studies are important among adults and children to understand the residual circulation and transmission of PCV13 types in a setting of herd effects in the community. Disease trends will continue to be monitored through 2018 to estimate the contribution of direct versus indirect effects to observed reductions in IPD and pneumonia. What is being observed are direct and indirect effects combined, so it will be challenging to tease those effects apart. Therefore, several approaches are being taken that involve mathematical modeling to understand the contribution of direct versus indirect effects. This will rely on understanding of vaccine uptake and how much of the observed reduction can be attributed to direct effects. There also is the PCV7 experience on indirect effects, as well as indirect effects post-PCV13 that are still being observed in certain adult age groups that will allow for projection of what the expected continued indirect effects should be. These studies will be important for IPD as well as pneumonia.

In terms of the impact on PCV13-type IPD burden among adults ≥65 years of age, PCV13-type IPD rates declined through 2014 due to indirect PCV13 effects. No additional declines were observed in 2015 and appear to have plateaued. PCV13-types accounted for 22% of IPD in 2015 compared to 43% pre-PCV13. Continued monitoring of disease trends among adults <65 years old is needed to evaluate the impact of herd effects. PCV13-type IPD burden continues to decline among adults without current indications for PCV13 use. PCV13-types accounted for 24% of IPD in 2014 compared to 48% pre-PCV13 among adults without indications for PCV13.

PCV13 case-control effectiveness study among adults ≥65 years of age mentioned earlier is ongoing, with the objectives were to: 1) evaluate the effectiveness of PCV13 against PCV13-serotype invasive pneumococcal disease; and the effectiveness of PCV13 and PPSV23 when given in series; and 2) evaluate risk factors for IPD among adults ≥65 years of age in a setting of PCV13 and PPSV23 use when given in series because this is the recommendation for adults ≥65 years of age. Cases of IPD among adults ≥65 years old are identified through ABCs. Pneumococcal isolates are serotyped, so they will be looking at the very specific endpoint of vaccine-type disease. Controls are being identified using a commercial database, with a goal to enroll 4 controls per case matched on age group and zip code of residence. For both cases and controls, vaccination histories are being obtained by identifying all medical care encounters and providers in the last 6 years, and then attempting to contact each of these providers who may have provided vaccines to the participant.

To date, 200 cases and 520 controls have been enrolled. Pneumococcal serotyping is ongoing to determine the number of vaccine-type (VT) cases that have been enrolled so far. In terms of the projection of the sample size estimates, at approximately 30% PCV13 coverage, the sample size estimation suggests that approximately 46 VT cases will be needed to demonstrate a VE of 75%. Enrollment began in about November 2015 and it is estimated that the end of enrollment will be in winter 2017-2018, based on the VT cases occurring and increases in coverage.

CAP is also a very important endpoint. The policy decision in 2014 was largely driven by the estimated vaccine-preventable burden of community-acquired pneumonia. Therefore, studies to monitor PCV13 impact on pneumococcal pneumonia are ongoing and are very important in contributing to review in 2018. Ms. Pilishvili highlighted three ongoing studies assessing various endpoints:

- A CDC study assessing the impact of PCV13 on all-cause pneumonia hospitalizations
- CDC population-based surveillance for non-invasive pneumococcal pneumonia
- Population-based surveillance for PCV13-type pneumococcal pneumonia being conducted at the University of Louisville, funded by Pfizer

The objectives of the CDC study assessing the impact of PCV13 on all-cause pneumonia hospitalizations are to: 1) measure the impact of PCV13 introduction in children on pneumonia hospitalizations across all age groups in terms of PCV13 indirect effects only; and 2) estimate the additional impact of the 2014 adult PCV13 recommendation on pneumonia hospitalizations among adults ≥ 65 years of age in terms of PCV13 direct effects. This is to tease apart the direct and indirect effects. For the first objective, the data source is statewide inpatient data from 2004-2014. The study methodology is a time-series analysis using "synthetic controls" to adjust for unmeasured confounding (e.g., changes in coding practices, change in healthcare seeking behavior). For the second objective pertaining to adults ≥ 65 years of age, the data source is statewide inpatient data from 2004-2014 and the CDC is collaborating with CMS to use Medicare Part B beneficiary data from 2008-2016 to assess hospitalizations and vaccination status. The study methodology is a time-series analysis using "synthetic controls" to adjust for unmeasured confounding with two intervention points, 2010 and 2014. Because these are administrative data using ICD-9 codes, a control measure is needed, so the new method of using synthetic controls has been proposed in order to adjust for unmeasured confounding. In terms of the outcomes, CDC is using the classification algorithm based on discharge codes to assess all-cause CAP and pneumococcal pneumonia hospitalizations.

The objectives of CDC's population-based surveillance for non-invasive pneumococcal pneumonia are to: 1) conduct population-based surveillance for noninvasive pneumococcal pneumonia for 2013 and onward; 2) measure the burden of non-invasive pneumococcal pneumonia in adults; and 3) measure the potential impact of adult PCV13 recommendations. This expands and builds on CDC's ABCs that conducts surveillance for invasive disease. Through the same sites, they are expanding to include non-invasive pneumonia in the surveillance. The case definition for this surveillance is positive pneumococcal urine antigen test (UAT) from January 2013 onward, hospitalized adult ≥18 years of age who are residents of the surveillance area, clinically or radiographically-confirmed pneumonia documented in the medical record, and no evidence of invasive disease. The catchment area includes 15.6 million persons. Hospitals are included that offer the UAT. In order to obtain incidence estimates, adjustments will be made to account for the fact that not all at-risk patients are tested by UAT at hospitals offering it, and not all hospitals in the catchment area offer UAT.

The objective of the population-based surveillance for PCV13-type pneumococcal pneumonia being conducted at the University of Louisville is to estimate the incidence and outcomes of hospitalized CAP among adults ≥18 years old in 9 adult hospitals. This is an active prospective population-based cohort. They are able to estimate the denominators of the catchment area and, therefore, estimate the incidence of CAP among adults. They have a very stringent inclusion criterion, which is pulmonary infiltrate on chest x-ray + ≥1 of the following: cough/sputum, or fever/hypothermia, or leukocytosis/leukopenia and no alternative diagnosis. Perhaps the only study that will look at more specific outcome of VT pneumococcal pneumonia, the serotype-specific urine antigen detection (SSUAD) study, is also funded by Pfizer and is ongoing at 20 hospitals. The objective of the SSUAD study is to estimate the proportion of adult CAP caused by PCV13 serotypes among adults ≥18 years of age. This is active prospective hospital surveillance that includes subjects who presented with suspected pneumonia and positive chest x-ray for CAP and had a discharge diagnosis of CAP.

Each of these studies has its own set of challenges in terms of monitoring the impact on pneumonia. The endpoint for the first study is all-cause CAP, which is a non-specific endpoint that may limit the ability to detect reductions of small magnitude. In addition, any replacement with non-vaccine types may wash out the effects that might be detected looking at all-cause CAP as an endpoint. To further complicate and add to the challenge, changes from ICD-9 to ICD-10 overlap with the vaccine introduction period for adult immunization with PCV13. Therefore, it will be important to eliminate bias that is related to the coding using ICD-10 codes. To address this, cross-validation studies are being conducted mapping ICD-9 algorithms to ICD-10 code algorithms.

For the study using the UAT to assess pneumococcal CAP, UAT does not distinguish pneumococcal serotypes. Again, replacement with non-vaccine types may wash out the effects. UAT sensitivity is 50% to 80% among non-bacteremic patients, so it may underestimate the burden. PPSV23 receipt prior to UAT or carriage may influence test results. For the PCV13-type CAP study, SSUAD is not commercially available so the results will be limited to this one study. SSUAD does not detect non-PCV13 serotypes, and PPSV23 receipt prior to UAT or carriage may influence test results.

As mentioned earlier, adult pneumococcal colonization studies are important to understand what strains are circulating in the community and what the residual circulation and transmission are of the VT strains in a setting with pediatric use of the vaccine, as well as the adult use of PCV13. To that end, CDC is conducting an adult pneumococcal colonization study. The objectives of this study are to: 1) define the prevalence and serotype distribution of *S. pneumoniae* carriage in seniors; 2) assess risk factors for colonization; and 3) provide baseline data to assess the impact of the new ACIP recommendation on carriage rates through later carriage studies. The study population is adults 65 years of age or older enrolled at outpatient clinics and senior centers who are not severely immunocompromised. Both nasopharyngeal (NP) and oropharyngeal (OP) swabs are being obtained, and vaccination history is being collected. To date, 2773 participants have been enrolled across 4 US states. The target is to enroll 3353 participants. Enrollment will continue through December 2016.

Measuring vaccine uptake of PCV13 and PPSV23 in the target population of adults ≥65 years old is crucial in order to understand the contribution of the direct effects and attribute the observed impact of vaccine use among adults. PPSV23 coverage has been assessed through the NHIS annually. PPSV23 coverage has been relatively stable through 2014 at 59.7% to 62.3%. A limitation of the survey is that the current survey question does not distinguish between PCV13 and PPSV23. In terms of PCV13 and PPSV23 coverage assessment since the

2014 recommendations, CMS data have been used for PCV13 and PPSV23 claims to estimate coverage among Medicare Part B beneficiaries. It is important to note that the Medicare Advantage Plus population is excluded from the CMS data analysis because CDC does not have access to those data. Based on the results of the CMS claims data analysis through October 2015, PCV13 uptake was 15.86% and PPSV23 uptake was approximately 45%. PPSV23 coverage is likely an underestimate based on other sources of information CDC has on PPSV23 coverage, so not including the Medicare Advantage Plus population might lead to some underestimate of the PCV13 coverage related to the data being limited to Part B population only.

In the study that was referred to in Dr. Ahmed's presentation, analysis of vaccine sales and Insurance Management Services (IMS) claims were used to estimate PCV13 coverage[1,2]. Modeling was done to attribute the vaccine doses given to adults versus children in various populations. Through July 2016, uptake of PCV13 by adults ≥65 was approximately 40%. At the end of 2015, uptake was estimated to be approximately 31% using the IPD data. In high-risk individuals 19 through 49 years of age, coverage was estimated to be 11%. Among high-risk individuals 50 through 64 years of age, coverage was estimated to be 10% [[1]QuintilesIMS, Anonymized Patient-Level Data (APLD), Oct 2016 (includes diagnostic and prescription utilization claims for PCV13); [2] Pfizer, Inc. internal sales data for PCV13, Oct 2016].

