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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 21-22, 2017
Atlanta, Georgia

Final - June 16, 2017

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
June 21-22, 2017

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 21			
8:30	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
9:00	**Hepatitis Vaccines**		
	Introduction		Dr. Arthur Reingold (ACIP, WG Chair)
	Hepatitis A vaccine background		Dr. Noele Nelson (CDC/NCHHSTP)
	Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children		Dr. David Rein (NORC, University of Chicago)
	Updated ACIP routine recommendations for use of hepatitis A vaccine	Information & Discussion	Dr. Noele Nelson (CDC/NCHHSTP)
	Updated ACIP recommendations for use of hepatitis A vaccine and immune globulin for post-exposure prophylaxis and for international travelers		Dr. Ruth Link-Gelles (CDC/NCHHSTP)
10:30	***Break***		
10:45	**Influenza**		
	Introduction		Dr. Emmanuel (Chip) Walter (ACIP, WG Chair)
	Influenza surveillance update		Ms. Alicia Budd (CDC/NCIRD)
	Vaccine effectiveness update	Information & Discussion	Dr. Jill Ferdinands (CDC/NCIRD)
	Vaccine safety update		Dr. Tom Shimabukuro (CDC/NCEZID)
	Flublok in pregnancy		Dr. Wayne Hachey (Protein Sciences)
	Public comment		
	Proposed recommendations	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
12:30	***Lunch***		
1:45	**Herpes Zoster Vaccine**		
	Introduction		Dr. Ed Belongia (ACIP, WG Chair)
	Zostavax Phase IV study	Information & Discussion	Dr. Nicola Klein (Kaiser Permanente Northern California)
	Zostavax GRADE		Ms. Angela Guo (CDC/NCIRD)
	Herpes Zoster vaccine revaccination data		Dr. Romulo Colindres (GSK)
3:00	***Break***		
3:30	Cost effectiveness models	Information & Discussion	Dr. Andrew Leidner (CDC/NCIRD)
	Considerations for the use of herpes zoster vaccines		Dr. Kathleen Dooling (CDC/NCIRD)
4:15	**Varicella**		
	Impact of the U.S. varicella vaccination program on the epidemiology of herpes zoster	Information & Discussion	Dr. Rafael Harpaz (CDC/NCIRD)
4:45	**Anthrax Vaccine Workgroup**		
	Introduction	Information	Dr. David Stephens (ACIP, WG Chair)
	Anthrax vaccine workgroup information		Dr. Kate Hendricks (CDC/NCEZID)
5:05	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
5:20	**Public Comment**		
5:35	**Adjourn**		
	Thursday, June 22		
8:00	**Agency Updates & Unfinished Business**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); *Ex Officio* Members
8:15	**Dengue Virus Vaccines**		
	Introduction	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair)
	Dengue epidemiology in United States and U.S. territories		Dr. Steve Waterman (CDC/NCEZID)
8:45	**Yellow Fever Vaccine**		

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	Introduction		Dr. Chip Walter (ACIP, WG Chair)
	Update on implementation of IND protocol and yellow fever vaccine distribution	Information & Discussion	Dr. David Greenberg (Sanofi Pasteur)
	Review of protocol inclusion criteria and current ACIP recommendations		Dr. Erin Staples (CDC/NCEZID)
9:15	***Break***		
9:45	**Mumps Disease and Vaccine**		
	Introduction		Dr. Kelly Moore (ACIP, WG Chair)
	Update on mumps epidemiology in the United States, 2017 and review of published studies of 3rd dose MMR for mumps outbreak control	Information & Discussion	Dr. Mona Marin (CDC/NCIRD)
	Effectiveness of a third MMR dose during a mumps outbreak in a highly vaccinated university population, 2015-2016		Dr. Cristina Cardemil (CDC/NCIRD)
10:45	**Meningococcal**		
	Introduction	Information & Discussion	Dr. David Stephens (ACIP, WG Chair)
	Meningococcal disease and vaccine response in patients receiving Eculizumab		Dr. Lucy McNamara (CDC/NCIRD)
11:30	**Vaccine Adverse Event Reporting System (VAERS)**		
	Vaccine safety: transition to the new VAERS 2.0 reporting form	Information	Dr. Tom Shimabukuro (CDC/NCEZID)
11:40	**Public Comment**		
11:50	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
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

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACA	Affordable Care Act
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Events
AFI	Acute Febrile Illness
AHIP	America's Health Insurance Plans
aHUS	Atypical Hemolytic Uremic Syndrome
AIGIV	Anthrax Immune Globulin Intravenous
AIM	Association of Immunization Managers
AN	Alaska Natives
ANA	American Nurses Association
ARI	Acute Respiratory
ASM	American Society for Microbiology
BARDA	Biomedical Advanced Research and Development Authority
BIDS	Border Infectious Disease Surveillance Program
BIO	Biotechnology Innovation Organization
BLA	Biologics License Application
BP	Blood Pressure
BSI	Bloodstream Infection
BSPB	Bacterial Special Pathogens Branch
CDC	Centers for Disease Control and Prevention
CFU	Colony Forming Units
CER	Cost-Effectiveness Ratio
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLD	Chronic Liver Disease
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
CVE	Center for Vaccine Equity
DEET	N,N-Diethyl-m-toluamide
DF	Dengue Fever
DHCPP	Division of High Consequence Pathogens and Pathology
DHF	Dengue Hemorrhagic Fever
DHA	Defense Health Agency
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DSS	Dengue Shock Syndrome
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
EAP	Expanded Access Program
EIS	Epidemic Intelligence Service
ED	Emergency Department
EHR	Electronic Health Record
EIP	Emerging Infections Program
EMA	European Medicines Agency

EMR	Electronic Medical Record
EMBASE®	Excerpta Medica Database®
Epi-X	Epidemic Information Exchange
ESG	Electronic Submissions Gateway (FDA)
ESRD	End Stage Renal Disease
FAO	(United Nations) Food and Agriculture Organization
FDA	Food and Drug Administration
FluSurv-NET	Influenza Hospitalization Surveillance Network
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
gE	Glycoprotein E
GMC	Geometric Mean Concentrations
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
GUP	General Use Prophylaxis
HAI	Hemagglutinin Inhibition
HAIVEN	Hospitalized Adult Influenza Vaccine Effectiveness Network
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Vaccine
HCP	Healthcare Personnel
HCUP	Healthcare Cost and Utilization Project
HD	High-Dose
HEDIS	Healthcare Effectiveness Data and Information Set
HELP	(US Senate Committee on) Health, Education, Labor, and Pensions
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Human Complement Serum Bactericidal Antibody
HZ	Herpes Zoster
HZ/su	HZ Subunit Vaccine
IAC	Immunization Action Coalition
ICD	International Classification of Diseases
ID	Identification
IDSA	Infectious Disease Society of America
IDU	Injection Drug Use
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHR	International Health Regulations
IHS	Indian Health Services
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IND	Investigational New Drug
IPV	Inactivated Polio Vaccine
IT	Information Technology
ITT	Intention-To-Treat
ISO	Immunization Safety Office
JAMA	*Journal of the American Medical Association*
JEV	Japanese Encephalitis Vaccine

JID	*Journal of Infectious Diseases*
KPNC	Kaiser Permanente Northern California
LAIV	Live Attenuated Influenza Vaccine
LLR	Log-Likelihood Ratio
LTPS	(SPS) Long-Term Persistence Study
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Meningococcal Vaccine
MDH	Minnesota Department of Health
MDHHR	Michigan Department of Health and Human Resources
MenB	Serogroup B Meningococcal Disease
MIC	Minimal Inhibitory Concentration
MMR	Measles, Mumps and Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NAIIS	National Adult Influenza and Immunization Summit
NAPNAP	National Association of Pediatric Nurse Practitioners
NCAI	National Coalition of Adult Immunization
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
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NG	Non-Groupable
NGS	Next-Generation Sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Inpatient Sample (HCUP)
NIS	National Immunization Survey
NNDSS	National Notifiable Diseases Surveillance System
NNT	Number-Needed-to-Treat
NNV	Number Needed to Vaccinate
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NYC	New York City
ODN	Oligonucleotides
ORISE	Oak Ridge Institute for Science and Education
PA	Protective Antigen
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PhRMA	Pharmaceutical Research and Manufacturers of America
pIMDs	Potential Immune Mediated Diseases
PHL	Public Health Laboratories
PHN	Post Herpetic Neuralgia
PNH	Paroxysmal Nocturnal Hemoglobinuria
PPE	Personal Protective Equipment
PPV	Positive Predictive Value
PrEP	Pre-Exposure Prophylaxis
PSA	Probabilistic Sensitivity Analysis
QALYs	Quality-Adjusted Life-Years
QIV	Quadrivalent Influenza Vaccine

RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
REMS	Risk Evaluation and Mitigation Strategy
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
S. aureus	*Staphylococcus aureus*
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SASG	Slide Agglutination
SBA	Serum Bactericidal Antibody
SBT	Serum Bactericidal Testing
sBLA	Supplemental Biologics License Application
SME	Subject Matter Experts
SPRT	Sequential Probability Ratio Test
S. pneumoniae	*Streptococcus pneumoniae*
SPS	Shingles Prevention Study
STPS	(SPS) Short-Term Persistence Substudy
TB	Tuberculosis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TDOC	Tauro Deoxycholate
TIV	Trivalent Influenza Vaccine
TLRs	Toll-Like Receptors
VASP	Varicella Active Surveillance Projects
VZV	Varicella Zoster Virus
UK	United Kingdom
UN	United Nations
US	United States
USVI	US Virgin Islands
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VRC	Vaccine Research Center
VSD	Vaccine Safety Datalink
VZV	Varicella Zoster Virus
WFS	Waterhouse-Friderichsen's Syndrome
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WWII	World War II
YF	Yellow Fever
ZEST	ZOSTAVAX® Efficacy and Safety Trial

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

Call To Order / Welcome

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett called the June 2017 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 June 2017 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. Stephanie Thomas, Ms. Natalie Greene, and Mr. Chris Caraway.

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 to 120 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, October 25-26, 2017. Registration for all meeting attendees is required and may be completed online at www.cdc.gov/acip. The registration deadline for Non-US citizens is September 25, 2017 and for US citizens registration closes October 5, 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 assist with any questions about the process. Member substitutions and new Liaison and *Ex-Officio* representatives announced during this meeting included the following:

Liaison Representatives

- ❑ Ms. Carol Hayes, representing American Nurses Association (ANA)
- ❑ Dr. Susan Lett, representing the Council of State and Territorial Epidemiologists (CSTE)
- ❑ Dr. Corey Robertson, representing Pharmaceutical Research and Manufacturers of America (PhRMA)
- ❑ Dr. Pamela Rockwell will be representing the American Academy of Family Physicians (AAFP)
- ❑ Dr. Alexandra Woodward, representing Biotechnology Innovation Organization (BIO)

Ex-Officio Members

- ❑ Dr. Angela Shen is representing the National Vaccine Program Office (NVPO)
- ❑ COL Margaret Yacovone is representing the Department of Defense (DoD)

New ACIP Liaison and *Ex Officio* Representatives

- ❑ Dr. Linda C. Lambert, National Institutes of Health (NIH)
- ❑ Dr. Caroline Quach-Thanh, Canadian National Advisory Committee on Immunization (NACI)

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. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide three 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 three minutes. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

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.

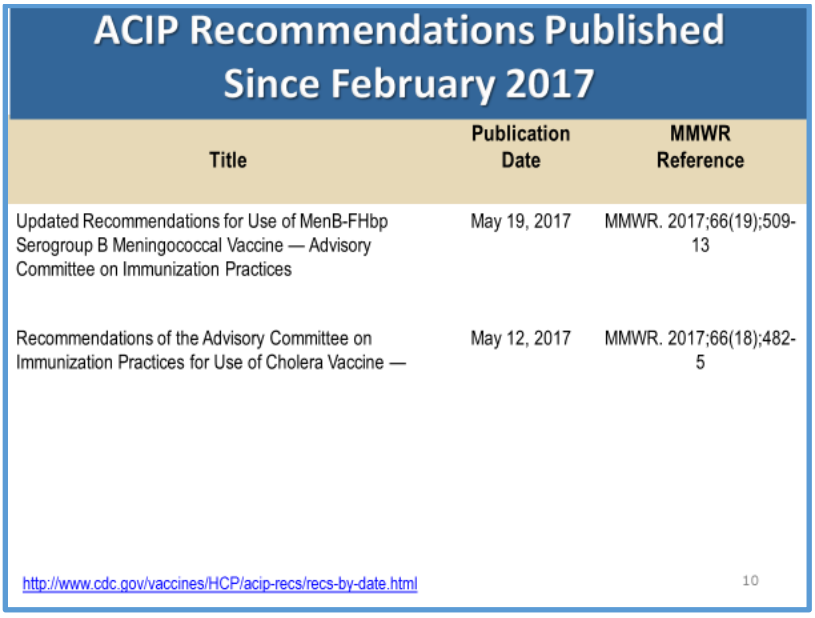
Applications for ACIP membership are due no later than August 1, 2017 for the 4-year term beginning July 1, 2018. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

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. Questions should be directed to Dr. Cohn or Stephanie Thomas.

Recommendations and immunization schedules can be downloaded from the ACIP website. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, revised, or retired. During every meeting, an update is provided on the status of ACIP recommendations. There have been two ACIP publications since February 2017, which are reflected in the following table:



ACIP Recommendations Published Since February 2017

Title	Publication Date	MMWR Reference
Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine — Advisory Committee on Immunization Practices	May 19, 2017	MMWR. 2017;66(19);509-13
Recommendations of the Advisory Committee on Immunization Practices for Use of Cholera Vaccine —	May 12, 2017	MMWR. 2017;66(18);482-5

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

Visitors / Farewells / Roll Call

Nancy Bennett, MD, MS
ACIP Chair

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

- ❑ Dr. Wakaba Fukushima, Professor and Chairperson, Department of Public Health, Osaka City University Faculty of Medicine, Osaka, Japan

- ❑ Dr. Megumi Matsunaga, Associate Professor, Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga, Japan

- ❑ Mr. Kazuya Ito, Research Associate, Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan

She then wished farewell to and thanked two ACIP members for their service who have completed their four-year terms, but agreed to remain until new members are appointed:

Dr. Allison Kempe

Dr. Kempe was a fearless leader as the Chair of the Human Papillomavirus (HPV) Vaccines Work Group (WG), taking them through a time of great progress and several truly challenging decisions. She focused the WG's attention on new responsibilities as a result of the Affordable Care Act (ACA), and pushed them to clarify the impact of their recommendations on health equity—a critical consideration. She brought her specific expertise on the realities of implementation of vaccine policy—also critical to the WG's decisions. Finally, she survived the Atlanta "snowstorm" during which no snowflakes were observed. However, Dr. Kempe's hometown got six feet of snow that day. Despite all of this, Dr. Kempe has begged for lifetime tenure on the ACIP and everyone would love to have her indefinitely.