In terms of the third question regarding what benefits would be expected from continued PCV13 use among adults and how direct and indirect effects could be teased apart, CDC is developing a mathematical model to evaluate the impact potential changes in the adult recommendations would have on the adult disease burden, given observed and expected herd effects ofthe pediatric PCV13 program. Again, the key from all of the parameters and data inputs presented is to estimate the relative contribution of the direct versus indirect effects on the adult disease burden. CDC will evaluate various policy options, including removal of the PCV13 recommendation versus continued use. The outcomes for each policy option will include the potential public health impact of changing the policy, including the cost-effectiveness.

The next steps are to continue to update ACIP on the changes in vaccine-preventable disease burden among adults due to PCV13 direct and indirect effects during the next 2 years, and update ACIP on the results of the ongoing studies. These data should inform revisions as needed to the proposed adult PCV13 recommendations in 2018. The declining burden of PCV13-type disease among adults over 65 years of age due to indirect effect of vaccinating children may signal that PCV13 is no longer needed. A revised cost-effectiveness evaluation incorporating changes in disease burden, uptake, and the cost of the vaccines will help align this recommendation with other adult vaccines in use.

In conclusion, Ms. Pilishvili posed the following questions for ACIP's consideration and discussion regarding a potential policy change in 2018:

- Is the proposed research agenda appropriate to help determine if a policy change is needed in 2018?

- What additional information will the committee need to help determine in 2018 whether continued PCV13 use in adults is warranted?

Discussion Points

Regarding the National Health Interview Survey on slide 14, Ms. Pellegrini asked whether that survey requests permission to correlate answers against patients' medical records.

Ms. Pilishvili replied that there is no cross-check with any medical or vaccination records for this survey.

Ms. Pellegrini said she was not sure she would be confident of the quality of responses from that survey. It is one thing to ask people if they have received one pneumococcal vaccine, but to expect them to know that they received both and if so, which one first and which one second may not be terribly useful.

Ms. Pilishvili said this was exactly the discussion that had been ongoing in terms of trying to determine whether they can use this survey to understand which vaccines have been given. For self-report, it is not expected that people would remember.

Dr. Belongia said he had one note of caution on the studies related to all-cause CAP based on his own research. In the influenza vaccine world, they learned about a decade ago that they could get wildly inaccurate estimates if they based their endpoint on a non-specific administrative data source. Fortunately, NCIRD has other studies planned that will assess very specific pneumococcal and serotype specific outcomes, so he thought that was good. He asked what a "synthetic control" is.

Ms. Pilishvili replied that this new methodology has been proposed by Dr. Dan Weinberger at Yale for the analysis of administrative data on CAP hospitalizations, which has been presented as an improved methodology to use administrative data to evaluate impact of vaccines. The idea behind his methodology is that in previous studies where administrative data were used to document the impact of PCV7 or PCV13, as a control measure/condition, specific ICD-9 codes unrelated to pneumonia diagnosis have been used such as fractures. Whereas, the methodology of synthetic control, rather than using a single ICD-9 code or single condition as a control, creates a composite control that adjusts for potential changes that may be occurring with each individual condition. It optimizes the control of potential bias due to changes to coding practices, or some inherent trends in any particular condition.

Dr. Stephens was struck by the fact that there was not a lot of emphasis on molecular typing or whole genome analyses. He knew they were doing whole genome analyses on most of the invasive isolates now. A lot was learned about 19A emergence in the replacement era with PCV7 through that methodology, and he wanted to get Ms. Pilishvili's comments about the role of molecular typing as it relates to these studies.

Ms. Pilishvili responded that in the ABCs surveillance, they are moving toward whole genome sequencing (WGS). This is still new and she does not think they have solidified how it will contribute to this particular question. Certainly, in terms of monitoring the trends and the emergence of new strains, they plan to use the WGS data.

Dr. Moore asked whether they are using immunization information systems (IISs) as a source for data for adult immunizations. It is hard for people to remember what they have had. Almost all states have lifelong registries, some of which are outstanding and would have good information on exactly what kind of vaccines people have had. It would be a great resource rather than recollection and other less direct methods.

Dr. Bennett pointed out that this is somewhat problematic because the adult registries are fairly new in most states, so the data for adults is not as good as it is for children.

Dr. Mel Kohn (Merck) raised the issue of series completion. The recommendation from ACIP includes both vaccines. He expressed his hope that series completion would be taken into account when the WG reevaluates the recommendations. Merck has reviewed some of the IMS data to determine how many of the people who received PCV13 went on to receive a second vaccine of PPSV23. The early indication with about 20 months of follow-up for the first month's cohort after the recommendation was passed suggests very low rates of about 12%. As they move into influenza season, he expects that number will increase. He said this also was an exhortation to anyone listening to go ahead and complete that series. He believes that yet another factor that will be important for the WG to consider is how well the series is being fully implemented.

Dr. Bennett agreed that many complexities to implementation are being observed in different settings that are not ideal, and they will want to try to figure that out.

Dr. Gemmill (NACI) indicated that Canada has not made a recommendation for use of PCV13 for healthy people over 65 years of age. They are very interested in all of these results, and may even look upon it as an opportunity to collaborate.

Dr. Paradiso (Paradiso Biologics Consulting) noted that it appeared that the indirect effect in the 19 through 64 year old healthy population was in the 70% range; whereas, in the high risk populations, the indirect effect was about 57% for the indications for polysaccharide or conjugate. There was an earlier discussion about a distinction or differences in those populations. He thought those would be interesting to look at, because when trying to estimate based on the coverage, what portion was direct and indirect, those differences will be important. In the case-control studies, they distinguished populations of people who got the conjugate based on whether they got it before or after polysaccharide. Many of the over 65 year olds would have had previous polysaccharide. It would be interesting to see the difference between those who had polysaccharide previously, and then subsequently got a conjugate vaccine.

Ms. Pilishvili replied that in their case-control study, they are identifying indication period or look-back period for both cases and controls. They are contacting providers and obtaining history of PCV13, PPSV23, and any other vaccines they have received. If they have sufficient power to look at various schedules, they certainly will be interested in looking at the sequence in which the vaccines were received as well. She agreed that the impact in terms of the ratio measure they have seen in healthy adults versus those with underlying conditions is higher; however, looking at the percent reductions alone is not quite sufficient. That is why they look at the absolute change as well. Looking at the absolute changes in rates, they actually were quite similar among healthy and those with underlying conditions. Taking both pieces of evidence into account, as well as looking at the remaining vaccine-preventable disease burden in both healthy and those with indications, and understanding what it means at the population level is important.

Dr. Hunter expressed concern about the cost of missed opportunities to vaccinate, and errors in vaccination that can occur when there are complicated recommendations for high risk individuals who have a higher rate of vaccine-preventable diseases. There are large numbers of lower risk healthy people who have lower risks of vaccine-preventable diseases. But if there are very complicated recommendations to implement the vaccine administration, people who

actually administrate the vaccines will be confused. He wondered if there was any way to capture in the research whether increasing the complexity of the vaccine recommendation for a small group of people affects the uptake amongst a large group of people.

Ms. Pilishvili thought this was a very good point that they would have to think about.

Dr. Sun (FDA) said he was struggling to understand how to tease out the indirect effect from an increase in the coverage rate of PCV vaccination for the elderly. One might imagine that there would be some indirect effect from having other elderly people around you vaccinated and, therefore, less pneumococcal disease, and the additional indirect effect on not being exposed to young children who do not carry pneumococcus as a result of vaccination. That is, the indirect effect from adults versus the indirect effects from children.

Ms. Pilishvili responded that this would not be simple, which was why they were proposing several approaches. It will not be simply subtracting one from the other, although there was a nice demonstration in Dr. Ahmed's presentation. Going forward, especially in the population that is receiving the vaccine and also experiencing the indirect effects, they will have to learn from the past data what the observed indirect effects have been and what is expected projecting those indirect effects, of course, making certain assumptions, and also understanding what the contribution of direct effects is by measuring the coverage and estimating what the contribution of the direct effects to indirect effects would be going forward. Though the answer is not simple, they have certain models that they are developing that will take into account various scenarios based on the observed data they have, and the data they will continue to observe in terms of indirect effects among adults who are not currently receiving the vaccine. This will be done using the modeling approach and performing various sensitivity analyses, because certain assumptions will have to be made as far as projecting the indirect effects going forward.

Influenza

Introduction

Chip Walter, MD
Chair, Influenza Work Group

Dr. Walter reported that since the June 2016 ACIP meeting, the 2016-2017 ACIP Influenza Statement was published in the *MMWR* August 26, 2016. In addition, there were two new licensures:

- AFLURIA® Quadrivalent manufactured by Seqirus™, which is a quadrivalent inactivated influenza vaccine (IIV) on August 26, 2016
- FLUBLOK® Quadrivalent manufactured by Protein Sciences Corporation, which is a quadrivalent recombinant influenza vaccine, on October 7, 2016

He indicated that the topics for this session would focus on an influenza surveillance update and AFLURIA® Quadrivalent vaccine. As a reminder, there was a discussion during the February 2016 ACIP meeting on FLUBLOK® Quadrivalent.

Epidemiology / Surveillance Update

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

During this session, Ms. Brammer provided updates on international influenza activity, recent US influenza activity, and the Southern Hemisphere vaccine recommendations recently made.

Regarding influenza activity for the last year in the Northern Hemisphere, influenza A(H1N1)pdm09 predominated along with some influenza B viruses and some H3N2 activity toward the end of the season. Currently, Northern Hemisphere activities are very low. The Southern Hemisphere's season started out predominated by H1N1 viruses, with an increase in H3N2 viruses toward the end of the season. Looking at the Southern Hemisphere and a few representative countries, Australia contributed a large proportion of the late season H3N2 viruses. That actually was their predominant virus for that season. South Africa had an interesting season. They started out as influenza-B predominant, went into an H3 predominant period, and then had a third wave of influenza activity during which H1N1 viruses predominated. Argentina and Chile are representative of what occurred in South America, with both having H1N1 predominant seasons with some influenza B activity.

In terms of recent activity in the US, 1.7% of specimens tested for influenza were positive for influenza at week 40 compared to the 24% seen at peak last season. Based on results from public health laboratories, recent influenza activity was low relative to what would be seen at peak. Influenza B viruses predominated going into the summer, but influenza A(H3N2) viruses became more frequently detected and predominated at about 90% by October. The public health laboratories submitted a subset of their influenza positives to CDC for genetic and antigenic characterization. Over the summer, 52% of the viruses reported by public health laboratories were H3N2 viruses. Among those that CDC was able to characterize genetically, there are three genetic groups among the H3s currently: 1) 3C.3a, which last year's A/Switzerland vaccine component represented; 2) 3C.2a, which is this year's H3N2 component A/Hong Kong/4801; and 3) 3C.2a1. From May 22, 2015 through October 8, 2016, 27% of the H3N2 viruses have been 3C.2a viruses, 34% have been 3c.2a1 viruses, and 39% have been 3C.3a viruses. Although there are multiple genetic groups among the H1 viruses, all of the ones detected in the US have been 6B.1 viruses. There is not a lot of diversity among either lineage of the influenza B viruses.

Looking at the genetic data on an international level just to put things into context, 3C.2a and 3C.2a1 predominated in most areas of the world. In North America, there were 3C.3a viruses at the end of the season last year. Those viruses seemed to be decreasing in prevalence, and North America was really the only one to see that level of 3C.3a viruses circulating. Of the A(H1N1)pdm09 viruses, there are 6B, 6B.1, and 6B.2 genetic groups. Almost all viruses worldwide are 6B.1 at this point, although 6B.2 viruses were being seen in Asia and Oceania.

Antigenically, all 8 of the A(H1N1)pdm09 viruses characterized from the US over the summer are similar to the A/California/7/2009-like vaccine component. Among the 53 A(H3N2 viruses, 44 (83%) are antigenically similar to the A/Hong Kong/4801/2014-like, the 3C.2a genetic group in this year's vaccine for the US. Some of those are low reactors. Among the viruses that reacted poorly with ferret antisera raised against A/Hong Kong/4801/2014-like viruses, 8 of 9 (90%) are more closely related to A/Switzerland/9715293/2013 (genetic group 3C.3a). Among the influenza B viruses, all 26 B/Victoria-lineage viruses were antigenically characterized as

B/Brisbane/60/2008-like, which is the influenza B component of the 2016-2017 Northern Hemisphere trivalent and quadrivalent influenza vaccines. All 33 B/Yamagata-lineage viruses were antigenically characterized using ferret post-infection antisera as B/Phuket/3073/2013-like, the influenza B component of the 2016-2017 Northern Hemisphere quadrivalent influenza vaccines.

In terms of geographic spread as of Week 40 in the US, 36 states and the Virgin Islands had sporadic activity. One state, New Hampshire, experienced local activity. Regarding outpatient visits for influenza-like illness (ILI) during the same week, 1.1% of outpatient visits were for ILI. This is what would be expected at this time of year compared to other recent seasons. There is no difference by state in that no states are experiencing more activity, with all states currently at minimal influenza activity. The percent of death certificates that have any mention of pneumonia or influenza is low at 5.4% for deaths that occurred for the week ending September 24, 2016 compared to the baseline of 6.3%. That is probably somewhat lower than what the final percentage will be, but there is no reason to believe that any influenza-associated mortality is being observed at this point.

The recommendation for 2017 Southern Hemisphere trivalent influenza vaccine components is as follows:

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus; and
- B/Brisbane/60/2008-like virus.

The recommendation for 2017 Southern Hemisphere quadrivalent influenza vaccine components are as follows:

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
- A B/Phuket/3073/2013-like virus

In summary, influenza A(H1N1)pdm09, A(H3N2), and both lineages of influenza B viruses continue to circulate worldwide. Activity in the US and other Northern Hemisphere countries remains low at this time. The recommended components for the 2017 Southern Hemisphere vaccine includes an updated H1N1 virus, which is the first change in the H1 component since the 2009 pandemic. Global laboratory data continue to indicate that most currently circulating viruses are antigenically similar to the vaccine viruses included in the 2016-2017 US vaccines. This suggests that vaccination with Northern Hemisphere influenza vaccine should offer protection against the majority of circulating viruses analyzed to date.

Discussion Points

Dr. Belongia asked whether there had been any antigenic characterization of the 3C.2a1 viruses.

Ms. Brammer replied that from what she understood, the 3C.2a1 viruses are antigenically very similar to the 2As.

Ms. Stinchfield (NAPNAP) inquired as to whether there was any indication of severity of the different genetic subgroups that would allow for predictive work.

Ms. Brammer responded that at this time, there were no data to indicate that the severity of any of these viruses would be different from what is typically observed with influenza viruses.

AFLURIA® Quadrivalent Influenza Vaccine

Gregg C. Sylvester, MD, MPH
Head of Medical Affairs
Seqirus™ A CSL Company

During this session, Dr. Sylvester presented the pivotal Phase 3 trial that led to the US approval of the AFLURIA® Quadrivalent Influenza Vaccine in adults 18 years of age and older. As a reminder, influenza is a highly infectious respiratory infection[1]. Seasonal epidemics occur predominantly during winter, with an annual incidence of 5% to 10% in adults[2]. Infection is associated with significant morbidity and mortality, with an estimated 250,000 to 500,000 deaths directly attributed to influenza annually worldwide[2]. Conventionally, influenza vaccines are trivalent, consisting of two influenza A subtypes and one influenza B lineage. However, two antigenically distinct B lineages co-circulate from year-to-year[3]. Predicting which B will predominate during the season can be problematic. Thus, the quadrivalent vaccines have been developed comprised of the 3 strains contained in the trivalent plus the additional B strain [[1]Bouvier NM, Palese P. Vaccine. 2008;26 Suppl 4:D49-53; [2]World Health Organisation. Influenza. factsheets/fs211/en/. 13 July, 2016; [3]Beran J, Wertzova V, Honegr K, Kaliskova E, Havlickova M, Havlik J, et al. BMC Infect Dis. 2009;9:2].

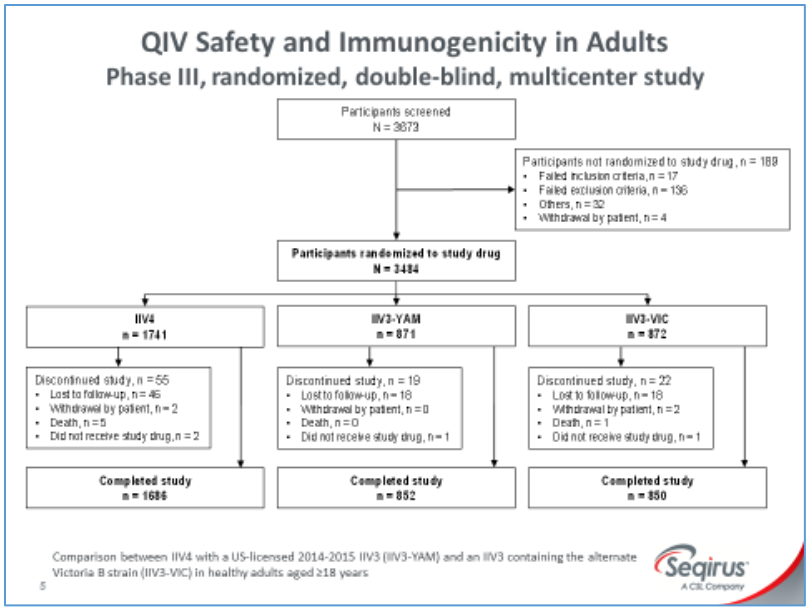
AFLURIA® is licensed in the US as a trivalent and quadrivalent vaccine. It is an egg-derived, purified, inactivated, split virion influenza vaccine. It is manufactured in Parkville, Australia. There are two vaccine formulations:

- 0.5mL pre-filled syringe, thimerosal-free
- 5mL multi-dose vial, thimerosal-containing

The FDA approved AFLURIA® trivalent influenza vaccine (TIV) for use in individuals ≥ 18 years of age in November 2007. AFLURIA® TIV was approved for use in individuals ≥ 5 to 18 years of age in December 2011. In August 2016, AFLURIA® quadrivalent influenza vaccine (QIV) was approved for use in individuals ≥ 18 years of age. The current ACIP recommendation for AFLURIA® is for use in individuals ≥ 9 years of age.

In terms of the Phase 3 adult QIV study, Seqirus™ is taking a stepwise approach to its quadrivalent clinical development program. The study for children ≥5 to <18 years of age is completed and will soon be submitted to the FDA. The QIV pediatric study among children 6 months to <5 years of age is underway, and the last Dr. Sylvester heard, about 300 participants were enrolled in that study.

Here is the clinical trial algorithm for the adult study, which was conducted in the US in 31 centers during the 2014-2015 Northern Hemisphere influenza season:



A total of 3484 participants were randomized into 3 groups in a 2:1:1 ratio. The vaccine group included 1741 participants, the AFLURIA® TIV B/Yamagata group had 871 participants, and the AFLURIA® TIV B/Victoria group had 872 participants. The demographics of the participants were well-balanced between groups. The mean age was 58 years, with a +/- of 18 years. The age groups were stratified, with half of them below 65 years of age and the other half 65 years of age and above. There were slightly more females than males, and the majority of the study participants were white. Nearly two-thirds of the study participants received an influenza vaccine in the prior year.

Healthy men and women ≥18 years of age who resided in the US were enrolled in the study. The exclusion criteria were:

- ❑ Allergic to egg proteins or any study vaccine component
- ❑ Acutely ill
- ❑ Immunocompromised
- ❑ Influenza vaccine within the preceding 6 months or any licensed vaccine within 14 days for inactivated vaccines or 28 days for live vaccines
- ❑ Immunoglobulins or blood products within the last 3 months
- ❑ Investigational product within the last 28 days
- ❑ Anticoagulant therapy, except antiplatelet agents
- ❑ History of Guillain-Barre Syndrome (DBS) or demyelinating disease
- ❑ History of drug or alcohol abuse
- ❑ Clinically significant disease in the investigator's opinion

The primary objective of the study was to compare the QIV to a US licensed seasonal vaccine, AFLURIA® TIV. A non-inferiority immunogenicity design was used with eight co-primary endpoints (2 endpoints, 4 viral strains). GMTs and seroconversion rates (SCRs) were analyzed for the 4 viral strains. These endpoints were defined in accordance with the FDA criteria for non-inferiority studies. For GMTs, the upper bound of the 95% confidence interval of the GMT ratios was not to exceed 1.5. For SCRs, the upper bound of the 95% confidence interval of the difference for the SCRs was to be ≤ 10%. If all 8 co-primary endpoints meet the pre-specified FDA criteria, then non-inferiority for the QIV compared to the TIV can be concluded.

For secondary endpoints, the same non-inferiority criteria were applied in each age group 18 to 64 years and ≥65 years. Superiority was assessed for the unmatched B strain included in the QIV, but not in the respective TIVs overall and in each age group (18 to 64 years and ≥ 65 years). This allowed them to use the FDA superior criteria which states that for the GMTs, the lower bound of the 95% confidence interval of the GMT ratio should be greater than 1 and the lower bound of the 95% confidence interval of the SCR differences should be greater than 0%. If these two criteria are met, superiority can be concluded for the alternative lineage B strain.