Dr. Art Reingold

Dr. Reingold brought tremendous expertise to the ACIP from his long tenure with the Emerging Infections Program (EIP) and as a veteran of the Strategic Advisory Group of Experts on Immunization (SAGE). He will be missed tremendously, especially his insightful but disarmingly simple questions that seem to summarize the content of any given session. Dr. Reingold also is entering the Guinness Book of World Records for having chaired and served on the largest number of ACIP WGs. Although he is rarely in the US, he does have a room set aside for him in the Tom Harkin Global Communications Center (GCC) at CDC. They knew he was always looking for a place to sleep as he has "so few" friends in Atlanta. He will be missed tremendously by ACIP, but the waiters at the General Muir are truly heartbroken.

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
- ❑ 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 is included in the appendixes at this end of the full document from the June 2017 ACIP meeting.

Hepatitis Vaccines

Introduction

Art Reingold, MD
Hepatitis Vaccines Work Group

Dr. Reingold reminded everyone that the last full set of recommendations, *Prevention of Hepatitis A Through Active or Passive Immunization*, was published in 2006. There have been several updates since that time relating to specific issues regarding Hepatitis A (HepA) vaccination, such as an alternative dosing schedule. Given that the most recent update was in 2009, those recommendations are ripe for updating. The WG has been working assiduously over the past couple of years to assemble the requisite information for ACIP to consider in support of the revised recommendations regarding Hepatitis A virus (HAV) infection prevention.

The WG has considered HepA disease burden and population protection, HepA catch-up vaccination for children and teens 2 through 18 years of age, and cost-effectiveness of Hep A catch-up vaccination. With that in mind, presentations for this session focused on the following:

- ❑ Hepatitis A vaccine background
- ❑ Cost-effectiveness analysis of catch-up HepA vaccination among unvaccinated and partially-vaccinated children
- ❑ Updated ACIP routine recommendations for use of HepA vaccine
- ❑ Updated ACIP recommendations for use of HepA vaccine and immune globulin for post-exposure prophylaxis (PEP) and for international travelers

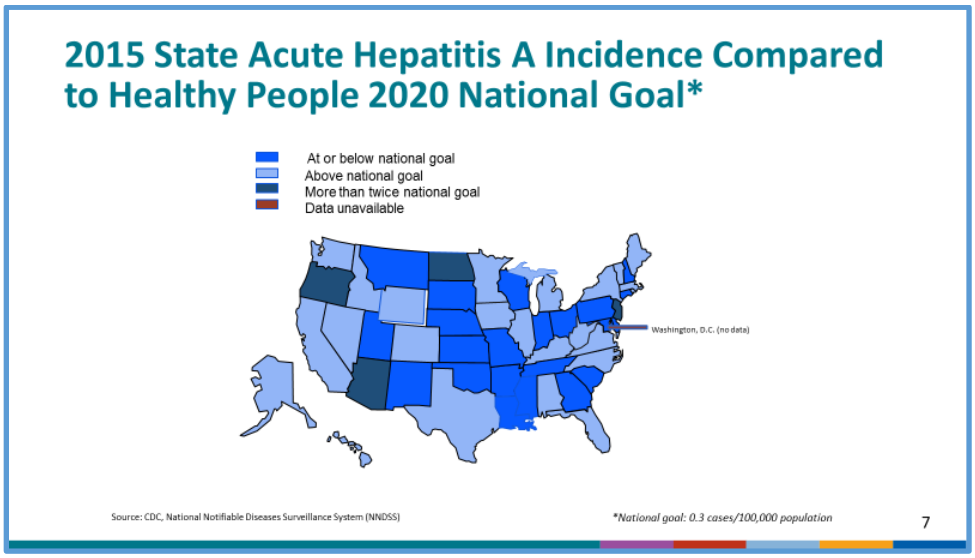
In terms of next steps, the WG plans to present the full updated HepA vaccine statement for a vote in October 2017. In addition, the WG will continue deliberations on adult Hepatitis B (HepB) vaccination.

HepA Vaccine Background

Noele Nelson, MD, PhD, MPH
CDC Lead, ACIP Hepatitis Vaccines Work Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Nelson discussed HepA epidemiology, background, vaccine recommendations, vaccine coverage, an Alaska example, and outbreaks. She indicated that the reported number of acute HepA cases in the US has declined substantially. In 2015, 1390 cases were reported. Data collection for HepA started in 1966. In 1971, there were approximately 60,000 cases at a rate of 30 cases per 100,000 population. In 1996 when vaccine was first recommended, there were 31,000 cases at a rate of about 12 cases per 100,000 population. Between 1996 and 2011, there was a 95.5% decline in the rate of cases. In 2015, the rate was about 0.4 and has remained stable over the last few years. In terms of the rates of reported acute HepA in the US by age, all children 0 through 19 years of age reached 0.3 cases per 100,000 by 2014. This is the Healthy People 2020 target. The highest rates are among adults 20 through 29 years and 30 through 39 years at 0.6 per 100,000.

The following map shows 2015 state acute HepA incidence compared to the Healthy People 2020 national goal:



Of the 50 reporting states, 22 (44%) were at or below the national goal, 28 states were above the national goal, and 4 states had rates more than twice the national goal. These states are distributed across the country despite the incremental recommendations that have been issued in the Western states [National Notifiable Diseases Surveillance System (NNDSS)].

About 60% of cases have available data on hospitalizations. The cases hospitalized have increased from 2009-2013 from 39.3% to 48%. In 2014, the rate decreased slightly to 45% but increased again in 2015 to 47%. That is, close to 50% of cases were hospitalized. A study conducted a few years ago assessing the primary discharge diagnosis of HepA in the National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) found that the mean age of persons hospitalized for hepatitis A increased significantly over the study time period from 37.6 years in 2002-2003 compared to 45.5 years in 2010-2011. This is important because disease is worse in older adults. [1]This study also showed a number of trends. The proportion of HepA hospitalized patients with Medicare coverage increased in 2010-2011 (22.7%) compared to 2002-2003 (12.4%), had an increase in comorbid liver disease 2010-2011 (38.3%) compared to 2002-2003 (25.1%), and had an increase in comorbid medical conditions in 2010-2011 (38.5%) compared to 2002-2003 (26.8%). However, there were no changes in the mean length of stay or in-hospital deaths identified over the study period. [2]Another study also showed an increase in the percent of HepA cases hospitalized from 1991-2011. Very few deaths were associated with HepA. [3]Data from the NNDSS also showed that the number of deaths reported from HepA were low at about 26 in 2014. [[1]Collier MG, Tong X, Xu F. Hepatitis A hospitalizations in the United States, 2002 - 2011. Hepatology. 2014 Sep 29; [2]Ly et al. JID Jul 15;212(2):176-82. 2015; [3]NNDSS].

Based on data from 1999-2000 and 2009-2010, the prevalence of antibody to HepA virus, or the seroprevalence, has increased among children due to childhood vaccination. However, it has decreased among adults. In children 6 through 11 and 12 through 19 years, there has been a significant increase in protection. There has been a minimal change in prevalence among adults 20 through 29 and 30 through 39 years of age. However, significant decreases occurred

in the proportion of adults with protection for ages 40 through 60 years of age. The overall prevalence of antibody among US residents remained about the same between the two surveys at 31.2% for 1999-2000 and 26.5% for 2009-2010, indicating that less than 1/3 of the US population had protection against HepA in 2009-2010 [NHANES, National Health and Nutrition Examination Survey; Murphy TV et al. Progress Toward Eliminating Hepatitis A Disease in the United States. MMWR Suppl. 2016 Feb 12;65(1):29-41].

The risk factors for HepA include international travel, food/waterborne outbreaks, men who have sex with men (MSM), injection drug use (IDU), sexual/household contact with HepA-infected persons, child/employee in a daycare center, contact with a daycare child or employee, and other contact with an HAV-infected person. These risk factors have informed the HepA vaccine risk group recommendations.

In the US, HepA vaccines are inactivated. These include the following:

- ❑ Monovalent: Merck CR326F strain, VAQTA®
- ❑ Monovalent: GSK HM175 strain, HAVRIX®
- ❑ Combination: GSK HM175 strain and recombinant hepatitis B surface antigen (HBsAg), TWINRIX®

The efficacy of HepA vaccines were studied in 1995 and 1996. Of approximately 1000 children 2 through 16 years of age in the Merck VAQTA® study, 100% were protected with 1 dose in a community while living in a community with a high HAV infection rates. The efficacy of HAVRIX® in protecting against clinical HAV infection was 94% among approximately 38,000 Thai children 1 through 16 years of age who received 2 doses 1 month apart while living in villages with high infection rates [[1]Werzberger, A et al. New Engl J Medicine. 1992;327:453–7; [2]Innis BL, et al. JAMA 1994;271:1328–34].

HepA vaccines are administered in a 2-dose schedule. VAQTA® is given on a 0, 6-18 month schedule and HAVRIX® on a 0, 6-12 month schedule. Of note when HAVRIX® was first licensed, it was given in a 3-dose schedule of 360 EL.U. per dose, which is one-half of the number of units given currently. The 3-dose schedule has been determined to be equivalent to the 2-dose schedule. TWINRIX® is licensed only for adults 18 years of age and older on an accelerated dosing schedule of 4 doses (1 mL each) given on days 0, 7, and 21-30 followed by a booster dose at month 12, particularly for travel. TWINRIX® cannot be used for PEP because of the decreased dose of the HepA vaccine component [Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006 May 19;55(RR-7):1-23].

In pre-licensure trials, adverse reactions to HAVRIX®, VAQTA®, and TWINRIX® were mostly injection site reactions and mild systemic reactions. The most frequent side effects are soreness or erythema at the injection site, fever, headache, and malaise. Multiple studies demonstrate no serious adverse events (SAE) definitively attributed to inactivated vaccine. Post-marketing surveillance for AEs following receipt of HepA vaccines has been performed primarily by two systems in the US, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). Recent analyses of these data show no unusual or unexpected safety patterns for any of the HepA vaccines. VAERS pregnancy reports following HepA were reviewed and no patterns of concern were observed [MMWR 2006;55(RR-7) IOM 2011. Moro PL, et al. Am J Obstet Gynecol. 2014 Jun;210(6):561.e1-6]. Currently, the VSD is conducting an ongoing safety study of HepA and HepB vaccines in pregnant women.

The contraindications of HepA vaccines include a history of severe allergic reaction to a previous dose of HepA vaccine or vaccine component. Precautions include vaccination of persons with moderate or severe acute illness, with or without fever, in whom HepA vaccine should be deferred until illness resolves as is the case with other vaccines [Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006 May 19;55(RR-7):1-23].

The duration of protection after vaccination is unknown. Anti-HAV has been shown to persist in vaccine recipients for at least 20 years in adults administered inactivated vaccine as children with a three-dose schedule. Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies. Protection following natural infection is lifelong and may also be lifelong following vaccination [Theeten H, et al. Vaccine. 2015 Oct 13;33(42):5723-7. Plumb ID, et al. Viral Hepat. 2017;00:1–5].

HepA vaccination recommendations were introduced incrementally in the US from 1996-1999. In 1996, vaccine was recommended for children at age 2 years in communities with high rates of disease and children through teen years in outbreaks. In 1999, vaccine was expanded to include children at age 2 years of age in 11 states with average annual HepA rates of two times the national average or $\geq$20 cases per 100,000 population. Vaccination was to be considered in 6 states with rates above the national average or $\geq$10 cases per 100,000 population. Notably, all of these states were in the Western region of the country [MMWR 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)].

In 2006, childhood vaccination was recommended for routine use at 12 through 23 months of age in all states. Vaccination programs for children 2 through 18 years of age were recommended to continue, which refers primarily to the Western states that had the higher rates of cases. Catch-up vaccination was to be considered in outbreaks and areas with increasing disease rates and for any person wishing to obtain immunity. However, no routine catch-up recommendation was made for children ages greater than 23 months [MMWR 2006;55(RR-7)].

ACIP HepA vaccine recommendations include groups at increased risk of HAV infection or severe HAV disease, including travelers, MSM, users of injection and non-injection drugs, persons with clotting-factor disorders, persons who work with non-human primates, persons who anticipate close personal contact with an international adoptee, persons with chronic liver disease (CLD), and healthy persons 12 months through 40 years of age for PEP [MMWR 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)].

Vaccine coverage for HepA is the lowest among childhood vaccines for children 19 through 35 months of age based on National Immunization Survey (NIS) data for 1994-2014. In 2014, 2-dose coverage for HepA vaccine among children 19 through 35 months of age was 57.5%. In 2015, HepA ≥ 1-dose coverage was 85.8% and ≥ 2-dose coverage was 59.6%. The Healthy People 2020 goal is 85% for 2-dose coverage, so the 2-dose coverage is still well below that goal [Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Dietz V. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2015. MMWR Morb Mortal Wkly Rep. 2016 Oct 7;65(39):1065-1071. doi: 10.15585/mmwr.mm6539a4. PubMed PMID: 27711036].

In 2013, national vaccination coverage for 1 and ≥2 doses of HepA vaccine among adolescents 13 through 17 years of age was 62.5% and 51.0%, respectively [unpublished]. The ≥2-dose coverage for adults ages 19 through 49 years was low at 12.1% overall, 18.8% among travelers, 8.1% among non-travelers, and 18.2% among persons with CLD based on 2014 data. As a reminder, travelers and persons with CLD are considered high-risk groups for whom vaccine is recommended [Williams WW, Lu PJ, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, Skoff TH, Nelson NP, Harpaz R, Markowitz LE, Rodriguez-Lainz A, Fiebelkorn AP. Surveillance of Vaccination Coverage among Adult Populations - United States, 2015. MMWR Surveill Summ. 2017 May 5;66(11):1-28].