Regarding the results, the ratios for GMTs were similar between vaccines in the entire age group. The pre-specified non-inferior criterion for the ratio of GMT was met for all 4 strains. The ratio for GMTs were similar for each of the age groups. SCR also were similar between QIV and each TIV comparator for the matched strains. The pre-specified non-inferiority criterion for the SCR difference was met for all 4 strains, as well as for each age cohort. The immunological superiority of the unmatched B strain was demonstrated for both B strains in the QIV when comparing the ratio of GMTs to each TIV in which the strain was absent. The superiority criterion also was met for the B strains contained in the QIV when analyzing the difference in SCRs for all participants 18 years of age and above, and for each age cohort.

All three vaccines were well-tolerated. The safety profile for the QIV was similar to that of the TIV comparators. Over half of the participants reported an AE during the study. The majority of those AEs were classified as Grade 1, meaning symptoms that are easily tolerated and do not interfere with normal everyday activity. No participants left the study due to an AE. The most common solicited local AE in all three groups was pain at the site of injection at 36.5% overall. The percentage of vaccine-related unsolicited AEs was slightly higher in the QIV group. There were 4 SAEs in 3 patients, which were assessed by the investigators as being related to QIV. One was asthma 2.5 weeks after the vaccine, one was acute pancreatitis 1 week later, one was hypoxia 10 days later, and one was pneumonia 4 days after receipt of the vaccine. Similar frequency and intensity were seen in all three vaccine groups, with the vast majority in the Grade 1 category. As mentioned earlier, pain at the site of injection was the most common local reaction. Myalgia and headaches were most commonly reported as systemic.

In terms of the strengths of the study, the trial design was prospective, double-blinded, and randomized. It was a Phase 3 with active-control, and it was a multicenter study in 31 centers in the US. The study was sufficiently powered to meet the primary endpoints. However, there are potential limitations. The use of immunogenicity as a surrogate for protection may not be a true representation of clinical efficacy. In addition, participants with moderate to severe acute illnesses were excluded from the trial.

In summary, AFLURIA® Quadrivalent Influenza Vaccine met non-inferior immunogenicity for all strains to both comparator TIVs in adults ≥18 years of age and in each age group 18 to 64 years and ≥ 65 years. Immunologic superiority of the alternate B strain (B/Yamagata and B/Victoria strain) was also met for both of the age cohorts by the GMT ratios and SCR for each virus strain. The vaccine safety profile was found to be acceptable. FDA approval was granted on August 24, 2016.

Discussion Points

Ms. Pellegrini noted that the study population had a very low percentage of minority participants despite the fact that it was conducted in 31 centers.

Dr. Sylvester replied that the study population was 82% white. As they heard the previous day, all industry is trying to do a better job of increasing the diversity within clinical trials. As they assess the population of under 6 to 59 months of age, they certainly will take that into consideration.

Dr. Messonnier requested that Dr. Sylvester discuss vaccine supply for this and next year.

Dr. Sylvester responded that both the QIV and TIV formulations are available in the US this year, and plan to do the same next year. He called on one of his colleagues to provide further details.

Aaron Rak (Seqirus™) added that because the QIV formulation was just licensed in August, the vast majority of the doses coming in are trivalent, although there has been a lot release of QIV. Next year, the plan is to have a mix of both QIV and TIV in addition to Seqirus's™ other licensed vaccines.

Dr. Belongia requested information on the relative price increase from the TIV to the QIV.

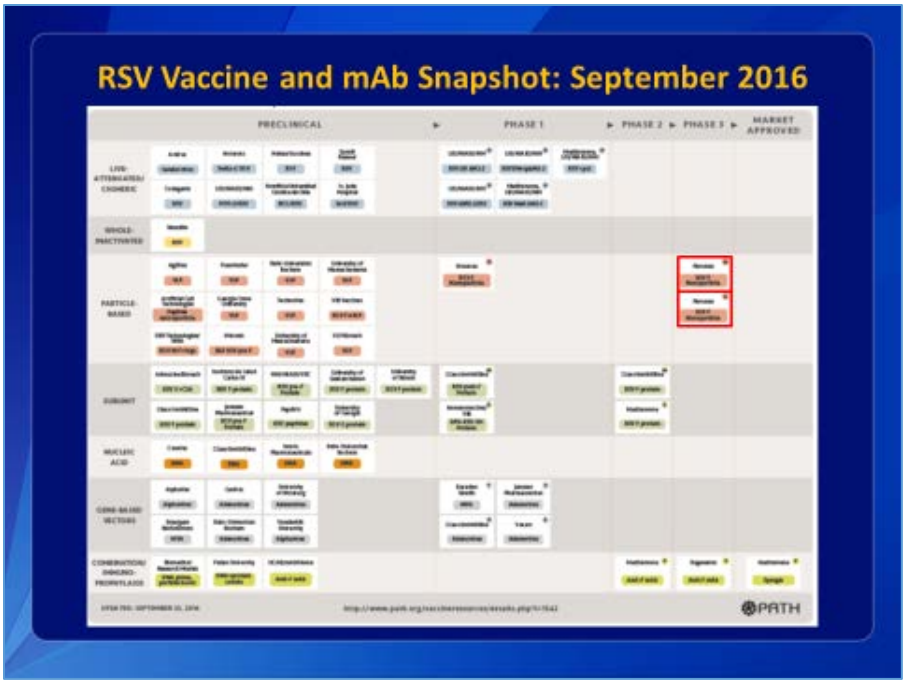
Aaron Rak (Seqirus™) replied that the list price for the TIV prefilled syringe is $14.92, and the list price for the QIV prefilled syringe is $16.61. That is a $1.70 increase for the prefilled syringe. They will bring in both formulations next year (prefilled and multi-dose vials), currently only the prefilled syringe is available.

Respiratory Syncytial Virus Vaccine

Introduction

Robert Atmar, MD
Baylor College of Medicine
Chair, ACIP RSV Vaccines Working Group

Dr. Atmar reminded everyone that the ACIP Respiratory Syncytial Virus (RSV) Vaccines WG was convened to evaluate vaccine use in adults ≥60 years of age and in adults with underlying medical conditions. This was in anticipation of results of a vaccine product that is in Phase 3 clinical trials. The RSV session during the June 2016 ACIP meeting focused on providing an overview of RSV and RSV vaccine development, including targeted vaccine populations. On September 15, 2016, top-line results from the NOVAVAX RSV F Vaccine Phase 3 clinical trial were released. This is a snapshot of RSV vaccine development:



This session included an update on the burden of RSV disease in older adults, as well as an update on NOVAVAX RSV vaccine development programs.

The next steps for the RSV Vaccines WG are to: 1) continue to review RSV vaccine product clinical trial data in targeted populations as they become available for older adults, pregnant women, and infants and young children; and 2) present to ACIP when new updates in RSV epidemiology and clinical trial data occur.

Burden of Disease in Older Adults

Ann R. Falsey, M.D.
University of Rochester

Dr. Falsey pointed out that people stop thinking about RSV when they leave medical school if they do not go into pediatrics. With that in mind, she gave an overview of the studies that suggest that RSV has a significant burden of disease in adults. First, she shared some history and basics.

In 1956, Morris described an outbreak of respiratory illness in a chimpanzee colony at Walter Reed. The cytopathic agent isolated from a chimp named Sue was called CCA, for chimpanzee coryza agent. The following winter, Dr. Robert Chanock recovered a similar virus from infants hospitalized with lower respiratory tract symptoms, and the virus was very sensibly renamed Respiratory Syncytial Virus (RSV) to reflect the giant syncytia seen in culture. For the past 40 years, the epidemiology of RSV has been exhaustively studied in infants and young children, in whom it is the single most important respiratory pathogen in the first year of life. It has been linked to 90,000 to 100,000 annual hospital admissions in the US and approximately 300 to 500 deaths. In 1966, there was a formalin inactivated vaccine trial that was a disaster. It resulted in enhanced disease, such that infants who got the vaccine had higher rates of hospitalization and

even some deaths. Needless to say, vaccine development has been very slow and cautious ever since and there still is not a vaccine for either children or adults.

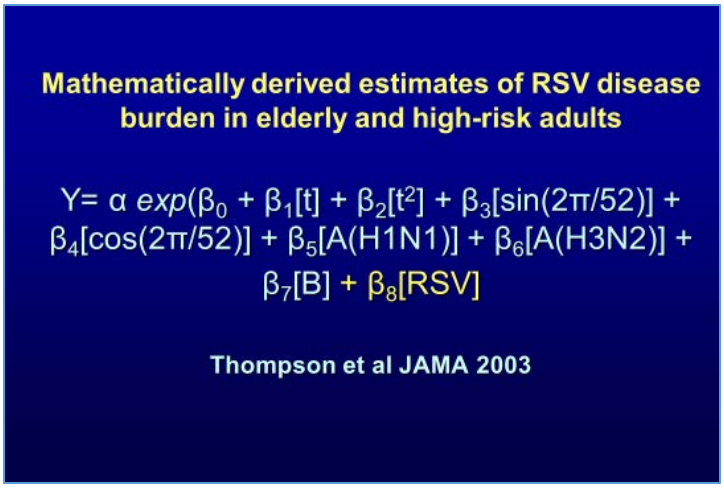
It was not until the 1980s that RSV was appreciated as a potential pathogen in adults. Before launching into the clinical descriptions, Dr. Falsey quickly reviewed a few relevant points about the virus structure. There are 10 genes that encode for 11 proteins. It is a single-stranded RNA virus with 8 structural proteins. There are two major surface glycoproteins, the F or fusion protein and the G which serves as the attachment protein, both of which induce neutralizing antibodies. The G protein has a fair amount of antigenic diversity and defines group A and B viruses. In contrast, the F protein is relatively well-conserved among RSV isolates and therefore has been identified as an important component of candidate vaccines. RSV is not like influenza in that it does not undergo major antigenic shift and drift, but it is likely that antigenic diversity plays some role in adult reinfection, but it is really not clear how much.

There is a variety of evidence that looks at RSV disease. Initially, most of the reports were just case reports or outbreaks, which were primarily in nursing homes. There is a body of indirect evidence that uses modeling studies. There are some illness-based studies that look at people presenting for medical care either to their general practitioner, the emergency department (ED), or the hospital. There are prospective studies following groups of people for respiratory illness, which are the most difficult and expensive to conduct.

As mentioned, RSV came to the medical community's attention when outbreaks started to be described in nursing homes. In these situations with closed populations, the attack rates can be quite high, up to 89%. Looking at prospective studies in nursing homes, the incidence of RSV can vary from 1% to 15%. Generally, it is considered a nosocomial infection that either the staff or family members are bringing into the facility. The reported severity in nursing home patients is highly variable, with reports of pneumonia ranging from 0% to 55% and reports of deaths ranging from 0% to 53%. Part of that probably is the population in a specific nursing facility. Some facilities have healthy older people who are only somewhat dependent, while others have very frail residents.

Only about 5% of older people reside in institutions, with 95% of older people living in the community. One of the first studies that examined community-dwelling elderly was conducted by Scott Dowell in which he looked at lower respiratory tract infections in hospitalized adults. Using serology, he found that RSV was third right after pneumococcus and influenza A and B as a cause of respiratory illness, in this study conducted over 2 winters with almost 1200 participants.

As a lead in to the modeling studies, Dr. Falsey shared the following formula emphasizing that modeling is an important way to predict disease burden:



Modelers basically correlate culture data and viral activity with events in other populations. The first and one of the best studies looking at RSV in all ages correlated viral activity with national death data for the time period 1976-1997, looking at deaths due to pneumonia, influenza, circulatory, and respiratory illness. They found that while flu dominated over RSV, what took everybody by surprise was that in the adult age groups, there were nearly 11,000 RSV deaths amongst older adults. This was not previously well-appreciated. Compared to influenza, it is about two-thirds to about half of influenza. This was one of the first assessments that suggested that maybe RSV is not like influenza in an older adult, but it is not insignificant either [Thompson et al JAMA 2003]. This approach was then used again to assess the next 20 years from 1997-2009. Using a very similar analysis to Thompson's, this group from GSK got very similar results looking at adult deaths in the US. These two studies looked at 40 years of data [Matias et al IORV 2014].

Douglas Fleming is from the UK and he has been looking at RSV in older adults for the last 20 years using modeling studies as well. In a very recent publication, he showed that influenza burden tends to go up and down over time. That may be because when there are major H3N2 years, a lot of excess deaths are observed among older people. However, RSV is more monotonous. Fleming then looked further and broke it down by age groups of 18 through 49, 50 through 64, 65 through 74, and over 75. This revealed that the greatest increase occurred in people over 75 years of age, and there was some increase in people 65 through 74 years of age. It is important to note that the population of people over 80, which geriatricians refer to as the old old, is growing significantly in most developed nations [Fleming DM et al BMC 2015].

Dr. Falsey pointed out that before moving into a discussion of studies looking at disease burden, it is important to understand diagnosis because the way RSV is diagnosed will alter the results of studies assessing disease burden. Children produce a lot of mucous. An infant with a primary infection has a great deal of virus in their respiratory secretions, and this produces a characteristic clinical symptom of bronchiolitis. So, it is not so hard to make the diagnosis in young children. When she began studying the virus, the tools available were viral culture and serology. Viral culture is very insensitive for making the diagnosis. RSV is more labile than influenza. It does not survive transit. There is not that much in secretions, and it would take a while for the virus to grow. While serology is good, it is necessary to have convalescent serology. The patient has to survive to be able to get that, and it also has to be well-timed. When the advent of PCR came along, it was anticipated to be able to solve all of the problems.

PCR has revolutionized the understanding of many viruses, because it allows them to be detected in many ways that could not be done before.

There are a number of diagnostic challenges in older adults. Unlike children, they lack distinctive syndromes (croup, bronchiolitis). Older people have a diminished febrile response. A lot of the studies looking at RSV are tag-on studies to influenza studies in which the case definition is ILI, which includes fever. The presence of a respiratory infection sometimes may be completely overshadowed by exacerbations of comorbid diseases when these individuals present to the hospital. They may be having a chronic obstructive pulmonary disease (COPD) or heart failure exacerbation, and so no one thinks about the fact that it all started with a virus. One of the most important things is that most people just do not even consider the diagnosis of RSV when an adult is admitted to the hospital. In addition, adults shed lower titers of virus for a shorter period of time in the nose than infants.

Based on some data from an epidemiologic study that the University of Rochester conducted using viral culture, PCR, and serology to define infection, it was not very surprising that in the study population, culture was not very sensitive, as it only detected 4.1%. PCR was a significant jump at 9%. Serology yielded the highest number of people with infection at 12.4%. Everybody had a PCR in that study, but not everybody had serology because they did not return or they died. Of the participants, 1,114 people had all of the tests available. A substantial proportion, 37, were positive by all three tests and an equal number were positive by PCR and serology, which is no surprise. Nobody was culture positive and PCR negative. It is worth pointing out that out of the 117 people with RSV, 30 people were serologically positive only and had negative PCR and culture. If just using PCR, those people would have been missed. That is not to say that serology is perfect, because 13 people were either PCR or culture positive and serologically negative.

If there is very well-timed serology in a prospective study; that is, there is a baseline antibody level and then good tight acute and convalescent serology, almost all older people do have a 4-fold serological response. The reason that serology sometimes is not so great is because if people are being evaluated at the time they present for medical attention, they usually are 5 to 6 days into their illness. In all adults, RSV is a reinfection so everybody has baseline immunity and they have a fairly rapid amnestic response. Antibody starts to rise around day 3 and by the time the patient presents at day 5 or 6, they have already had a 2-fold rise in antibody. So the rise in antibody might be missed in people presenting to the hospital because nobody goes in with a runny nose. In the typical RSV illness, the patient gets a cold. They have a runny nose for a few days. They then begin to get wheezy. Then they get more short of breath. It really takes 5 or 6 days for them to decide that they need to see a doctor.

In terms of the location of the sample, as the illness progresses, it may be that the virus is no longer in the upper airway and has moved down to the lower airways. When thinking about viral testing, people always think about the swab up the nose and really do not think about testing sputum. Angela Branch at the University of Rochester conducted a study in which she assessed the improved diagnostic yield by combining sputum and nasal swab testing. It was not specific to RSV, but 63 people were RSV positive and 22% were positive only in their sputum. Nasal swab positive only was mostly because they did not have a sputum. They could not cough it up. One of the issues with sputum is that not everyone can raise a sample. However, if it can be collected, it can add to the diagnosis, particularly if someone has been sick for a while [Branche et al *JMC* 2014].

To summarize the sensitivity of RT-PCR and serology, the timing of samples is important for both PCR and serology. Early in illness, in the first couple of days, a nasal swab for PCR is very sensitive. Later in illness PCR may be negative, but sputum may be of value. Well-timed serology is very sensitive in older adults. However, the rapid amnestic response may obscure antibody rises in people presenting for medical attention 5 to 6 days into illness. The sensitivity of diagnostic methods in the elderly varies widely. Standard culture is 5% to 40% sensitive, but only in a research institution where someone runs right to the laboratory with the cultures. It is still not a great way to make the diagnosis. The rapid antigen tests with 0% to 24% sensitivity are next to worthless and they are not recommended. PCR (75% to 82% sensitive) and serology (85% to 90% sensitive) are the best ways to make the diagnosis. Obviously, in a clinical scenario, only PCR is needed. But when thinking about vaccine and epidemiologic studies, these two tests are complementary and each have an advantage.

One of the major problems with RSV is that it has an identity crisis. Looking at the discharge medical record of a women who was diagnosed with RSV, she presented with congestion, difficulty breathing, poor appetite, and dehydration. She eventually went into respiratory failure, was intubated, required dialysis, had a gastrointestinal (GI) bleed, and then died. She had a PCR that was positive for RSV and an illness that was fairly characteristic at the onset. But her ICD-10 discharge diagnoses were hypotension, hyperkalemia, dehydration, diabetes mellitus, and chronic kidney disease (CKD). Nowhere in there was RSV. Dr. Falsey said she would propose that none of these other things would have happened had she not had RSV and it began a cascade of bad outcomes.

Dr. Falsey presented some data from a study that she and Dr. Edward Walsh conducted a number of years ago. This was a prospective diagnosis-based study conducted for 4 winter seasons between 1999 and 2003. They conducted prospective surveillance of healthy older people living in the community and adults with underlying cardiorespiratory disease in the community. At the same time the prospective evaluations were being done, they evaluated adults who were hospitalized at their institution with acute cardiopulmonary conditions, with the exception of an acute myocardial infarction (MI). To diagnose RSV, they used culture, one tube nested RT-PCR, and serology. At this point, it was new that thought was being given to developing vaccines and drugs for RSV. Everybody would agree that influenza is a major problem in the elderly, so they used influenza as a yardstick. They enrolled over 600 healthy elderly and over 500 high-risk and evaluated nearly 1500 illnesses in the hospital over the 4 years.

Regarding the incidence data in the prospective group, RSV ranged from 3.2 in a low year to 7.6 in a high year, with an average of 5.5 infections per 100 per season. That was about twice as common as influenza A, which was 2.1. It is important to point out that this is a heavily vaccinated population. These numbers would likely look very different if there was not influenza vaccination. It is also important to point out that this is infection, not only symptomatic infections. Among both the influenza and RSV patients, 10% had asymptomatic serological rises from baseline to the end of season. It is not clear whether these people had illnesses they did not report because they were mild illnesses, or if they were truly asymptomatic. Most of these individuals, 90%, had symptomatic illnesses that were evaluated.

Also important to address in older adults is functional impact. To assess this, they looked at whether the patients were housebound, bedbound, or unable to do their activities of daily living at any point during their illness. Influenza had a greater effect on the healthy elderly, but it is important to point out that 39% of the healthy elderly could not do their activities of daily living

when they were sick. In the high-risk patients, the influenza and RSV differences were less dramatic and there was a more functional impact.

In terms of utilization of healthcare resources, in the high-risk group, there were 54 infections, 16% were hospitalized, and 5% died. While the healthy older persons might have felt terrible and might have gone to see their doctors, nobody was hospitalized and nobody died. The medically attended rates of illness in the healthy group varied between 0.50 - 1.20 / 100 depending on the year. For the high-risk group, it was about double at 1.8 - 4.4 / 100. Using the population of Rochester, the investigators estimated a hospitalization rate of about 1 / 1000. With regard to admissions due to RSV and influenza, there was a dramatic seesawing for influenza because year 1 and year 3 were big H3N2 years. RSV was somewhat steadier. Over the 4 years, RSV accounted for 9.0% of the wintertime hospitalizations due to cardiopulmonary diseases and influenza A accounted for 9.5%. The characteristics of those presenting with RSV and influenza were very much the same. The mean age was 76 and there were very high rates of underlying heart and lung disease. The people who are hospitalized are not the healthy older adults, with the exception of the old old.