One example of vaccine implementation comes from Alaska where from 1950-1990, there were cyclic HAV epidemics every 10 to 15 years. Of Alaska Natives (AN) born before 1945, 85% were anti-HAV positive. Universal HepA vaccination was introduced in 1996 for persons 2 through 14 years of age. In 1997, the age was expanded to persons 2 through 18 years of age. In 2001, HepA vaccination became a daycare and school attendance requirement. For the remainder of the country in 2006, the recommendation was for persons 12 through 23 months of age. In 2006, the age was expanded to 1 through 18 years of age. From 2002-2007, an estimated 2052 symptomatic cases were prevented with vaccine. In 2006, there was 65% ≥1 dose vaccine coverage among AN children 2 through 18 years of age. By 2008, there was 94% 2-dose coverage among AN children 11 through 17 years of age. This resulted in a 99.9% reduction in cases among AN people at 0.3/100,000 persons, which is the current Healthy People 2020 goal. This illustrates that transmission in Alaska was halted due to high vaccination coverage, routine childhood vaccination, and mandatory school vaccination.

To highlight some recent outbreaks, there was a multi-state outbreak associated with frozen pomegranate arils imported from Turkey in 2013. Of 165 cases, 7% were among people <18 years of age and 93% were among people ≥18 years of age. In terms of complications, 42% were hospitalized, there were 2 cases of fulminant hepatitis, and 1 case required a liver transplant [Collier MG, et. al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet Infect Dis. 2014 Oct;14(10):976-81]. A cost analysis of this outbreak was performed, which estimated that the per-patient cost of healthcare and productivity loss was approximately $13,500 for hospitalized and approximately $2000 for non-hospitalized patients and about $1.3 million for all 165 outbreak-related cases. State and local public health personnel expenditures included 82 hours and about $3200 per outbreak-related case. While this was not a large number of cases, the public health resources and expenditures were substantial.

In 2016, there was a food-associated outbreak in Hawaii. On August 15, 2016, the Hawaii Department of Health (HDOH) identified raw scallops served at Chain A restaurants on Oahu and Kauai as a likely source of the ongoing outbreak. The product was Sea Port Bay Scallops (Wild Harvest, Raw Frozen) that originated in the Philippines and were distributed by Koha Oriental Foods and True World Foods. The product was embargoed and there was a temporary closure of all Chain A restaurants on Oahu and Kauai. As of January 11, 2017 there were 292 confirmed cases and 74 hospitalizations. The onset of illness occurred between 6/12/16 to 10/9/16 [http://health.hawaii.gov/docd/hepatitis-a-outbreak-2016/].

Also in 2016, there was a multistate outbreak of HepA linked to frozen strawberries in 9 states. The likely source was frozen strawberries imported from Egypt. The location was Smoothie Restaurant A Cafés. The product was removed on August 8, 2016. As of September 28, 2016 there were reports from 143 people with HepA from 9 states. Of these cases, 129 reported eating a smoothie from Smoothie Restaurant A Café, 14 had no direct exposure to Tropical Smoothie Café, 12% were <18 years of age, and 88% were ≥18 years of age. The age range of cases was 12 through 70 years of age. Of these cases, 56 were hospitalized and there were no deaths [http://www.vdh.virginia.gov/blog/2016/09/10/hepatitis-a-investigation; and www.cdc.gov/hepatitis/outbreaks/2016/hav-strawberries.htm].
There have been outbreaks in 2017 in San Diego, Southeast Michigan, Colorado, and New York City as follows:

San Diego
- ❑ 160 total confirmed or probable outbreak-associated cases
- ❑ Hospitalizations: 120 (75%)
- ❑ Deaths: 4 (2.5%)
- ❑ Primarily in homeless individuals and/or IDU
- ❑ Secondary infections in inmates

Southeast Michigan
- ❑ 144 total confirmed, probable, or secondary outbreak associated cases
- ❑ Hospitalizations: 121 (84%)
- ❑ Deaths: 9 (6%)
- ❑ Primarily in homeless individuals and IDU

Colorado
- ❑ 26 cases
- ❑ Gender: 72% are male
- ❑ Age: median 52 years
- ❑ Primarily in MSM, second cluster in females who consumed smoothies

New York City
- ❑ 16 cases
- ❑ Primarily in MSM
- ❑ Linked to HAV strains circulating in Europe

In summary, HepA vaccine is largely responsible for the marked reduction in HepA cases. However, an increasing proportion of adults in the US are susceptible to HAV. This is due to reduced exposure to HAV early in life and significant decreases in seroprevalence in older adults ≥ 40 years. In addition, there is low 2-dose vaccination coverage among adults, including high risk adults (travelers 18.8%; CLD 18.2%). Morbidity and mortality increases with age. The mean age of persons hospitalized for HepA increased significantly from 2002-2003 to 2010-2011. Hospitalization rates for reported HepA cases increased from 2005 to 2011. There is suboptimal HepA vaccination 1- and 2-dose coverage among young children as well, and there is no routine HepA vaccine recommendation for adolescents or adults. HAV remains endemic in many areas of the world resulting in ongoing risks for travelers to intermediate and high endemic countries, as well as the risk for consumption of imported HAV contaminated food from global sources. Of note, herd immunity does not protect against foodborne exposure.

Cost-Effectiveness Analysis of Catch-Up HepA Vaccination Among Unvaccinated and Partially Vaccinated Children

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NORC at the University of Chicago

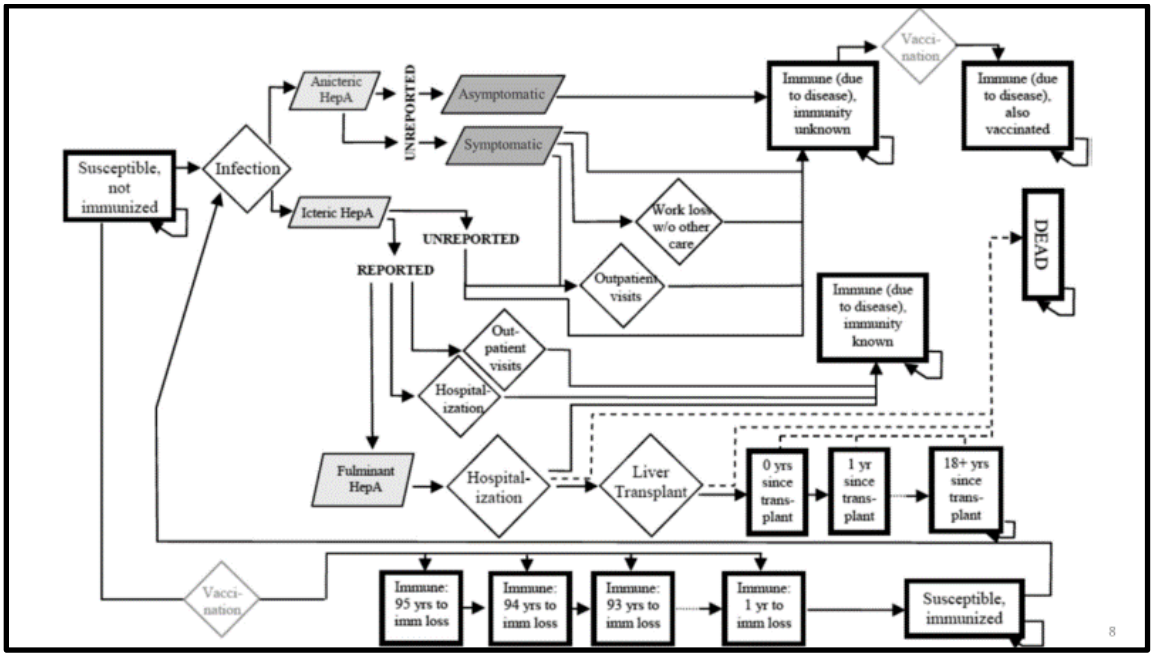
Dr. Rein reported on work that he did for the Hepatitis Vaccines WG in 2015. He emphasized that the motivation behind the cost-effectiveness analysis of catch-up HepA vaccination among unvaccinated and partially vaccinated children was that a large population of adolescents and young adults remain unvaccinated against HepA. Due to lower rates of incident infection in childhood, there are lower rates of disease-acquired HAV immunity among the US adult population. This increases vulnerability to outbreaks. Several HAV outbreaks due to contaminated food have been observed as well. An interesting point to note about HepA is that the severity of HAV symptoms increases with age of infection. Decreased incidence leads to older average age of infection, which has been observed to lead to more severe outcomes when infection occurs. Consequently, catch-up vaccination may be necessary due to decreasing population anti-HAV seroprevalence. HepA vaccine is the only vaccine on the childhood vaccination schedule without a catch-up recommendation. In order to contemplate a recommendation change regarding catch-up, the cost-effectiveness of catch-up vaccination needed to be assessed. This study assessed the cost-effectiveness of a one-time, age-cohort-based, catch-up vaccination campaign for US children 2 through 17 years of age.

Regarding the timeline, from February to April 2015, the ACIP Hepatitis Vaccines WG discussed HepA vaccination, including the methods and results of this study. The results of the study were published in July 2016 in *Vaccine*[1]. The ACIP Hepatitis Vaccines WG resumed discussing the findings, both these and others, in the context of HepA catch-up vaccination from March to May 2017 [[1] Hankin-Wei A, Rein DB, Hernandez-Romieu A, Kennedy MJ, Bulkow L, Rosenberg E, Trigg M, Nelson NP. Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children. Vaccine. 2016 Jul 29;34(35):4243-9].

In terms of the methods for the cost-effectiveness study, a previously published Markov model of HepA vaccination was utilized that was used for the 2005 ACIP HepA vaccination discussions. The study tested the cost-effectiveness of a policy of catch-up HepA vaccination of unvaccinated and partially vaccinated children as compared to no catch-up, with catch-up defined as a probability and cost of two doses of HepA vaccine for children with no documentation of previous vaccination, and a separate probability and cost of a second dose for children with documentation of only a single prior dose.

Simulated outcomes were used in succession for each age from 2 to 17 and outcomes and costs were summed in Excel to calculate final results. The model simulated patient progression between eight possible HAV-related states based on the probability of vaccination, HAV infection, and health complications due to vaccination or infection. Model parameters included vaccine costs, rates of HAV infection, probability of disease complications and associated healthcare costs, gradual loss of vaccine-acquired immunity following vaccination, public health costs for an HAV-associated outbreak, costs of productivity loss, and all-cause probability of death due to non-HAV causes among the lifespan of the age cohort. Costs and quality-adjusted life years (QALYs) were assigned by state annually [Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Cost-effectiveness of routine childhood vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21].

The following figure shows the different states included in the model:



All persons start the model in a susceptible, non-immunized state when born. From that point, their lives are simplified into two possible outcomes. They could be infected or not be infected and have a probability of vaccination: 1) Those who are infected develop either asymptomatic or mildly symptomatic anicteric HepA. The mildly symptomatic cases can incur some work loss or outpatient visits with small costs, and then go on to being immune due to disease immunity; or 2) Those who are icteric cases with more severe outcomes, including more extensive outpatient visits, hospitalization, or fulminant disease. Fulminant disease could result in a liver transplant, death, or resolve on its own. Those who are vaccinated acquire immunity, but have a probability of losing vaccine-acquired immunity at different stages in their lives from 1 year to 95 years following vaccination, at which point they become susceptible and immunized. There also is a chance that people who developed asymptomatic infection not detected would be vaccinated again and incur those costs.

Like all simulation models, the model is governed by a series of parameters. In terms of incidence, probably the most important parameter in the model, the average national incidence between 2008 to 2012 was used. This was increased somewhat because the model's baseline settings from when the model was built in the early 2000s would not allow an incidence lower than 1 case per 100,000. An incidence of 1 case per 100,000 was used. Unlike earlier recommendations, there is no current evidence of regional variation. The annual incidence for under-reporting was adjusted using a ratio of 1.95 unreported cases for every 1 reported case observed. This also is lower than previous analyses and comes from recent work. The probability of symptomatic disease increased with age according to published estimates. The distribution of disease severity was updated based on surveillance data, and loss of vaccine-acquired immunity was updated by year estimated based on new data obtained from Alaska [Klevens RM, Liu S, Roberts H, Jiles RB, Holmberg SD. Estimating acute viral hepatitis infections from nationally reported cases. Am J Public Health 2014;104:482–7; Van Herck K, Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. J Med Virol 2001;63:1–7; Armstrong GL, Bell BP. Hepatitis A virus

infections in the United States: model based estimates and implications for childhood immunization. Pediatrics 2002;109:839–45; Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Costeffectiveness of routine childhood vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21; Taylor RM, Davern T, Munoz S, Han S-H, McGuire B, Larson AM, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. Hepatol Baltim Md 2006;44:1589–97; McMahon BJ, Williams J, Bulkow L, Snowball M, Wainwright R, Kennedy M, et al. Immunogenicity of an inactivated hepatitis A vaccine in Alaska Native children and Native and non-Native adults. J Infect Dis 1995;171:676–9].

In terms of existing coverage levels, NIS estimates for children 19 through 35 months and 13 through 17 years of age was used. Age-specific coverage was estimated linearly based on the two estimates by literally drawing a line between the mid-points of those two estimates and using the slope of that line to linearly estimate the expected vaccine coverage rates for each individual age between ages 2 through 17. For catch-up vaccination, an assumption was made because there is no comparable catch-up program to estimate vaccine uptake. Therefore, an assumption was made that 50% of those unvaccinated and unaware of prior infection would receive the first dose of vaccine, and that 50% of those who received the first dose would receive the second dose. For adult vaccination, it was assumed that adults 18 through 64 years of age were vaccinated at a rate of 0.5% per year based on proprietary sales data generously provided by GlaxoSmithKline (GSK) [Centers for Disease Control and Prevention (CDC). Hepatitis A vaccination rate weighted estimates for 19–35-month-old children in U.S. 50 States + DC, 2003; Centers for Disease Control and Prevention (CDC). Hepatitis A vaccination rate weighted estimates for 13–17-year-old children in U.S. 50 States + DC, 2008
Trofa A, personal communication, 2 April 2015].