With big groups of people with RSV and influenza, it is possible to get nice p-values and find that there is more nasal congestion, dyspnea, and wheezing among those with RSV; whereas, influenza patients have higher rates of fever. However, it is not possible to tell the difference on an individual basis. A case-based definition cannot be developed that provides any kind of discriminatory ability. It is necessary to perform a test, and studies require a laboratory component. In terms of outcomes in the hospitalized subjects, rates of pneumonia, intensive care use, ventilator support, and death rates were nearly identical. Once someone is frail enough to end up in the hospital with either one of these viruses, the outcomes are very similar. Falsey et al estimated that about 177,000 people would be hospitalized and there would be about 14,000 deaths in the US. Thompson estimated 11,000 using modeling. So, they felt very good that these were pretty close using very different methodologies. Therefore, she does believe that is roughly the attributable mortality each year [Falsey et al *NEJM* 2005;352:1749].

There is nothing unique about the extremely long, cold, dreary, snowy Rochester weather. In 2012, Dr. Keipp Talbot and her group at Vanderbilt used only PCR and estimated that 6.1% of their wintertime hospitalizations were due to RSV. If the serological results were added, this would be very similar to the Rochester data. They did some estimates using the population of Davidson County and calculated a hospitalization rate of 1.5 / 1000. So again, in a different geographic location, this team came up with similar data [Widmer et al *JID* 2012].

Dr. Edward Belongia and colleagues at Marshfield Clinic conducted some studies in conjunction with influenza vaccine efficacy studies to assess influenza vaccine efficacy using a test-negative case design. They had periods of surveillance when influenza was very active. RSV activity is usually just a broader base, so they were missing some of the times that RSV was active and needed to fill in with some modeling in addition to specific viral testing. They used PCR to do testing. Their estimate of medically attended respiratory illness in adults ≥50 was 1.54 / 100 [McClure et al Plos One July 2014 ;9:e1025].

One of the questions sometimes pertains to how variable RSV is in a season in adults in terms of mild versus bad years, so Dr. Falsey put together some of the Rochester data from the prospective cohort studies to illustrate the variability because they have been conducting these studies for a long time. The low one year was 2.5 and the high year that was a banner year among their COPD patients was 10.7. It is variable, so investigators may have the misfortune to

conduct a vaccine study in a low year. Looking at illness-based data, there was a low of 4% of the respiratory illnesses being RSV and a high in another study of 13%.

A number of studies are being conducted throughout the world. It is important when evaluating other studies to look at the way they diagnosed the infection. Van de Hoogen in the Netherlands, who is a superb virologist, found 0 RSV infection. The diagnostic methodology used was serology and culture. Culture is insensitive, but it would seem that some serological infections would have been picked up. A German study found 25% RSV infection rates using purely PCR. That is so high that it may suggest something about the specificity of the PCR or whether there was contamination of results. There are a lot of studies being conducted in many countries around the world that typically use a multiplex PCR that generally has 15 targets. It is important to remember that when a test is optimized for 15 different targets, it is going to lose some sensitivity for a specific target. But these data coming from around the world report a low of <1% RSV to a high of 7%. It is always important to remember with these studies to determine whether they were conducted over an entire year, in which the incidence would be lower, or if they focused on the winter season.

Turning to some data from China, Dr. Falsey noted that Nelson Lee has been conducting some very good influenza work. He works in Hong Kong and has more recently turned his attention to RSV and has some interesting data coming from Hong Kong. In a 3-year study, he and his team identified 607 adults hospitalized with RSV at the same time that there were 547 with influenza A. The mean age was almost identical to the other side of the world in Rochester where it was 76. They also found that those who were hospitalized had a lot of chronic medical conditions. One thing that differed was the fact the people in Hong Kong seemed to go to the hospital quicker than people in the US. Influenza patients present earlier than RSV patients. A high fever in an older adult is likely to drive them to medical attention more quickly than the runny nose that evolves into shortness of breath [Nelson Lee et al CID 2013;57 1069].

One thing that is not known is the complication rate—the downstream problems that result from RSV. Dr. Falsey believes there are plenty, but it is just not well-understood at this point. This would include functional decline, bacterial complications, and cardiovascular events. This is clear with influenza. In large influenza epidemics, there is a clear spike in heart attacks and strokes, but this is not clear with RSV. Dr. Falsey and her colleagues conducted a study recently to assess the issue of bacterial complications with viral infections. It is much talked about, and clearly there is a relationship between viral infection and bacterial superinfection. However, it is very hard to diagnose a bacterial infection with any specificity and sensitivity. In this 3-year study, they evaluated people presenting with respiratory illness. In addition to comprehensive viral and bacterial testing, they did a serum biomarker of procalcitonin. Procalcitonin is high in people with bacterial infections and normal in viral infections. By combining traditional bacteriology with high procalcitonin, they found that 31% of RSV patients admitted to the hospital had some evidence of a bacterial infection. There did not seem to be any major differences between the common respiratory viruses [Falsey et al JID 2013].
While Dr. Falsey said she could find almost nothing on cardiovascular complications in RSV, she did find a study from Volling in Toronto. This was an observational study in which 22% of their RSV patients who were admitted had some type of cardiovascular complication [Volling *BMC* 2104].

To summarize the rates that the evidence provides, infection ranges from 2 to 6 per 100 per season, medically attended disease from 0.5 to 4 per 100, hospitalization from 1 to 1.5 per 1000, and death rates from 0.4 to 7 per 10,000. Secondary complications are unknown.

Discussion Points

Dr. Atmar said he was interested in Dr. Falsey's thoughts on the use of serology in vaccine studies. For example, they found with influenza that vaccinees are less likely to have serologic responses than are non-vaccinees, which can bias in favor of vaccine efficacy. He asked whether she anticipated that this could be a problem using that diagnostic method in the evaluation of vaccine efficacy or effectiveness.

Dr. Falsey replied that she did not think an antigen could be used that is in the vaccine. Most of the RSV vaccines in development are based on the fusion protein, so another purified antigen could be used, the attachment protein could be used, the nuclear protein could be used—it would just be important to eliminate whatever antigen happens to be in the vaccine.

Dr. Hahn (CSTE) asked whether anything was known on the source of infection in elderly. For example, are caregivers of young children at higher risk of becoming hospitalized with RSV?

Dr. Falsey replied that it is certainly sensible to think that young children are the origin. RSV exposure during the winter is probably fairly prevalent, even if not exposed to young children. They have assessed exposure to children as a risk factor for infection, and have found that it is a factor. However, it is not an overwhelming factor. They recently conducted a study with MedImmune to examine whether there was any group who could be at really high-risk. They enrolled people who had regular exposure to school-aged children and underlying heart and lung disease, and found that the rate of infection in that group was almost 14%.

Evan Anderson (Emory) noted that several groups have now described cross-reactive antibodies between RSV and human metapneumovirus (hMPV). He asked whether she had seen any evidence in her data of RSV serologic conversion due to a recent hMPV infection.

Dr. Falsey indicated that in the large epidemiologic study, they did do serology for metapneumovirus and did not find that it was an issue. They were very distinct.

Update on NOVAVAX RSV Vaccine Development Programs

Dr. Jeffrey Stoddard
Vice President Medical Affairs
Novavax, Inc.

Dr. Stoddard shared a high-level company overview indicating that they have a proprietary vaccine technology platform that involves baculovirus (BV) transfection of and *Spodoptera frugiperda* (Sf9) insect cell line for the production of recombinant immunogenic nanoparticles. They have 5 facilities, including Gaithersburg and Rockville, Maryland and Uppsala, Sweden. There is a high degree of experience across their management team, and the development and commercialization infrastructure necessary to bring products to market. They have commercial grade GMP manufacturing capacity, a strong balance sheet, and substantial funding support from the Bill & Melinda Gates Foundation for maternal programs.

In terms of Novavax's history of leadership in RSV vaccine development, they have achieved several milestones. Their Vice President of Preclinical Vaccine Research, Gale Smith, was the original discoverer in the early 1980s of the Sf9 insect cell line that could grow and produce recombinant protein nanoparticles based on transfection with the BV. The company's work in RSV vaccine development dates back to about 2009, for which they have reached a number of

milestones. Their development experience focused primarily on viral pathogens. They use the technology platform alluded to in that effort. They divide the RSV at-risk population into three groups:

- Older Adults ≥60 years of age
- Infants, particularly in the first few months of life
- Children 6 months to 5 years of age

They have work ongoing that is either in preclinical or early clinical state in pandemic and seasonal influenza, combination respiratory (RSV + influenza), and some emerging virus work (Ebola and Zika).

The RSV F vaccine is a BV-Sf9 insect cell-derived recombinant nanoparticle vaccine. It is known to produce broadly neutralizing antibodies to three separate epitopes, so it is a purified recombinant protein nanoparticle that has at least three epitopes that produce neutralizing antibodies. Those are Sites I, II and IV. This vaccine is known to protect animals from challenge with wildtype RSV challenge. That has been shown in cotton rat and baboons. Multiple Phase 2 trials have been conducted in various populations.

Beginning with the Phase 2 study in 1600 older adults ≥60 years, this study was conducted during the 2014-2015 season. It is a notable trial because it was the first late-stage human trial to show vaccine efficacy for any RSV vaccine in any population. It was a randomized 1:1, observer blind, placebo controlled trial that utilized 135µg of the RSV F vaccine with no adjuvant. The subjects were followed for 1 year for safety, immunogenicity, and efficacy endpoints. The study demonstrated a high degree of tolerability and a safety profile that was notable for no imbalances between the placebo group and the vaccine group. There were 5-fold increases in both Palivizumab-competing antibodies (PCA) and Anti-F antibodies measured at Day 28 post-vaccination. Importantly, there was a 4.9% placebo attack rate for RSV-acute respiratory disease (RSV-ARD) confirmed by RT-PCR. That is comparable to the 5.5% average attack rate that Dr. Falsey just presented from the 4-season study in Rochester. Vaccine efficacy of 41% was demonstrated against RSV-ARD, which was the primary pre-specified endpoint. A post-hoc analysis assessing a more severe endpoint defined as moderate to severe lower respiratory tract disease (msLRTD) showed a 64% efficacy against RSV-msLRTD. While that was a post-hoc analysis, that was compelling enough in the end of Phase 2 discussions with the FDA that they decided to make that a primary endpoint for the Phase 3 trial. They embarked on that Phase 3 trial at the end of November 2015.

To summarize the Phase 2 trial, it was well-tolerated and had an acceptable safety profile. It was the largest ever prospective study of the RSV attack rate in community dwelling older adults. Of the older adults in the placebo group, 4.9% had symptomatic RSV and 88% of these illnesses were associated with LRTI. In terms of immunogenicity and efficacy, there were robust and specific anti-F IgG and PCA responses. There was a 41% to 44% reduction in symptomatic RSV in vaccinees, and a 64% to 75% reduction in RSV LRTD with ≥3 or ≥4 LRTI signs / symptoms, respectively.

The Phase 3 was called RSV-E-301. This was a large randomized, observer-blind, placebo-controlled trial in 60 US sites with almost 12,000 subjects ≥60 years of age randomized 1:1. There were 5921 active arm subjects and 5935 placebo arm subjects. The placebo was formulation buffer and the test agent was 135µg RSV F nanoparticle vaccine without adjuvant. The primary endpoint for this trial was defined as PCR-confirmed PCR positive msLRTD. For mild LRTD, there had to be at least 3 signs or symptoms of LRTD. For severe LRTD, there had

to be at least 4 or more signs or symptoms of LRTD. Enrollment was conducted from November 9, 2015 through December 12, 2015. Immunogenicity was assessed at 5 time points after enrollment. The last patient's last visit was in June 2016.

Efficacy was not demonstrated in the Phase 3 trial. There were 28 cases of RSV msLRTD in the vaccine arm and 26 cases in the placebo arm, yielding a point estimate of -7.9% with confidence intervals ranging from -84 to 37, which is essentially zero efficacy. Comparing that to Phase 2 results, there were 5 cases in the RSV-msLRTD arm and 14 in the placebo arm, with confidence intervals of 1 to 87. There is about a 4-fold difference in the attack rate in Phase 3 for this primary end point case definition of 0.44% in the placebo arm versus 1.7% in the Phase 2 trial. It can be very difficult in Phase 3 trials to demonstrate efficacy when the attack rates are this low. The secondary endpoint for efficacy was not met either. There was arguably a modest trend toward efficacy with a 12.6% point estimate with confidence intervals of -14 to 33. For comparison, there was a sizeable difference in the attack rates in the Phase 2 study. The attack rate was under 2% in the Phase 3 trial and almost 5% in the Phase 2 trial, so about a 2.5-fold lower attack rate in Phase 3.

In summary, the safety profile for the Phase 3 trial was consistent with Phase 2 results. There were no safety signals, and there were no imbalances between the placebo and vaccine arms. The tolerability and reactogenicity profiles were virtually identical with placebo. The RSV-ARD and RSV-msLRTD attack rates were markedly lower than expected based on the Phase 2 trial and the work that Dr. Falsey conducted in Rochester. The Phase 3 trial failed to show efficacy against RSV msLRTD and RSV ARD. There were trends that suggested some positive impact on the RSV ARD endpoint and associated healthcare utilization outcomes, but none of these was statistically significant. The immunogenicity results observed in the Phase 3 trial are broadly consistent with Phase 2 results. This work is still ongoing and has demonstrated robust PCA and Anti-F responses and modest increases in microneutralizing antibodies. Analyses in search of correlates are ongoing.

In conclusion, unlike E-201, E-301 failed to show efficacy against RSV ARD or msLRTD, although non-significant trends suggest a reduction in RSV ARD and healthcare utilization outcomes. However, a few points deserve call-out. The trial was operationally well-conducted and randomization was executed correctly. The immunogenicity was exactly what would have been expected, demonstrating exactly what was observed in Phase 2 across 3 different assays. Investigations to date suggest that there were no product integrity issues. The safety profile of the RSV F vaccine remained similar to the placebo and is consistent with E-201. There was no clear decrement in the immunogenicity of the vaccine, although work is still being done with respect to the immunogenicity data. The RSV attack rate was 2.5- to 4-fold lower than seen in E-201 for both msLRTD and ARD, and may have had an impact on the detection of vaccine efficacy. This has been an issue with other vaccines. Work that has been done in influenza when there was a very low attack rate, made it very difficult to demonstrate vaccine efficacy.

In terms of moving forward, Novavax is committed to further development of the RSV F vaccine construct in older adults. They understand that there are still questions that need to be answered with respect to immunogenicity, which is notably more robust in younger adult subjects. There are several avenues available for enhanced immunogenicity and / or efficacy and Novavax is actively exploring those. The current suite of immunologic endpoints may not adequately capture protective responses in the elderly, and additional assay development is needed. There also is a need for additional epidemiologic understanding and a more sophisticated epidemiologic level of understanding is important, so Novavax appreciates the CDC's work in that respect. The differences observed in the attack rates is one example of

where the epidemiology is still something of a conundrum. RSV is only the second annually recurring respiratory virus for which late-stage vaccine development has been attempted, and RSV appears to evade or modify population immunity in a manner that is different from that of influenza. Influenza does this through antigenic drift. It is not exactly clear how RSV does what it does, but it seems to modify population immunity in ways that are less than 100% clear. Novavax is currently considering dosing or formulation approaches that may overcome heterogeneity in background immunity and / or seasonal attack rate differences.

Novavax's infant-maternal program is in Phase 3. As far as Dr. Stoddard is aware, this is the only RSV vaccine in Phase 3 currently. Three separate Phase 2 trials have been conducted of Novavax's maternal vaccine—2 in women of childbearing age and 1 in pregnant women. Multiple animal studies have been conducted, including vaccine challenge studies and transplacental antibody transfer studies and a host of other types of studies. An enormous amount of work has gone into getting into Phase 3 in the maternal program.

With respect to the formulation, it is a different vaccine than what is used in older adults. It is the same antigenic construct, but with a slightly lower dosage of 120 µg and it is aluminum-adjuvanted. It is known from the Phase 2 trials that there is no advantage to giving more than one dose. A single dose results in the same response as 2 doses, which is good from a pragmatic and programmatic point of view. It is also known that a single aluminum-adjuvanted dose provides enhanced neutralizing antibody responses, particularly in young women with the lowest pre-immunization titers. That is, those women who have the highest risk of having their infants develop RSV bronchiolitis get the most robust response to a single dose of the aluminum-adjuvanted vaccine.

The Phase 2 trial in pregnant women was initiated in September 2014. It involved 50 pregnant women at 8 sites in the US during the 2014-2015 RSV season. As mentioned, a 120 µg dose of RSV F vaccine + 0.4 mg of aluminum. In the Phase 2 trial, all of the women received the vaccine between 33 and 35 weeks of gestation. That window was opened up for the Phase 3 trials.

In terms of the safety summary from the Phase 2 trial, the only imbalance of AEs were solicited and local. They were predominantly mild to moderate transient injection site pain, which is consistent with prior trial in women of child-bearing age. This is expected with any aluminum-adjuvanted vaccine in a younger population. There were no SAEs attributed by the investigators as causally related. Regarding infant safety, there were no imbalances of AEs noted between the placebo and active groups. There were no SAEs attributed as causally related to the vaccine. With respect to labor and delivery events, the events monitored were determined by Brighton Collaboration guidance. Only a single imbalance was noted, which was that the C-section rate was higher in the active group. This was attributed to past obstetrical history and not vaccine-related.

In summary of the Phase 2 RSV F vaccine trial in pregnant women, the vaccine was well-tolerated with an acceptable safety profile. The response to the RSV F vaccine in pregnant women replicated the immune responses in non-pregnant women from the other two Phase 2 trials. Maternal antibody seems to peak 14 days post-vaccination. Anti-F, PCA, and neutralizing transplacental antibody transfer were all confirmed. There was also noted to be a balance of vigorous early antibody response and 100% or higher transplacental transfer in women immunized >30 days prior to delivery, which offers flexible timing for antenatal immunization. The observed half-life of 41 days for the PCA through the first 60 days post-delivery was also an important finding. This suggests protection of infants for a minimum of 90

days based on simple first-order decay kinetics, meaning that protective levels might persist longer if late elimination kinetics are slower. This will be important in terms of the Phase 3 data.

The Phase 3 infant-maternal study is now a very large global initiative underway in multiple countries throughout the world. A major effort has been made to include many RSV experts from around the world, as well as many of the top vaccine clinical trial sites throughout the world. This is a randomized, observer-Blind, placebo-controlled, group sequential trial design that will be conducted over at least 3 seasons. The trial is currently in season 2. The trial may enroll up to 8616 subjects in total globally. In the first year, there were sites in the USA, South Africa, Australia, New Zealand, and Chile. Second year additions included Argentina, the UK, Spain, Italy, Mexico, and the Philippines. The length of study participation is 9 months for the mothers and 1 year for their infants. The window of injection has been extended down to 28 weeks gestational, making the window of vaccination 28 to 36 weeks.

A lot of thought and effort were put into defining the primary endpoint for efficacy. Novavax had conversations with many top RSV experts from the pediatric community and the pediatric infectious disease community and WHO.

The primary efficacy endpoint is:

> To determine the efficacy of maternal immunization with the RSV F vaccine against RSV lower respiratory tract infection (LRTI) with hypoxemia (SpO_2 <95% at sea level or <92% at altitudes >1800 meters) through the first 90 days of life in infants of maternal RSV F vaccinees as compared to placebo recipients.
>
> In the event that efficacy is shown through the first 90 days of life, sequential hypothesis tests will be carried out to examine efficacy at 120, 150, and 180 days of life.

The secondary efficacy endpoint is:

> To determine the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of RSV LRTI with severe hypoxemia (SpO_2 <92% at sea level or <87% at altitudes >1800 meters) or the need for high flow nasal cannula or mechanical ventilatory support; RSV LRTI leading to hospitalization; RSV LRTI resulting in death; and all RSV LRTI.

There is a DSMB that is actively engaged. It is comprised of both pediatric and obstetrical experts. They review the study on a regular basis. To date, the formal recommendations made by the DSMB have been to continue with this trial with no alternations. There have been no apparent safety concerns and no advisements to modify or halt the study to date.

To summarize, Novavax is committed to pursuing clinical development programs to fully assess the safety and efficacy of the RSV F vaccine in populations at highest risk of RSV LRTI. That includes RSV LRTI in older adults, as well as RSV LRTI in infants and young children, with maternal immunization as the central approach to protecting the youngest infants from bronchiolitis and pneumonia. Novavax has a distinguished history of RSV vaccine development, with multiple noteworthy contributions to the field and an unwavering commitment to addressing a major unmet medical need and a public health priority.

Discussion Points

Given the window of vaccination of pregnant women, Dr. Riley asked whether Novavax is also assessing the impact of concomitant immunization with influenza and Tdap vaccines.

Dr. Stoddard replied that they were not doing this in the Phase 3 trial. It is an important question programmatically, and there is some reason to think that based on the older adult trial that there may be some immunologic interference between the RSV F vaccine and the influenza vaccine. Partly on the basis of that and partly on the basis of needing to run a really clean, straightforward, and scientifically pure study, Novavax is not permitting concurrent immunization. As important as those vaccines are, in the Phase 3 protocol, they cannot be given concurrently with the RSV vaccine because of the confusion it could cause. To be very clear, they are not precluding the pregnant women in the Phase 3 trial from getting those vaccines, but they are making sure in the protocol that there is some separation in time.