QALYs were updated using Global Burden of Disease (GBD) study values. Basically, the morbidity weight was applied to different disease states based on the viral hepatitis stages estimated in the GBD study. Costs were updated using four case studies of US HepA outbreaks for mild symptomatic disease, unreported icteric infection, reported icteric infection, hospitalization, and fulminant liver failure with and without transplant. Productivity losses were estimated for parents/caregivers and death from HAV. The model used a lifetime time horizon and a 3% annual discount rate [2011 Health Care Cost and Utilization Report | HCCI n.d. http://www.healthcostinstitute.org/2011report (accessed August 31, 2015); Bownds L, Lindekugel R, Stepak P. Economic impact of a hepatitis A epidemic in a mid-sized urban community: the case of Spokane, Washington. J Community Health 2003;28:233–46; Berge JJ, Drennan DP, Jacobs RJ, Jakins A, Meyerhoff AS, Stubblefield W, et al. The cost of hepatitis A infections in American adolescents and adults in 1997. Hepatology 2000;31:469–73; Dalton CB, Haddix A, Hoffman RE, Mast EE. The cost of a food-borne outbreak of hepatitis A in Denver, Colo. Arch Intern Med 1996;156:1013–6; and Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Cost-Effectiveness of Routine Childhood Vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21. doi:10.1542/peds.2006-1573].

As a reminder, incremental difference in costs and QALYs are reported from cost-effectiveness studies. The incremental cost-effectiveness ratio is a measure of the incremental difference in costs and QALYs between the intervention scenario (in this case, catch-up vaccination) minus the baseline scenario (in this case, no catch-up). Costs are assessed in terms of differences in vaccine costs, vaccine administration costs, HAV infection and adverse event-related medical costs, productivity losses, and public health response costs. Sensitivity analyses were performed for the 10-year-old cohort, the midpoint age for catch-up vaccination. Threshold

analyses were conducted for disease incidence to determine the incidence that would be required to reach certain cost-effectiveness thresholds.
The following table summarizes outcome measures per age cohort included in the analysis, and for all age cohorts pooled together:

Incremental summary outcome measures per age cohort included in the analysis and for all age-cohorts pooled together.

Cohort			Incremental Results						
Age	Year of birth	Starting population	Infections	Discounted QALYs	Discounted life years	Discounted costs	$/person	QALY/person	ICER*
2	2012	3,952,841	−772	13	4	$9,172,919	$2.32	0.0000033	$694,240
3	2011	3,953,590	−679	13	3	$9,522,024	$2.41	0.0000033	$717,691
4	2010	3,999,386	−652	14	4	$9,896,821	$2.47	0.0000035	$724,814
5	2009	4,130,665	−665	17	6	$10,414,199	$2.52	0.0000041	$627,967
6	2008	4,247,694	−685	19	7	$10,775,540	$2.54	0.0000045	$569,416
7	2007	4,316,233	−710	21	9	$10,992,191	$2.55	0.0000049	$512,475
8	2006	4,265,555	−699	21	9	$10,834,800	$2.54	0.0000049	$511,802
9	2005	4,138,349	−721	22	11	$10,418,910	$2.52	0.0000053	$476,165
10	2004	4,112,052	−741	23	10	$10,199,218	$2.48	0.0000056	$452,239
11	2003	4,089,950	−762	23	11	$9,933,351	$2.43	0.0000056	$436,144
12	2002	4,021,726	−774	25	13	$4,679,302	$1.16	0.0000062	$189,782
13	2001	4,025,933	−802	24	12	$9,174,316	$2.28	0.0000060	$386,316
14	2000	4,058,814	−837	26	14	$8,884,981	$2.19	0.0000064	$338,425
15	1999	3,959,417	−852	27	14	$8,265,037	$2.09	0.0000068	$307,849
16	1998	3,941,553	−876	27	15	$7,618,023	$1.93	0.0000069	$294,083
17	1997	3,880,894	−889	27	15	$7,016,799	$1.81	0.0000070	$268,626
All years		61,141,811	−12,116	342	157	$147,798,431	$2.42	0.0000056	$432,159

* ICER is not exactly equal to discounted costs divided by discounted QALYs due to rounding.

Hankin-Wei A, Rein DB, Hernandez-Romieu A, Kennedy MJ, Bulkow L, Rosenberg E, Trigg M, Nelson NP. Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children. Vaccine. 2016 Jul 29;34(35):4243-9.

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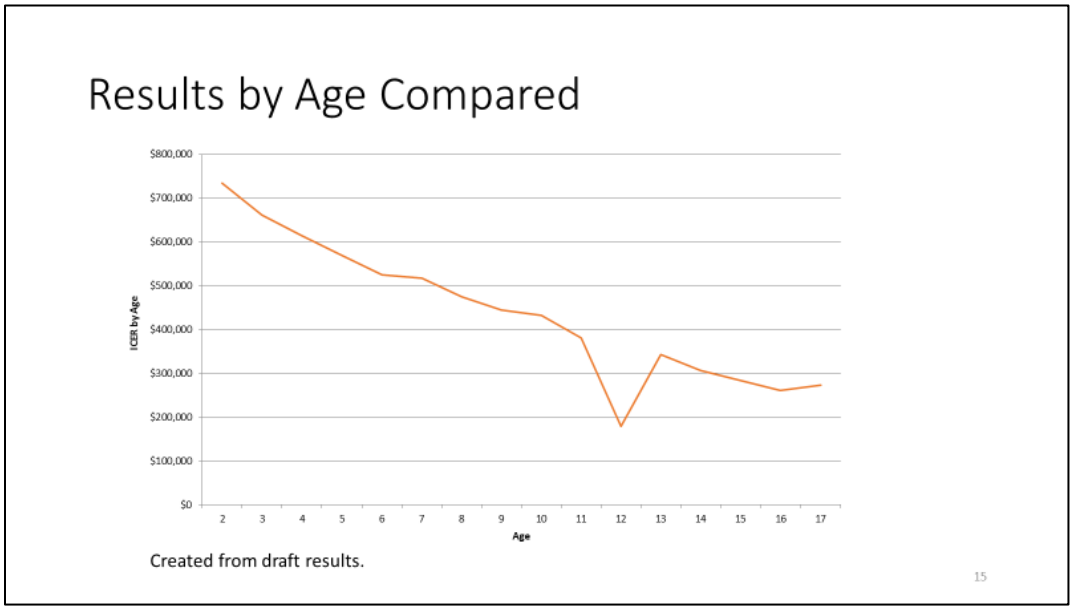
To summarize that information, across all ages 2 through 17, the incremental costs or extra costs expected to be associated with catch-up vaccination was $146 million including all discounting. The incremental QALYs that would be gained from that were 357. This resulted in an overall incremental cost-effectiveness ratio (ICER) of approximately $430,000 per QALY, with an ICER range by age of about $190,000 to $750,000. The following graph shows the ICER results by age for each individual age cohort:



In terms of some examples of the results for the Age 10 Cohort, catch-up vaccination reduced total HAV infections by 741, with 556,989 additional vaccine doses administered. For every 752 additional doses administered, one case of HAV infection would be averted. Catch-up vaccination increased total discounted QALYs across the 10-year-old cohort by 23, or 0.000006 QALYs per person. Catch-up vaccination increased net costs by $10.2 million or $2.38 per person. The catch-up vaccination intervention increased vaccine and administration costs for children, but decreased these costs for adults, as individuals vaccinated by the catch-up campaign would not require HAV vaccination in adulthood. The incremental cost of the HAV vaccine catch-up at age 10 years was $452,239 per QALY gained.

Looking across all of the results, cost-effectiveness of catch-up vaccination decreased with the age of the cohort targeted for vaccination, with catch-up becoming more cost-effective when targeting children in late adolescence. This effect was due to several factors:

- Higher probability of symptomatic disease among older children
- Less discounting of future costs of disease
- Vaccination of older children, which averted the need for higher-cost adult vaccination with less delay in averting these costs

The cost-effectiveness of catch-up vaccination was most favorable at age 12 years, resulting in an ICER of $190,000 per QALY gained. The model assumes that the administration costs of HepA vaccination were split with other vaccines routinely administered at age 12 years, thus lowering the cost of vaccination.

The results were most sensitive to the following:

- Discount rate: ICER = $24,000/QALY when the discount rate is 0%
- Cost of child vaccine in the public and private market
- Annual rate of adult vaccination; catch-up is more cost-effective when it is assumed to replace more adult vaccination
- Incidence at baseline of 1/100,000, with ICER being $47,000 at an incidence of 5/100,000 and cost-saving at an incidence of 12/100,000

These results were similar to and consistent with the results found in the 2005 analysis when discussing the national recommendation. Results were insensitive to the rate of catch-up adoption, QALY decrements, and rate of loss of vaccine acquired immunity.

The study has several limitations, as all modeling studies have. The values of certain parameters used in the model are uncertain. The most important among these are the rates of HepA vaccine catch-up uptake and adult vaccination rates. Sensitivity analyses indicate that the ICER of catch-up is insensitive to uptake, but is sensitive to the adult vaccination rate. Since catch-up vaccination is assumed to replace adult vaccinations, as the annual rate of adult vaccination increases, the cost-savings associated with replacing more expensive adult vaccine with less expensive children's formulations increases. However, some of that is diminished if people would be vaccinated again as adults. The annual rate of adult vaccination might be underestimated because adult vaccination data could be obtained only from GSK at the time of the study. The model output is based on HepA incidence from 2008 to 2012, and the cost-effectiveness conclusions are tied to factors related to disease transmission patterns, which may change over time and alter future cost. Only the current US ACIP two-dose recommendation was used. World Health Organization's (WHO's) SAGE has advised that

national immunization programs may consider inclusion of single dose HepA vaccine in immunization schedules. Herd immunity effects of vaccination were excluded from the model; however, previous analyses indicate that herd immunity associated with routine vaccination would result in even lower incidence and less favorable cost-effectiveness for catch-up.

In conclusion, the findings suggest that given the current US HAV disease incidence, a catch-up vaccination program would not be cost-effective at thresholds of $50,000, $100,000 or $200,000 per QALY saved. The ICER of vaccination falls below $50,000/QALY saved at an HAV incidence of 5.0 cases per 100,000 persons. The incremental cost per QALY given current US HAV disease incidence ranged from a low of $190,000 per QALY gained at age 12 years to a high of $725,000 per QALY gained at age 4 years. Relative to the cost per QALY projected for hepatitis A catch-up vaccination, studies assessing the economic impact of catch-up interventions for other vaccinations show lower cost per QALY. The improved cost-effectiveness of these catch-up vaccination interventions (e.g., HPV vaccine, meningococcal conjugate vaccine) relative to HepA are driven by higher baseline disease incidence, higher case-fatality ratio, and higher costs of care for complications. Because incidence is so low, the cost-effectiveness of catch-up vaccination is poor. However, catch-up vaccination could be justified based on offsets to adult vaccination if such substitution occurs. There may be other important reasons to consider catch-up vaccination.

Discussion Points

Regarding the baseline incidence of 1/100,000, Dr. Atmar pointed out that from the epidemiological data, the incidence appeared to be 0.06 or lower for most age groups. He wondered whether that would make the ICER even higher.

Dr. Rein replied that it would make the ICER higher.

Given that this modeling is of a cohort of children and adolescents, Dr. Kempe said she was having difficulty understanding how the herd immunity which affects the elderly, who are the expensive cases, is taken into account or if this is not included in the model.

Dr. Rein replied that no herd immunity effects were accounted for in this modeling exercise.

Dr. Reingold noted that while the assumption was made in the model that 50% of the children who receive a catch-up vaccination would get only one dose, the data in Dr. Nelson's back-up slides show that the efficacy of one dose is actually quite high. With that in mind, he inquired as to what efficacy was assumed in the model for a single dose. He also thought it would be more cost-effective to administer a vaccine that offers long-term, potentially lifetime, protection at a younger age. However, the graph showed the opposite and was counter-intuitive.

Regarding Dr. Reingold's first question, Dr. Rein responded that if efficacy is the same or similar with 1 dose as 2 doses, the cost would be cut in half and there would be a much more favorable cost-effectiveness ratio. He did not have those results to share. In terms of the vaccination becoming more cost-effective at older ages, the model behaves oddly at an incidence this low and with adult vaccination. This relates to the discounting being done to the adult vaccination and the amount of adult vaccination being replaced. Considering vaccination of a 2-year old, replacing the adult vaccination that would occur at age 18, which is the first year the model would consider that, the cost of adult vaccination would be discounted at a rate of 3% per year from age 18 down to age 2. That would probably decrease the cost of the adult vaccination below the cost of the child vaccination, so there would still be an incremental cost of the

vaccine. Essentially, getting increasingly closer to the date when adult vaccination occurs, the present-day value of the adult vaccination increases. This has the effect of making the total vaccine cost lower, because adult vaccination costs are subtracted from the childhood vaccination cost, which leads to a lower incremental cost-effectiveness ratio. The simplified answer is that it is a product of the adult vaccine offsets, which are occurring closer in time in older children than in younger children.

Dr. Messonnier asked whether there is a geographic aspect to current vaccination coverage being so low. For example, do the Western states identified as being at higher risk have higher coverage? She said she presumed that few states have school requirements for hepatitis. She wondered about anticipated coverage with a catch-up campaign.

Dr. Nelson replied that approximately 50% of states have school mandates. In terms of coverage, there is variability across the country. There is higher coverage in the Western states, but there is more even distribution as time goes on.

Dr. Messonnier asked whether the states that have mandates have high coverage.

Dr. Rein responded that there have been a couple of publications that predicted higher coverage in states with mandates.

Dr. Moore reported that Tennessee has well over 80% coverage at 24 months of age, and has had a mandate in place for 1 dose for daycare and 2 doses for kindergarten entry since 2009. Compliance with immunization requirements for kindergarten entry is approximately 95%. In terms of whether the model's 50% coverage estimate with a catch-up campaign is a reasonable starting point, she thought this would vary by state. The 50% of states with existing mandates are going to have much higher coverage. The concept of a national catch-up campaign makes sense at 12 years of age when other vaccines are being given. What troubles her about this model is that things are so sensitive to the discount. The benefit to adults is discounted so much by giving childhood vaccines, she worries about doing this for HepA vaccine when most of the disease burden is in older adults. Thus, she thinks the model had to be taken "with a grain of salt."

Dr. Nelson has a study that has been submitted showing that mandates do influence the coverage rates.

Dr. Szilagyi asked what the effect would be on the ICER if the coverage rate was 60%, 70%, or 80%. Because the model is so sensitive to the underlying baseline incidences, he also wondered whether there was any evidence of a trend in incidence in the US or other similar nations.

Dr. Rein replied that there would be very little effect on the ICER if the coverage rate was 60%, 70%, or 80%. The ICER pertains to the benefit per person. Since the model does not account for extra herd immunity effect, it would be essentially the same. Herd immunity was excluded because the current incidence was assumed to be related to foodborne outbreaks or other environmental exposures, which would not be affected by herd immunity. By definition, the model could only account for herd immunity among people who are already within the cohort. The point about children potentially affecting their grandparents for example would be a benefit that could possibly be excluded from the model; however, those grandparents would not be covered in the catch-up recommendation other than effects from children.

Dr. Nelson responded that the incidence has remained relatively stable in the US over the last few years between 0.4 to 0.5 cases/100,000 population. Fluctuations have been noted in other countries around the world and most recently in terms of infections among MSM.

Dr. Hunter said he thought there is a cohort of people about 20 to 50 years of age who have low immunity because they have not been immunized and have not been exposed to natural infection, and if they were trying to prevent infections/complications in that group, he wondered how catch-up vaccination of children 2 through 18 years of age would help them.

Dr. Nelson replied that it would not help that particularly population immediately, but will help improve population protection overall. As more children through 18 years of age are vaccinated, coverage among adults will increase over time.

Dr. Wharton (SME) pointed out that the NIS-Child data assesses coverage in children 19 to 35 months of age, which may not fully capture the impact of school immunization requirements implemented at school entry. For instance, as Dr. Moore mentioned, it might capture the first dose but not necessarily the second dose. There probably is more variability in how this particular program has been implemented state-to-state than is typical with pediatric immunization.

Dr. Jane Zucker (NYC Immunization Program) noted that after the CDC presentation in 2014 showing the data about HepA epidemiology impact in older groups, NYC changed its recommendations for catch-up for everyone through 18 years of age. Basically, that entailed changing the NYC Immunization Registry recommendations. At 12 months, there is a “do now” recommendation and everyone who was not fully vaccinated after 2 years, received a recommendation to be given HepA vaccine to complete their 2 doses. Their coverage for 19 to 35 months of age ranges about 76% for 1 dose and 49% for 2 doses. For adolescents 11 through 18 years of age, coverage is approximately 93% coverage for 1 dose and 88% coverage for 2 doses. It has been their experience that the numbers are generally much higher than typically can be achieved with catch-up vaccination. Catch-up has been very feasible because it is allowed to be given at any visit during which a child is receiving other vaccines.

Dr. Lee noted that the state-based approach appeared to be very effective when implemented in a way that allows a systems-based approach to occur. One way to do that is to mimic in the model what is being observed in the various states without necessarily changing the model. That would help ACIP understand how these recommendations might be implemented. From a strategy standpoint, it also would be helpful to have information available from the economic models about 1 versus 2 doses. She emphasized that since the incidence is lower nationally on average, it would be helpful to have the model go below 0.1. While she recognized that this seemed to be a challenge, it would give them some additional information to counterbalance the potential for herd immunity effects. Another challenge for ACIP is to understand what the QALYs mean. She asked whether the QALY decrements were considered to be temporary specifically for mild, symptomatic, or asymptomatic infection or if they were assumed to be accumulated over time aside from those who may receive a liver transplant. In addition, she wondered whether the number of hospitalizations, liver transplants, and deaths averted had been assessed. That would offer more information about what the QALYs mean and would help ACIP understand whether the model is calibrated to what is being observed in national data.

Dr. Rein replied that the QALY decrements are associated with the duration of the symptoms or outcomes. For symptomatic disease, it is related to varying durations of disease ranging from very short for mildly symptomatic anicteric disease to longer for fulminant disease with hospitalization. For deaths from HepA, it includes full losses of QALYs for each year after death. They have and can provide the results for the number of hospitalizations, liver transplants, and deaths averted. He was not certain whether they retained all of these from each age cohort simulation, but they have the output from each so they can pull those and put them together.

Dr. Reingold clarified that he chaired the SAGE WG that recommended giving 1 dose if 2 cannot be afforded. SAGE had a tolerance for that, but this is licensed as a 2-dose vaccine in the US. Therefore, he did not think ACIP was contemplating recommending a 1-dose schedule. However, there is very good evidence that 1 dose offers a high-level of protection. The interest is in making sure that it is modeled appropriately.

It appeared to Ms. Pellegrini that the spacing on the doses would allow for them to be administered at the 12- and 13-year old child well visits, which would reduce the burden on families. When accounting for administrative costs, she wondered whether they were reduced for both doses or just the first.

Dr. Rein recalled that they had one administration cost that was cut in half.

Dr. Moore thought administratively, it could be given with both doses of human papillomavirus (HPV) vaccine. Since the Healthy People 2020 goal is 0.3/100,000 or less and there is a lot of state-to-state variability, she would be interested in seeing how that correlates with states that do have mandates and, therefore, are in less need of catch-up because they have a consistently high level of coverage. It would be interesting to see whether the states that have mandates already have achieved the Health People 2020 coverage goal.

Dr. Hunter observed that based on slide 22 titled “Long-Term Protection,” in Dr. Nelson’s presentation, it seemed like there would not be much of a decline in immunity among the immunized younger cohort. This shows that anti-HAV antibodies have been shown to persist at least 20 years in adults who received 3 doses of inactivate vaccine as children, and detectable antibodies have persisted for 40 years or longer in mathematical models. However, it looked like there might be a decline based on Slide 9 of Dr. Rein’s presentation. There seemed to be an adjustment in the QALY in the cost-effectiveness for some decline in vaccine-acquired immunity by year based on recent data, and he wondered about the magnitude.

Dr. Rein responded that there is loss of immunity that occurs more rapidly at first and then more gradually over time. It is a complicated 3-point spline equation in which there is greater loss of immunity in earlier ages, then there is a slower loss of immunity between the next two points, followed by an even slower loss of immunity after that. While he did not have the results with him, he will share that with ACIP. This was based on new data collected in Alaska on a cohort of individuals who were vaccinated 20 years ago and then observed over time.

Dr. Hunter clarified that he was trying to understand the 3 general cohorts consisting of those who are younger who have been immunized, those who have not been immunized and have not been exposed much to natural disease (20 to 50 years of age), and those over 50 who have natural disease. He wondered whether the immunized cohort would have less persistent immunity than the natural immunity group, and if there would be an ongoing issue of aging cohorts having less immunity.

Dr. Rein replied that this is an ongoing and unknown question that cannot yet be answered. This is all speculation and it is not clear what the actual answer is. There has been speculation that with severity of disease after infection or level of protection even after antibody titer falls below detectable levels, some level of protection persists.

Dr. Wharton added that based on the NIS, even if the second dose is given exactly at 24 months, some interviews are conducted at 19 months of age. So, the ability of the survey to precisely estimate 2-dose coverage is limited.

Updated ACIP Routine Recommendations for Use of HepA Vaccine

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In terms of HepA vaccine considerations, Dr. Nelson indicated that the Hepatitis Vaccines WG has deliberated on the following topics:

- ❑ HepA catch-up vaccination
- ❑ Vaccination of pregnant women
- ❑ Vaccination of persons with CLD
- ❑ Vaccination of persons in institutions for persons with developmental disabilities
- ❑ PEP

In the future, the WG plans to take into consideration vaccination of HIV and immunocompromised persons.

Despite the cost-effectiveness results, the WG proposes updating the permissive catch-up language to a routine catch-up recommendation for children 2 through 18 years of age in order to improve population protection from HAV and vaccine uptake in children aged greater than 2 years. Decreasing HepA incidence in the US and reduced exposure to HAV has resulted in decreasing anti-HAV seroprevalence among adults, and an increasing proportion of susceptible adults. Vaccinating adolescents will lead to increased adult protection quicker than waiting for the universal vaccine cohort to reach adulthood. Of note, the cohort of children vaccinated in 2006, when HepA vaccine was routinely recommended for all children 12 through 23 months of age will reach adolescence (age 13) in 2018 and adulthood (age 19) in 2024. National vaccination coverage among adolescents 13 through 17 years in 2013 for 1 and ≥2 doses of HepA vaccine was 62.5% and 51.0%, respectively. The current and draft proposed recommendations are compared in the following table:

Hepatitis A Catch-Up Vaccination	
Current Recommendation (2006)	**Draft Proposed Recommendation**
• Recommended for use at age 12-23 months in all states • Continue existing vaccination programs for ages 2-18 years • Consider catch-up vaccination in outbreaks and areas with increasing disease rates • Any person wishing to obtain immunity	• Recommended for all children age 12-23 months • Children and adolescents age 2-18 years who have not previously received hepatitis A vaccine should be vaccinated routinely at any age with an appropriate dose and schedule • [OR Recommended for all children aged 12 months to 18 years] • Consider adult catch-up vaccination in outbreaks and areas with increasing disease rates • Any person wishing to obtain immunity

The 2006 pregnancy recommendation states that the safety of HepA vaccination during pregnancy has not been determined; however, because HepA vaccine is produced from inactivated HAV, the theoretic risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A infection in pregnant women who might be at high risk for exposure to HAV. However, since those recommendations more data are available on vaccination during pregnancy. The 2017 Immunization Schedule states that HepA vaccines during pregnancy should be recommended for adults with additional medical conditions or other indications, meaning pregnant women who are at risk for HAV infection. The Moro et al study conducted in 2014 searched VAERS for AEs reports in pregnant women who received HepA or HepAB vaccines from January 1, 1996 to April 5, 2013. VAERS received 139 reports of AEs in pregnant women of which 7 (5.0%) were serious. No maternal or infant deaths were identified, and 65 (46.8%) did not describe any AEs. The conclusion of the study was that VAERS reports did not identify any concerning pattern of AEs in pregnant women or their infants following maternal HepA or HepAB immunizations during pregnancy. The current and draft recommendations are compared in the following table:

Pregnancy	
Current Recommendation (2006)	**Draft Proposed Recommendation**
• The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated HAV, the theoretic risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who might be at high risk for exposure to HAV.	• Pregnant women with any of the conditions that increase the risk of either acquiring or having a severe outcome from HAV infection (e.g., having chronic liver disease, clotting-factor disorders, travelers, users of injection and non-injection drugs, and women who work with nonhuman primates) should be vaccinated during pregnancy if not previously vaccinated. • Pregnant women at risk for HAV infection during pregnancy should also be counseled concerning all options to prevent HAV infection.

Regarding CLD, the WG is interested in changing the language to make it parallel with the HepB vaccine statement. The current and draft proposed recommendations for CLD are compared in the following table:

Chronic Liver Disease	
Current Recommendation (2006)	**Draft Proposed Recommendation**
• Susceptible persons with chronic liver disease should be vaccinated. Available data do not indicate a need for routine vaccination of persons with chronic HBV or HCV infections without evidence of chronic liver disease. Susceptible persons who are either awaiting or have received liver transplants should be vaccinated	• Epidemiology: Persons with chronic liver disease (e.g., cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis) are not at increased risk for HAV infection unless they have fecal-oral exposure to hepatitis A. However, concurrent acute HAV infection may increase the risk for more severe liver disease. • Vaccination: Vaccination for persons with chronic liver disease (including, but not limited to, those with hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and liver function tests >2 times the upper limit of normal). Susceptible persons who are either awaiting or have received liver transplants.

Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities. As fewer children have been institutionalized and as conditions in institutions have improved, the incidence and prevalence of HAV infection have decreased, although outbreaks can occur in these settings.

A study by Bohn et al published in 2015 described a HepA outbreak in group homes in Michigan in 2013 in which there were 8 cases among 5 group homes. There were 261 contacts who warranted PEP, and 225 (86.2%) were confirmed to have received Ig or HepA vaccine or both during this outbreak. Since disabled adults are now typically cared for in group homes, where residents live in close quarters, and residents are often incontinent and non-verbal, this is a population in which vaccination could be beneficial [Bohm SR, Berger KW, Hackert PB, Renas R, Brunette S, Parker N, Padro C, Hocking A, Hedemark M, Edwards R, Bush RL, Khudyakov Y, Nelson NP, Teshale EH; Centers for Disease Control and Prevention (CDC). Hepatitis A outbreak among adults with developmental disabilities in group homes--Michigan, 2013. MMWR Morb Mortal Wkly Rep. 2015 Feb 20;64(6):148-52.

A study by Lim et al in 2013 described a HepA hepatitis A outbreak in a residential facility for the disabled in South Korea that occurred in 2011. There were 16 cases who had contact with 51 residents and 31 teachers and staff members. The initial source of infection was not identified; however, the possibility that the HAV outbreak was started by person-to-person spread is high, and volunteers were suspected to be the most likely infection source [Lim HS, Choi K, Lee S. Epidemiological investigation of an outbreak of hepatitis A at a residential facility for the disabled, 2011. J Prev Med Public Health. 2013 Mar;46(2):62-73. doi: 10.3961/ jpmph.2013. 46.2.62. Epub 2013 Mar 28.

The current recommendations and draft proposed recommendations based on these studies for settings providing services to children and adults are compared in the following table:

Settings Providing Services to Children and Adults	
Current Recommendation (2006)	**Draft Proposed Recommendation**
• Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities. As fewer children have been institutionalized and as conditions in institutions have improved, the incidence and prevalence of HAV infection have decreased, although outbreaks can occur in these settings.	• Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities. Now, persons with developmental disabilities typically live in group homes or residential facilities. Outbreaks can occur in these settings. • All residents and health care personnel should be offered hepatitis A vaccination if they have not previously completed vaccination.