Dr. Lee said it was great to see this much progress. She requested further information regarding the effect modification in the older adult Phase 3 trial in terms of the differences in the responsiveness based on whether they had co-administration of influenza vaccine on the same day.

Dr. Stoddard responded that they did observe differences according to concomitant influenza and RSV vaccine immunization. For those subjects who received the vaccinations concomitantly, there was about a 10% reduction in efficacy observed in the Phase 2 trial. There was roughly a 10% reduction in immunogenicity as well. The impact is unidirectional. The influenza vaccine negatively impacts the immunogenicity and efficacy of the RSV vaccine, not the other way around.

Given the uncertainty in the attack rates, which seems to be a year-to-year fluctuation, it seemed to Dr. Thompson (NVAC) that it would be a good idea to inflate the power calculations assuming that the attack rates might be low. It seemed like the sample size was significantly too low given the attack rates.

Dr. Stoddard replied that increasing the sample size in a low attack rate year probably would not have made a difference. It is very difficult to demonstrate VE in an exceptionally low attack rate year. The point is a good one in terms of better understanding the variation that might occur in terms of attack rates with RSV. They may have been naïve in retrospect thinking that 5% was about what could be expected year in and year out. Thinking about the data from Fleming in the UK that Dr. Falsey discussed, that consistent pattern year in and year out was something that investigators had come to believe based on relatively few data points. There needs to be a better understanding of what the attack rate is and how much it varies year-to-year. The data Dr. Falsey presented are very good in that they captured the fact that there could be broader ranges than Novavax anticipated going into its Phase 3 older adult trial. For the maternal trial, they do not think this is an issue because they are working in multiple geographies over several seasons.

Dr. Bennett asked if they have hypothesized why the attack rate was so low last year. There was variability but also some stability in Dr. Falsey's data.

Dr. Stoddard said they wish they knew the answer. It is a great question, but they just do not have an answer. There is a lot about RSV epidemiology that is enigmatic and humbles them, but they are not giving up.

Dr. Messonnier thanked Dr. Stoddard and Novavax for coming before ACIP during this meeting to present these data. Everybody likes to present great data, so CDC offered its appreciation for Novavax's willingness to present disappointing data and for the transparency and engagement that they have had with ACIP and CDC's SMEs.

Dr. Gorman (NIH) commented that understanding that the multiple year study delays approval might mitigate Novavax's risks going forward in the elderly. Regarding the adult study, he asked whether Dr. Stoddard was free to discuss which direction they were leaning toward in terms of dose or adjuvanting the product.

Dr. Stoddard replied that they are probably leaning toward both. They are looking at all potential options to optimize the immunogenicity of the vaccine in the older adult population. Dose and adjuvantation are the two considerations. They will have more to say specifically on that in the ensuing weeks. They are still working on exactly what the next study design should look like.

With the wide geographic range and 8000 births, Dr. Gorman (NIH) asked how they will operationalize the reality that some of them will be premature and some of them will have lung disease.

Dr. Stoddard responded that this is a complex trial. The premature births will be very difficult to analyze. This is going to be a trial that is directed toward analyzing the efficacy in the full-term population.

Paul Offit (Children's Hospital of Philadelphia) indicated that in the Southern Hemisphere, RSV alternates with peaks and troughs. He asked whether Novavax had the capacity in its adult trial to follow up those recruits these season, which may be quite a different season than last.

Dr. Stoddard replied that they are exploring all possibilities, including conducting a Phase 2 clinically. They are no longer in Phase 3 in the older adults, but are interested in going back to Phase 2 for dose ranging and formulation assessments potentially in the Southern Hemisphere. That is certainly in the realm of possibilities for them in the coming season.

Evidence Based Recommendations Work Group Update

Wendy Carr, PhD
ACIP Evidence-Based Recommendations Work Group Lead
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Carr reminded everyone that the purpose of the Evidence-Based Recommendations WG (EBRWG) is to provide a forum for discussion of best practices for the evidence-based recommendation process for ACIP, including development and use of GRADE evidence tables and an evidence to recommendation framework to ensure consistency and enhance transparency in the development of ACIP recommendations, with the goal of developing a uniform approach to evaluation and use of the evidence base for ACIP recommendations.

In support of this purpose, the aims of the WG defined in the Terms of Reference propose additional guidance for the ACIP evidence-based recommendation process, including GRADE and subsequent use of an evidence to recommendation framework, specifically for three areas:

- Improving and harmonizing the development and use of GRADE evidence tables by the ACIP WGs
- Developing criteria to guide the determination of when GRADE evidence tables should be prepared in support of a given recommendation
- Further defining the process of going from the certainty of the evidence base as presented by the GRADE tables to recommendations, in particular ensuring that the additional factors that contribute to decision-making are considered and communicated.

Regarding the first aim to harmonize development and use of GRADE tables, several CDC WG leads presented their experience using GRADE methodology for past recommendations to the WG. Several areas were identified for which additional guidance would be useful. These included: 1) applying GRADE methodology to the evaluation of immunogenicity data, including further clarifying when evidence should be rated down for indirectness when used as a surrogate outcome for efficacy; 2) the acceptability of rating up a body of evidence after previously rating it down; 3) the assessment of observational data using GRADE, in particular ensuring that the confidence generated by strong observational data is reflected in the ultimate evidence rating; and 4) evaluating burden of disease.

The next steps for moving forward with this goal of harmonizing the development of GRADE Tables are to develop draft Frequently Asked Questions (FAQ) documents that provide more explicit guidance on how to consistently approach topics that often generate questions during the use of GRADE by ACIP WGs. The hope is to draft and gather feedback on these materials with a goal of presentation to the ACIP during the June 2017 meeting.

With respect to the second aim of the WG which centers around providing reference materials, to clarify when GRADE should be used to evaluate the evidence for recommendations, the intent is to develop a checklist or flowchart to enable WGs to more efficiently determine whether GRADE tables should be prepared for a given topic. The intent is to develop draft materials, incorporate feedback, and present to ACIP during the June 2017 meeting.

For the third aim of the WG, to provide additional structure and clarity for the process during which factors in addition to the evidence base are considered when formulating recommendations, the GRADE WG, a collaboration of methodologists, clinicians, and others working to develop, refine, and provide guidance regarding the GRADE evidence-based recommendation approach have outlined a process to support movement from evidence to decisions. This has been termed Evidence to Decision (EtD) or Evidence to Recommendation (EtR) framework. The framework is presented as a table that includes key background information, criteria that should be considered, and conclusions. Of note, the certainty of the evidence as depicted in GRADE tables is only one consideration in this process and as such is only one of the elements of the framework. One advisory group that has adopted the EtR framework is the WHO Strategic Advisory Group of Experts on Immunization (SAGE). Members of the SAGE Secretariat presented the EtR methodology currently used by SAGE to the EBRWG in addition to the discussion of the successes and challenges that have been so far

encountered. A recent example of a completed SAGE EtR table can be found at the WHO website at this link: http://www.who.int/immunization/policy/position_papers/dengue/en/

When queried about potential development of a similar EtR framework for ACIP, feedback from members of the EBRWG was positive. Each element of the framework would be customized to the needs of ACIP to provide additional structure and clarity in the communication of the spectrum of elements considered during recommendation development. The next step is to develop a draft ACIP-specific EtR framework, which would be first used to solicit feedback from the EBRWG and CDC WG leads for refinement, with a goal of presenting draft materials to ACIP during the February 2017 meeting.

The following is a summation of the proposed timeline for development of additional guidance materials:

- ❑ During November / December 2016 and January 2017, the EBRWG meetings will focus on specific elements of the EtR framework
- ❑ The draft EtR framework will be presented during the February 2017 ACIP meeting
- ❑ During March, April, and May 2017, the EBRWG will revise the framework and further define the elements and will develop and review proposals to address harmonization of GRADE usage and when to GRADE evidence
- ❑ The proposals to address key questions will be presented during the June 2017 ACIP meeting
- ❑ During the October 2017 ACIP meeting, the final proposals will be presented for an ACIP vote on the proposed modifications

Discussion Points

Dr. Schaffner (NFID) thought it was wonderful that the EBRWG was addressing the GRADE process and adapting it to public health needs. One issue that has frequently arisen in discussions as GRADE has been applied is that the indirect effect of vaccines was not represented in GRADE, but is often thought to be a huge advantage. He asked whether she could address this.

Dr. Carr acknowledged that indirect effects are not specifically addressed, but pointed out that one of the advantages of developing an EtR framework is that it would allow that sort of evidence to be incorporated and those considerations to be more clearly presented.

Dr. Bennett noted that the committee had an opportunity to discuss this at some length the previous day and to offer comments at that time.

Vaccine Supply

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

During this session, Dr. Santoli presented an update on the DTaP-containing vaccine Pentacel®, BEXSERO®, and adult vaccines.

In December 2015, Sanofi Pasteur announced a manufacturing delay with Pentacel® (DTaP-IPV-Hib) vaccine. As a result, Sanofi Pasteur is only able to meet approximately 70% of historical Pentacel® vaccine demand. At this time, sufficient supplies of the relevant individually administered vaccine antigens are available to address the anticipated gap in the Pentacel® supply. Sanofi Pasteur anticipates resolution of this Pentacel® delay sometime during the fourth quarter of 2016.

GSK is currently on back order for both presentations of BEXSERO® (1-pack and 10-pack). They anticipate beginning to clear back orders in October. CDC received communication from GSK on October 19th that they would be able to resume shipping in the next couple of days. However, they anticipate that there will be some shipping delays throughout the fourth quarter of 2016. GSK does maintain a medical reserve that can be used to fill public or private orders in the event of an immediate need, such as an outbreak. The reserve is still available, and GSK is currently using this to fill orders as appropriate.

In terms of adult vaccines, two vial presentations of Merck's adult vaccines are currently unavailable for shipping, the single dose PNEUMOVAX® vial and the 10-pack of single dose adult VAQTA® vials. Availability of both of these products is expected to resume the week of November 17th. Until that time, Merck has a sufficient supply of the syringe presentation of both of these two adult vaccines available to meet the historical demand for both the vial and syringe presentations.

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

Day 2: Public Comment

No public comments were offered during this session.

Certification

Upon reviewing the foregoing version of the October 19-20, 2016 ACIP meeting minutes, Dr. Nancy Bennett, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster

September 26, 2016
Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2016 through June 30, 2017

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Co-director, Clinical and Translational Science Institute
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Term: 07/01/2015-06/30/2018

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Term: 7/1/2016 – 6/30/2020

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