Dr. Nelson invited ACIP members to discuss and provide their opinions on the following:

- ❑ Routine hepatitis A catch-up vaccination
- ❑ Vaccination of pregnant women with any of the conditions that increase the risk of either acquiring or having a severe outcome from HAV infection
- ❑ Vaccination of persons with chronic liver disease
- ❑ Vaccination of persons in institutions for persons with developmental disabilities

Discussion Points

Regarding the pregnancy issue, Dr. Belongia noted that primarily a VAERS analysis was cited that assessed 139 reports and there was a suggestion that the WG would be interested in a recommendation for women who are considered at risk for complications. He asked whether the WG considered parsing that recommendation into first, second, and third trimester. Safety data in general for vaccines are much harder to acquire for the first trimester than for the second and third. Given that in any 9-month period in a disease with a very low incidence overall, the incidence of getting HAV infection in that period is pretty low. He asked what the thinking was on this in terms of recommending vaccination throughout pregnancy for women at risk, versus deferring it, versus administering it only in the second and third trimester given the lack of data.

Given the lack of data, Dr. Nelson indicated that the WG did not engage in extensive deliberations on administering the vaccine. It was thought that it would be given in the second or third trimester, but that is still up for discussion.

Dr. Kempe inquired as to whether this issue has been examined in the VSD, which would offer a lot more granularity and better data.

Dr. Nelson replied that an assessment of VSD data on this issue is in progress.

Dr. Messonnier suggested that the WG provide more context during the October 2017 meeting regarding the burden of disease of HepA in pregnancy, the number of cases that are potentially preventable, and other outcomes that are potentially preventable with vaccination.

Dr. Nelson indicated that one of the primary considerations of the WG was concern about complications during pregnancy if a mother was to acquire HepA disease during the pregnancy. There are a couple of studies she can present that document this issue.

In response to the routine catch-up recommendation, Ms. Finley (AIM) noted that only 21 states have mandates. Of the states with mandates, 3 or 4 have two times the national goal of hepatitis incidence. Therefore, it may be necessary to further consider how to increase the rates.

Dr. Bennett thought that analysis would be helpful.

Dr. Moore inquired as to how this discussion fits with any consideration of PEP during pregnancy.

Dr. Nelson indicated that this would be addressed in the next presentation by Dr. Link-Gelles.

Dr. Hunter noted that the current catch-up recommendation was somewhat equivalent to a Category B recommendation as he read it, which should mean that the Vaccines For Children (VFC) program would cover it, and if the new draft language recommendation would shift it to a Category A recommendation.

Dr. Messonnier clarified that the draft language had not yet been through the Grading of Recommendation Assessment, Development and Evaluation (GRADE) process. There will be a presentation in October 2017 or February 2018, depending upon how things move, on the GRADE findings on the evidence for a catch-up campaign. The Category B recommendation is covered in the VFC program, but the goal is to move from a permissive to a proactive recommendation.

Dr. Lee inquired as to whether it would be helpful to expand the recommendation for persons with developmental disabilities to residential facilities in order to be broader.

Regarding the catch-up recommendation, Dr. Atmar expressed interest in knowing what the WG thought of the cost-effective analysis, particularly given the limitations of the analysis that were discussed.

Dr. Reingold thought it was fair to say that it turns out to be quite expensive to prevent these cases, and the WG felt that ACIP should consider that issue as a full committee. There were mixed views among WG members regarding whether this would be a good use of limited funds.

Dr. Whitley-Williams (NMA) requested that the WG consider any data regarding the simultaneous use of or the timing of giving the HepA vaccine to pregnant women with Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) and Inactivated Influenza Vaccine (IIV).

Regarding the catch-up issue, Dr. Kempe requested more information about the WG's considerations of different groups. Essentially, the data presented pointed out increased hospitalizations and costs as people age. The cost analysis did not take into account herd immunity presumably because most of the disease is being caused by international contamination of food, so there is a disconnect. She wondered whether the WG considered what the relative cost would be of vaccinating those at highest risk of bad disease, such as the elderly. While she understood the rationale in wanting to get adults vaccinated in the future, she wondered about how to deal with the current problem.

Dr. Thompson (NVAC) asked whether there would be an opportunity to perform some additional modeling that would integrate cost-effectiveness and transmission modeling in a way that might enable ACIP to assess the herd immunity benefits. The fact that the draft catch-up recommendations begin with "Despite the cost-effectiveness results . . ." sounded to her like the WG was having trouble reconciling these issues. She suggested assessing other specific populations with the cost-effectiveness and economic analysis.

Dr. Belongia noted that the best-case scenario in the analysis presented during this session, $189,000 per QALY gained was thought to be optimal at age 12 years. He wondered if there were examples of other catch-up recommendations that are comparable in terms of the cost per QALY.

Given the time, Dr. Messonnier invited the members to submit additional suggestions and requests to be worked on between now and the October 2017 and February 2018 meetings.

Updated Recommendations for Use of HepA Vaccine and Immune Globulin for PEP and for International Travelers

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Dr. Link-Gelles presented draft updates to the 2007 ACIP recommendations for PEP for HepA and prevention of HepA in international travelers. She explained the current ACIP recommendations for PEP, discussed the current context and ACIP Hepatitis Vaccine WG process, presented draft updates to the recommendations for PEP, presented proposed updates for international travelers, and proposed some specific questions for ACIP member input.

According to the 2007 ACIP recommendations, HepA vaccine or Ig is recommended for PEP in a variety of circumstances. First, PEP is recommended for previously unvaccinated persons who have close personal contact with persons who have serologically confirmed HAV infection including household and sexual contacts, and persons who have shared illicit drugs. Additionally, persons with other types of ongoing, close personal contact can be considered for PEP.

If HepA is recognized in children or employees of child care centers, PEP should be administered to unvaccinated staff and attendees. In outbreak settings, household members of children attending child care in diapers should also be vaccinated. In common-source outbreaks, food handlers at an institution where another food handler has been diagnosed with HepA should be vaccinated, as should patrons after exposure to a food handler who also had poor hygiene, but only if the patron can be administered PEP within 2 weeks of exposure. Finally, PEP is recommended in schools, hospitals, and work settings only if an epidemiologic investigation indicates transmission at the facility. Hospital staff do not need to receive PEP after treating a person with HAV infection, as long as staff used appropriate personal protective equipment (PPE) [Advisory Committee on Immunization Practices, Centers for Disease Control & Prevention. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2007;56:1080-1084].

According to the 2007 ACIP recommendations, the type of PEP depends on age and immune status. Children under 12 months of age, immunocompromised individuals, those with CLD, and those with a vaccine contraindication should receive immunoglobulin, or Ig, only. Healthy individuals 12 months to 40 years receive vaccine only, and adults over 40 years, regardless of immune status, are recommended to receive Ig only, with vaccine as a back-up if Ig cannot be obtained. All PEP should be administered as soon as possible after exposure, ideally within 2 weeks [*MMWR*. October 19, 2007:mmwr/preview/mmwrhtml/mm5641a3.htm].

For the past 6 months, the ACIP Hepatitis Vaccine WG has been focused on updating the existing HepA recommendations. Discussion led to a consensus that concerns about the use of Ig for PEP require updated recommendations. There are a number of concerns about the current recommendations. First, Ig may have decreased potency in settings such as the US with low HepA prevalence[1,2]. As rates of HepA have decreased in developed countries where HepA vaccine has been introduced, so too has the prevalence of HAV antibodies in plasma donations, leading to decreased potency of Ig. A recent study from CDC and the Food and Drug Administration (FDA) comparing 9 intramuscular Ig preparations from developed countries yielded low anti-HAV Ig potencies. Even in lots that achieved protective levels of IgG, modeling indicated that immunity would wane before the expected 3 months [[1]Zaaijer HL, et al. Hepatitis A antibody titers after infection and immunization: implications for passive and active immunization. *J Med Virol*. 1993;40(1):22-27; [2] Tejada-Strop A, et al. Evaluation of Potencies of Immune Globulin Products Against Hepatitis A. *JAMA Intern Med*. 2017;177(3):430-432].

Second, reports from state and local partners during 3 recent, large outbreaks in the US indicated limited availability of Ig for use in outbreak settings, mostly due to health departments and providers not keeping Ig in stock. Control of these outbreaks has therefore relied primarily on vaccine, regardless of the age or immune status of exposed individuals. Combined with identification and recall of the source product, all 3 outbreaks were ended, despite limited availability or use of Ig. Additionally, a recent report from New York City (NYC) on the handling of hepatitis A cases in food handlers indicated logistical concerns with administration of Ig, particularly during a mass exposure. Finally, Ig has a shorter duration of protection than vaccine, so administering Ig alone to persons for whom vaccine is not contraindicated represents a missed opportunity to provide long-term immunity and increase herd protection.

The 2007 ACIP recommendations were largely based on work done by Victor et al in Kazakhstan[1]. The study, published in 2007, randomized household and day-care contacts 2 to 40 years of age to receive either Ig or hepatitis A vaccine within 14 days of exposure and then followed individuals for 56 days to determine effectiveness. Despite slightly higher rates of disease in vaccinated individuals, vaccine was found to be non-inferior to Ig. With modeling, the authors showed that, assuming 90% efficacy of Ig, vaccine efficacy (VE) was estimated to be 86%. If IG efficacy was assumed to be 80%, vaccine efficacy (VE) was estimated at 73%. Risk of HepA in the vaccine group was never greater than 1.5% above that in the Ig group. No studies have been conducted to assess differences between Ig and vaccine or to explore effectiveness of Ig alone in discrete age groups over 40 years. With this in mind, a systematic review was conducted of available data on HepA vaccine in adults over age 40[2] [[1] Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007;357:1685-1694; [2]Link-Gelles, Hofmeister, Nelson, Vaccine (in preparation)].

In the Link-Gelles et al study, existing data were reviewed on the use of vaccine versus Ig for adults over 40 years of age, including a look at existing guidelines in other countries. PubMed® and Excerpta Medica Database® (EMBASE®) were searched for articles and guidelines published since 1992 and included only articles with data on HAVRIX® or VAQTA® administered to adults over 40 years of age. Articles were included with both immunogenicity and disease endpoints, as well as surveillance data and case studies. For immunogenicity data, only results within 2 weeks of vaccine or Ig administration were included, which is the window in which PEP would need to be administered to be effective. Each abstract was read by 2 reviewers and consensus was obtained on inclusion or exclusion of the abstract. Results of this systematic review are pending publication and will undergo a GRADE review in the coming months.

The search yielded 782 abstracts from PubMed® and 257 abstracts from EMBASE®. Of these, 936 abstracts were excluded, primarily because they focused on children or younger adults or did not report data less than 28 days post-vaccination, which is needed for assessing use for PEP. More than half of the articles focused on vaccine introduction, including cost-effectiveness of routine vaccine, serosurveys before and after vaccine introduction, and opinion pieces that did not provide the necessary data. The full articles were reviewed for the remaining 103 abstracts, of which 8 were retained and 2 additional articles were added from searching references of the retained articles. Of these studies, 4 directly compared HepA vaccine protection in adults over the age of 40 at 15 days and 30 days after the first dose of vaccine. However, it should be noted that there were some differences in the studies. First, some studies used Havrix® 1440 ELU, which is currently licensed in the US for adults. Other studies used different variations of VAQTA®, including 25, 50, and 100-unit formulations. In the US, the 50-unit formulation is licensed for adults. Second, because no absolute protective level has been defined, the lower limit of detection of the particular assay being used has generally been considered the protective level. In the studies presented, some used anti-HAV ≥ 10 mIU/mL as the cutoff for seroprotection and some used anti-HAV ≥ 20 mIU/mL, which is the common standard today.

Briem et al compared adults aged 20 through 39 years and 40 through 62 years at 15 and 30 days after the first dose in 1994 as part of an observational cohort study. Seroprotection in this study was considered ≥20 mIU per mL. They found that at 15 days, 90% of those in the younger age group had responded, compared to 77% in the older age group. By 30 days, 97% of individuals in both groups had responded [Briem H, Safary A. Immunogenicity and safety in adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. J *Med Virol* 1994;44:443-445].

Reuman et al was also an observational cohort study that looked at responses to a 25-unit dose of VAQTA® in adults less than 40 years of age compared with adults greater than or equal to 40 years of age and found, as with Briem, that response was better in younger adults, although the cutoff for seroprotection in this study was anti-HAV ≥ 10 mIU/mL versus ≥ 20 mIU/mL in Briem. Reuman also provided geometric mean titers (GMTs), which is a measure of average HAV antibodies. However, it should be noted that the 25-unit dose of VAQTA used in this study is half the dose that is licensed in the US for adults [Reuman PD, Kubilis P, Hurni W, Brown L, Nalin D. The effect of age and weight on the response to formalin inactivated, alum-adjuvanted hepatitis A vaccine in healthy adults. *Vaccine* 1997;15:1157-1161. NOTE: 4-week seroprotection percentages and all GMTs include only individuals who were not revaccinated at 2 weeks].

In Nelson et al, the authors reanalyzed data from a randomized trial published in 2000 by Williams et al that did not include results by age. In Nelson, the results were reported in 3 age groups and showed a similar trend to previous studies, with the youngest age group, those 40 through 49 years of age, having the best response. Although the sample size is small, especially in the oldest age category, it should be noted that this is the only study that included discrete age groups over 40 years [Nelson NP, Murphy TV, McMahon BJ. Hepatitis A vaccination for post-exposure prophylaxis in persons aged 40 years and older. *Vaccine* 2014;32:2939.

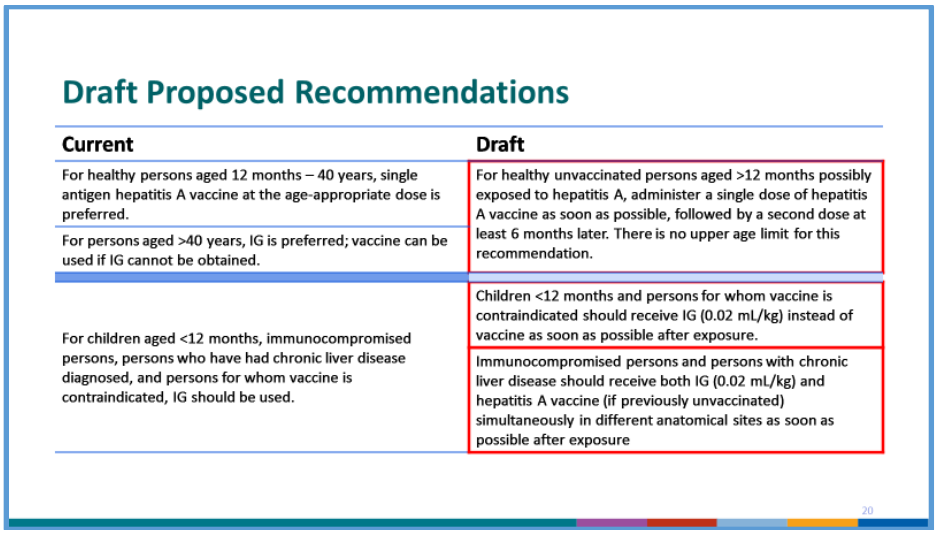
Van Der Meeren and colleagues in 2015 did a retrospective pooled analysis of randomized trial data and compared 20 through 30 years olds with individuals 40 and over and found relatively high seroprotection in both age groups 15 days after the first dose, with almost 100% achieving protective antibody levels by 30 days. Geometric mean concentrations (GMCs) were higher in both groups than in other studies [Van Der Meeren O, Crasta P, de Ridder M. A retrospective pooled analysis assessing the effect of age on the immunogenicity of Havrix in healthy adults. *Hum Vaccin Immunother* 2015;11:1729-1734].

The remaining studies included in the systematic review did not directly compare age groups or did not provide detailed results by age. In general, age was found to be significantly associated with response to vaccine. Three studies looked at surveillance or post-outbreak data, including retrospective chart reviews, in which case contacts were vaccinated[1,2,3]. Very few vaccine failures were identified in adults over 40 years of age[1,2], but little additional information on timing of vaccine administration was provided. Finally, one study looked at 3 VAQTA® formulations, 25 units, 50 units, and 100 units, and found a clear dose response relationship. Of adults who received 50 units, the currently licensed dose in the US, 46% had seroconverted by 2 weeks post-vaccine and 89% had seroconverted by 4 weeks[4]. No studies were identified which directly compared vaccine and Ig in adults over 40 years for use as PEP [[1] Whelan J, Sonder GJ, Bovee L, Speksnijder A, van den Hoek A. Evaluation of hepatitis A vaccine in post-exposure prophylaxis, The Netherlands, 2004-2012. PLoS One 2013;8:e78914; [2] Parron I, Planas C, Godoy P, Manzanares-Laya S, Martinez A, Sala MR, Manuel S, et al. Effectiveness of hepatitis A vaccination as post-exposure prophylaxis. Hum Vaccin Immunother 2016:0; [3] Freeman E, Lawrence G, McAnulty J, Tobin S, MacIntyre CR, Torvaldsen S. Field effectiveness of hepatitis A vaccine and uptake of post exposure prophylaxis following a change to the Australian guidelines. Vaccine 2014;32:5509-5513; and [4] Bertino JS, Jr., Thoelen S, VanDamme P, Bryan JP, Becherer PR, Frey S, Hayden FG, et al. A dose response study of hepatitis A vaccine in healthy adults who are > or = 30 years old and weigh > or = 77 kg. J Infect Dis 1998;178:1181-1184].

In addition to a literature review, the WG reviewed current HepA PEP recommendations in other countries. Countries generally agree on use of vaccine for PEP in healthy adults 1 through 40 years of age. Likewise, there is general agreement that Ig, with or without vaccine, is ideal for immunocompromised individuals and those with chronic liver disease. However, the US and Israel are the only 2 countries identified which recommend Ig alone for healthy individuals over 40 years of age.

To summarize, there are a number of potential benefits of vaccine over Ig for PEP. First, vaccine provides long-term protection, which Ig does not. Therefore, vaccinating individuals in the context of an outbreak helps boost herd protection. Second, while local health departments and many provider offices have ready supplies of vaccine, reports from recent outbreak investigations to CDC indicate that Ig is frequently not kept in stock, leading to potential delays in administration compared to vaccine. Additionally, switching to vaccine would bring the US in line with most other countries. Finally, it should be noted that vaccine (HAVRIX®/VAQTA®: VFC $26/$28; Private sector $64/$67) and Ig ($75 for 2 mL single dose vial) are very similar in price depending upon the Ig dosage required for an individual.

With all of this in mind, the WG's current draft recommendations focus on vaccine wherever possible. The following draft recommendations are not exact wording, but summarize the current wording:



Draft Proposed Recommendations

Current	Draft
For healthy persons aged 12 months – 40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred.	For healthy unvaccinated persons aged >12 months possibly exposed to hepatitis A, administer a single dose of hepatitis A vaccine as soon as possible, followed by a second dose at least 6 months later. There is no upper age limit for this recommendation.
For persons aged >40 years, IG is preferred; vaccine can be used if IG cannot be obtained.	
For children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.	Children <12 months and persons for whom vaccine is contraindicated should receive IG (0.02 mL/kg) instead of vaccine as soon as possible after exposure.
	Immunocompromised persons and persons with chronic liver disease should receive both IG (0.02 mL/kg) and hepatitis A vaccine (if previously unvaccinated) simultaneously in different anatomical sites as soon as possible after exposure

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Specifically, the draft proposes changing the recommendation for healthy adults over the age of 40 from Ig, as the preferred method for PEP, to vaccine as the preferred method. Children under 12 months of age and persons for whom vaccine is contraindicated would continue to be recommended to receive Ig as soon as possible after exposure. Finally, immunocompromised persons, who were previously recommended to receive Ig alone, would now be recommended to receive both Ig and HepA vaccine simultaneously, if previously unvaccinated.

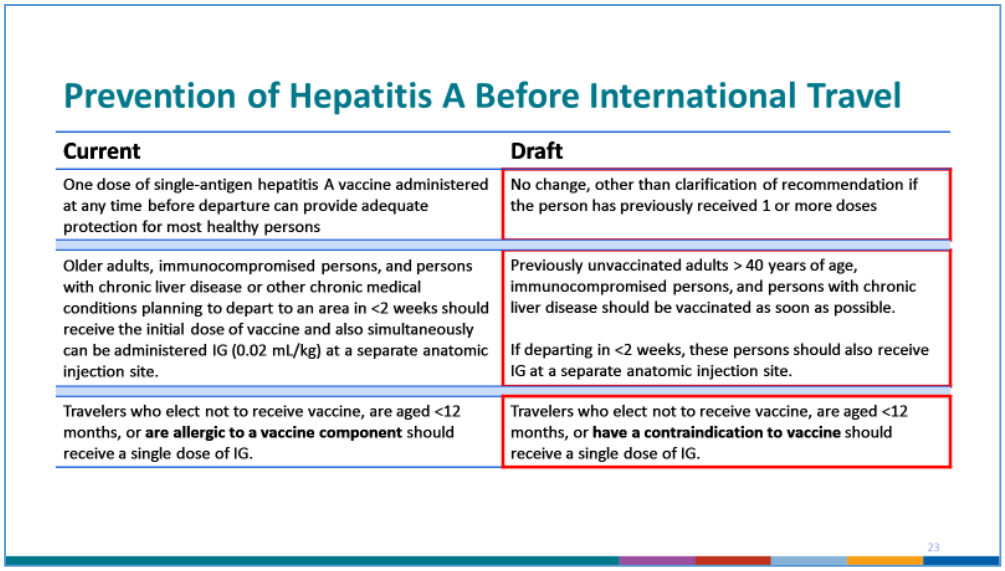
Under the draft recommendations, Ig alone would be recommended only for infants and those with a vaccine contraindication. Persons with CLD and immunocompromised individuals would be recommended to receive vaccine and Ig, including persons with any of the following:

- ❑ Congenital or acquired immunodeficiency
- ❑ HIV/AIDS
- ❑ Chronic renal failure/undergoing hemodialysis
- ❑ Receipt of solid organ, bone marrow, or stem cell transplants
- ❑ Iatrogenic immunosuppression
- ❑ A contraindication for HepA vaccine
- ❑ Those otherwise less capable of developing a normal response to immunization

As was previously mentioned, inclusion of persons with chronic liver disease is an ongoing WG discussion.

Under the current guidelines, there are no specific pregnancy-related recommendations for HepA PEP and the vaccine has not been widely tested in pregnant women, although the theoretical risk is low. The WG discussed a number of issues relating to HepA and pregnancy. First, an additional study of HepA vaccine safety during pregnancy has been published since the 2006 guidelines and found no pattern of AE in pregnant women or their infants following vaccination during pregnancy. Second, the WG discussed a review published in 2015 that found that generally, infants born to mothers with HepA infection are healthy, with rare exceptions. However, the review also found that while HAV infection during pregnancy is generally not associated with serious outcomes, there is some association between infection and preterm labor, placental abruption, and premature rupture of membranes. There does not appear to be an increased risk of mortality for either the mother or baby associated with HAV infection during pregnancy. Third, the workgroup discussed adding a specific recommendation for vaccinating pregnant women at high risk of HAV infection, including PEP. Finally, the workgroup discussed the potential for confusion if both Ig and vaccine are recommended for pregnant women given that for other inactivated vaccines, ACIP generally recommends vaccine only for pregnant women, the same as for non-pregnant individuals. At this time, the WG had not included pregnancy as an indication for Ig for PEP.

Regarding draft recommendations for prevention of HAV infection before international travel, the current recommendation for susceptible persons traveling to countries with intermediate or high HepA endemicity is to receive hepatitis A vaccine or Ig. Under the proposed draft recommendations, no substantial changes would be made for healthy persons greater than 12 months. HepA vaccine would continue to be recommended, with clarification added for individuals who have previously received one or more doses to complete the series. Currently for older adults, immunocompromised persons, and persons with chronic liver disease, vaccine is recommended, with a permissive recommendation for Ig if the individual is departing in less than 2 weeks. This permissive recommendation has resulted in some confusion, with CDC subject matter experts (SMEs) receiving numerous inquiries from providers. Therefore, the WG's draft proposal includes some clarification. Previously unvaccinated adults over 40 years of age, immunocompromised persons, and persons with chronic liver disease should be vaccinated as soon as possible. If departing in less than 2 weeks, these persons should also receive Ig at a separate anatomic injection site. Finally, the recommendation for travelers who elect not to receive vaccine will be revised slightly to align the wording with other parts of the recommendation as shown here:



Prevention of Hepatitis A Before International Travel

Current	Draft
One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons	No change, other than clarification of recommendation if the person has previously received 1 or more doses
Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in <2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site.	Previously unvaccinated adults > 40 years of age, immunocompromised persons, and persons with chronic liver disease should be vaccinated as soon as possible. If departing in <2 weeks, these persons should also receive IG at a separate anatomic injection site.
Travelers who elect not to receive vaccine, are aged <12 months, or **are allergic to a vaccine component** should receive a single dose of IG.	Travelers who elect not to receive vaccine, are aged <12 months, or **have a contraindication to vaccine** should receive a single dose of IG.

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In addition to general discussion of PEP and international travel, the WG posed the following specific questions for ACIP members:

- Based on the evidence presented, what are ACIP members' opinions on the recommendation for PEP for healthy individuals > 40 years? Are there differences in age groups over 40?

- Should pregnancy be considered an indication for administration of both Ig and HepA vaccine for PEP or is vaccine alone enough?

Discussion Points

Dr. Moore noted that practically, Ig is usually not in stock in health departments when recommended and it has to be ordered. In the interest of time, vaccine is always on hand and a dose of vaccine is typically given because it can be given right then. Often when someone is in need of PEP, they are at the end of the 2-week window. Since time is of the essence, vaccine is given while awaiting Ig and Ig is given as soon as it arrives as long as it is within the 2-week window for those who really need it because of health conditions. She asked whether that is okay since doing this simultaneously was mentioned. Because Ig is usually not in stock, simultaneous administration is often a challenge.

Dr. Nelson said as far as she knows, it is okay to do that. The wording can be clarified that indicate that Ig should be given as soon as it is available.

Dr. Moore asked why a second dose is recommended, noting that the PEP recommendation mentions in the first category giving a first dose of vaccine and then a second dose at least 6 months later. However, the second dose would not be essential for PEP. It should just state "if that person remains at risk or is in a category for whom full HepA immunization is recommended," because otherwise if they have no other risk factors a single dose is all that is needed for PEP.

Dr. Link-Gelles noted that as discussed earlier, the vaccine is licensed on a 2-dose schedule, recommendations would generally be drafted such that a person would have a first dose for PEP, but then would complete the licensed schedule. There certainly could be permissive wording to encourage the first dose as being the most important for PEP.

Dr. Moore emphasized the importance of making it clear that the second dose has nothing to do with PEP, because that raises an issue of affordability in terms of responding to an outbreak. That would be a challenge.

Dr. Romero inquired as to whether ACIP should consider increasing the prophylactic dose of Ig given the low levels of antibody found in the American supply.

Regarding the use of HepA vaccination during international travel, Dr. Fryhofer (ACP) quoted a paragraph written by some of the authors who write the Yellow Book. This is an excerpt from "Medical Considerations before International Travel" published in the *New England Journal of Medicine* (*NEJM*) pertaining to HepA vaccine, "A single dose of hepatitis A vaccine given any time before travel, even on the way to the airport, provides more than 94% seroprotection."

Dr. Moore strongly questioned the justification for the draft proposed recommendation that people over 40 years of age would need both Ig and vaccine before international travel. Just because someone is traveling internationally does not mean they already have been exposed to HepA. In general, someone over 40 going to the airport being told to get the vaccine is not the same thing as PEP in which someone already has been exposed and immediate protection is essential.

Dr. Walter expressed confusion about what was presented in the recommendations. It seemed like they saw some data that showed decreased immunogenicity for elderly; however, the recommendations for PEP dropped the use of Ig. As mentioned, vaccine for travelers over 40 years of age included Ig. He was not certain how to reconcile all of that.

Dr. Nelson clarified that for those who are at increased risk, Ig is recommended. The concern was to provide them with long-term protection from vaccine as well as for future potential exposure.

Dr. Riley expressed gratitude to the WG for considering pregnancy, given that these conversations often leave out pregnancy. When discussion is left out about pregnancy, obstetricians and gynecologists will do nothing because everyone assumes that it is unsafe. If there is no comment at all, the assumption will be that it is unsafe and pregnant women who need the vaccine will not get it. In an outbreak setting, a bad HAV infection during pregnancy would not be in the best interest of the mother or her baby. An increase in her risk for pre-term labor probably would be the most common risk.

From a local public health perspective in terms of responding to these types of events, Dr. Zahn (NACCHO) reported that there are two types of events that require PEP. One example would be for a batch of tuna that has been found to be infected, which is a risk even if no one has gotten sick yet. Another example would be of someone who has HepA and someone in their household is exposed. The nature of those exposures is different in terms of the numbers of people exposed and the likelihood of the risk. California has told their local health departments that for those 40 through 59 years of age, either vaccine or Ig may be given depending upon the situation. Functionally what happens is for someone with disease and a 55-year old wife who is not immune in the same household, that is only one person and Ig can be found. However, if

hundreds of people eat pomegranates, a lot of vaccine would be given. He is on the WG and he suggested that at some point consideration be given to the nature of exposures not being exactly the same.

Dr. Messonnier congratulated the team on Herculean effort to conduct the literature review, which represented an incredibly impressive amount of work. To ACIP and the WG, she pointed out that this is a very specific recommendation to a very narrow subset of people. Generally, clinicians in the US are not going to be called upon to interpret these recommendations. It is much more narrowly focused on outbreaks and health departments. As such, she felt like they should differentiate between an ACIP recommendation versus the implications in terms of clinical applications. ACIP cannot possibly get to the granularity of the level that health departments need to make decisions. Perhaps they could separate the recommendation and then provide guidance that would help health departments as they are trying to make strategic decisions about how to implement the recommendation.

Dr. Kimberlin (AAP Red Book) said he was puzzled because during the June 2007 ACIP meeting, the vote taken for Ig being preferred over vaccine for persons 40 years of age and older specifically said, “Ig is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of HepA.” Data have now been presented showing that vaccination is less good in older people; however, a recommendation was being proposed to change. Looking historically at how ACIP has deliberated on this in the past relative to the current set of data being presented seemed to have a disconnect.

Dr. Link-Gelles clarified that no papers were found that directly compared vaccine and Ig, so the situation is still that there are not great data comparing the two head-to-head. Everything comes anecdotally from outbreak investigations. In the interim, there have been a lot more concerns about Ig potency. There are recent analyses by FDA and CDC showing that Ig potency has declined quite a bit in the US. As Dr. Moore pointed out, there are also issues regarding the logistics, especially in terms of a mass exposure situation and getting Ig to a health department to administer to a wide group of people. She thought the WG weighed the limited evidence with the very real logistical problems of getting Ig within the 14 days during which it would need to be administered, and the reality that vaccine is almost always readily available and can be administered immediately.

Dr. Bennett thought some of the discomfort they were experiencing was due to inconsistency across the recommendations for travelers and PEP. Perhaps the WG could think through that further. Also, the question was raised about Ig potency and whether the dosage should be changed.

Regarding whether differences in age groups should be considered, Ms. Pellegrini noted that only the Nelson study had data that would allow that type of grouping. In addition, the N for the 60 through 69-year-old cohort was tiny at 9 or 10 people and that may not be enough to support a recommendation.

Influenza

Introduction

Emmanuel (Chip) Walter, MD, MPH
Chair, Influenza Work Group

Dr. Walter reminded everyone that during the February ACIP meeting there was an update on FluMist® (LAIV4), a presentation on Afluria® (IIV3) and investigation into the Southern Hemisphere 2010 AEs of febrile reactions/seizures, and a discussion of the study of Fluzone® High-Dose (HD-IIV3) among long-term care residents.

Since the February 2016 ACIP meeting, the WG has engaged in calls twice a month, during which members discussed development of 2017-2018 ACIP Influenza Statement and heard updates on influenza vaccine effectiveness and safety.

The agenda for this session included the following topics:

- ❑ Influenza Surveillance Update
- ❑ Influenza Vaccine Effectiveness Update
- ❑ End-of-Season Update: 2016-2017 Influenza Vaccine Safety Monitoring
- ❑ Flublok® Pregnancy data
- ❑ Proposed Recommendations/Vote

Influenza Surveillance Update

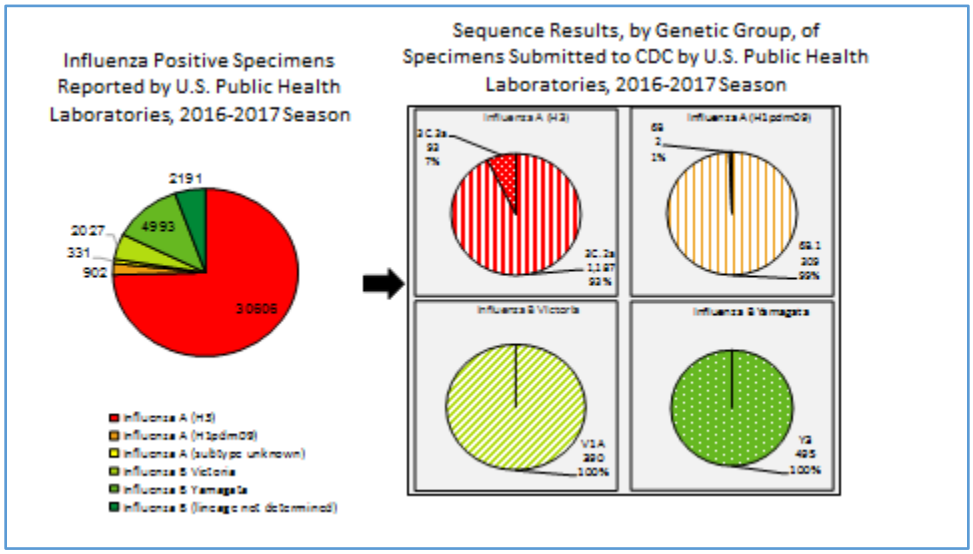
Alicia P. Budd, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Ms. Budd provided a brief update on influenza activity that occurred in the US for the 2016-2017 season. She reminded everyone that these data are preliminary and could change slightly as reports continue to come in.

Based on data reported to CDC by US Clinical Laboratories as of June 16, 2017 that include data through the week ending June 10th, testing was done on almost 900,000 specimens for the season as a whole. Of the greater than 120,000 of those specimens that were positive for influenza, 70% were influenza A viruses and 30% were influenza B viruses. Nationally, the percent of specimens testing positive for influenza peaked at approximately 24% during the 3 weeks from mid- to late-February. Regional differences were observed in timing of influenza activity across the country, with the Northwest and West (HHS Regions 8 and 10) peaking in late December, followed by the Southwest (Region 9) peaking in January, and the rest of the country peaking in February. As often occurs in influenza seasons, there was an increase in influenza B later in the season. In fact, each week since late March, influenza B viruses were reported more frequently than influenza A viruses.

To examine the virologic data in more detail, Ms. Budd presented data from the US Public Health Laboratories (PHLs) on the number of influenza positives by influenza A subtype and influenza B lineage. So far this season, PHLs have reported testing more than 85,000 specimens, of which more than 41,000 were positive for influenza. Influenza A(H3N2) was the predominant virus overall this season, accounting for 75% of all of the viruses reported by the PHLs and 97% of the influenza A viruses reported by these laboratories. These data also show the increase in influenza B activity later in the season. Overall, influenza B viruses comprised 22% of the viruses reported by PHLs. Of those viruses for which lineage information is available, 71% were Yamagata lineage and 29% were Victoria lineage viruses.

CDC performs additional genetic and antigenic characterization of a subset of the viruses submitted by the PHLs. The results of genetic characterization of nearly 2500 viruses collected in the US since October 1, 2016 are depicted in the following pie charts:



The single pie chart on the left above depicts the relative proportion of the various subtypes and lineages reported by the PHLs. On the right are pie charts showing the distribution of the genetic groups within each influenza A subtype and influenza B lineage. There was only a small amount of variability in terms of the genetic groups that were circulating this season in the US, with 93% of the H3 viruses tested belonging to the 3C.2a genetic group, 99% of the H1 pdm09 viruses belonging to the 6B.1 genetic group, and all of the B Victoria and B Yamagata viruses belonging to the V1A or Y3 genetic groups respectively.

CDC also performed antigenic characterization on more than 1800 influenza viruses collected in the US since October 1, 2016. Of the A (H1N1)pdm09, 294 of 296 (99.3%) were antigenically characterized as A/California/07/2009-like, the H1N1 component of the 2016-2017 vaccine. Of the A (H3N2), 730 of 772 (94.9%) were antigenically characterized as A/Hong Kong/4801/2014-like, the H3N2 component of the 2016-2017 vaccine. Of the B/Victoria lineage, 283 of 327 (86.5%) were antigenically characterized as B/Brisbane/60/2008-like, which is included in quadrivalent and trivalent vaccines for the 2016-2017 season. Of the B/Yamagata lineage, all 429 were antigenically characterized as B/Phuket/3073/2013-like, an influenza B virus included in the quadrivalent influenza vaccines for the 2016-2017 season. Some of the B Victoria viruses that had reduced titers against the B/Brisbane/60/2008-like virus had similar genetic changes that appear to be altering the antigenic properties of the viruses. These viruses in general have

comprised a very small proportion of the circulating viruses during this season, but CDC is continuing to monitor to see if there is any change in the prevalence of these viruses. All of the Yamagata lineage viruses tested were similar to the reference virus included in the vaccine this year.

In terms of the percentage of outpatient visits for influenza-like illness (ILI) reported by healthcare personnel (HCP) participating in the ILINet surveillance system, the weekly percent of ILI nationally was at or above the national baseline of 2.2% from mid-December through early April and peaked at 5.1% during the week ending February 11, 2017. It felt like a particularly long influenza season. This was actually borne out by the fact that this season, ILI was at or above baseline for 17 consecutive weeks. In comparison, the average over the last 15 seasons was above baseline for 13 weeks.

Through the Influenza Hospitalization Surveillance Network (FluSurv-NET), CDC has population-based surveillance for laboratory-confirmed ILI-related hospitalizations for persons hospitalized between October 1 and April 30 of each year. This season, more than 18,000 laboratory-confirmed hospitalizations were reported, resulting in a cumulative incidence for all age groups of 64.9 hospitalizations per 100,000. By age group, the cumulative rate to date is highest for persons 65 years of age and older at 290.5 hospitalizations per 100,000. Hospitalizations in this age group accounted for approximately 60% of all of the reported hospitalizations this season. The cumulative rate for the other age groups ranged from a high of 65.1 per 100,000 among adults 50 through 64 years of age to a low of 16.7 per 100,000 among children and adolescents 5 through 17 years of age.

CDC monitors pneumonia- and influenza-related mortality using data from the National Center for Health Statistics (NCHS) Mortality Surveillance System. During this season, the percent of deaths attributed to pneumonia and influenza peaked at 8.3% during the week ending January 21st and was at or above the epidemic threshold for 12 consecutive weeks beginning at the end of December and continuing until the middle of March.

CDC also monitors influenza-associated deaths in children less than 18 years of age. This year, 99 influenza-associated pediatric deaths have been reported. This is slightly more deaths than were reported during the 2015-2016 season (N=92), but fewer than were reported during the 2014-2015 (N=148) and 2013-2014 (N=111) seasons. Of the deaths this season, 64 were associated with influenza A virus infection. Of those with subtype information available, 94% were H3N2 viruses. Of the deaths this season, 34 were associated with influenza B virus infection and 1 was associated with an infection for which the type was not determined.

In summary, influenza activity during the 2016-2017 season in the US was moderate with severity indicators that were within the range of what has been observed during previous influenza A (H3N2) predominant seasons. Activity peaked nationally in February, but there were regional differences. Western Regions (HHS regions 8, 9 and 10) peaked earlier in the season between late December and mid-January. The remainder of the country (HHS regions 1-7) peaked about a month later in mid- to late-February. Influenza A(H3N2) viruses predominated overall, but influenza B viruses have been reported more frequently than influenza A viruses since late March. The majority of circulating viruses that were antigenically characterized at CDC were similar to the reference viruses included the 2016-2017 influenza vaccine.

Vaccine Effectiveness Update

Jill Ferdinands, PhD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ferdinands reviewed end-of-season estimates of 2016-2017 influenza VE from the US Flu VE Network, introduced the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), and presented preliminary 2016-17 VE estimates during this session.

The US Flu VE Network is CDC's annual study that estimates influenza vaccine effectiveness against outpatient influenza infection. The sites and principal investigators are as follows:

- Baylor Scott and White Health (Manju Gaglani)
- Centers for Disease Control and Prevention (Brendan Flannery, Alicia Fry)
- Kaiser Permanente Washington Health Research Institute (Mike Jackson, Lisa Jackson)
- Marshfield Clinic Research Institute (Ed Belongia, Huong McLean)
- University of Michigan (Arnold Monto, Emily Martin)
- University of Pittsburgh (Rick Zimmerman, Tricia Nowalk)

The network is comprised of outpatients aged 6 months or older who present with acute respiratory (ARI) illness with cough of 7 days' duration or less. It uses a test-negative case-control design, with which the odds are estimated of polymerase chain reaction (PCR)-confirmed influenza among vaccinated compared to unvaccinated enrollees. In this network, vaccination is defined as receipt of at least one dose of 2016–2017 influenza vaccine according to medical records, immunization registries, and/or self-report from patients who can provide both a date and location. The estimation of VE is calculated as 1 – adjusted odds ratio in a multivariate logistic regression model x 100%. This is adjusted for a number of confounding factors, including age, sex, race/ethnicity, self-rated general health status, days from onset to enrollment, and calendar time of illness onset.

In summary, 7205 patients were enrolled in the US Flu VE study in the 2016-2017 season. Overall, the pattern was similar to what was presented by Ms. Budd. It was a late and somewhat long season, peaking in mid-February. A little over 2000 cases occurred in the outpatient network. Of those, 67% were A/H3N2 infection, 28% were B/Yamagata, and 3% were B/Victoria.

In terms of VE observed this season, about 43% of the influenza-positive cases were vaccinated and about 54% of the influenza-negative controls were vaccinated. That resulted in an unadjusted VE of 35% and an adjusted VE of 42%, which was statistically significant with a confidence interval of 35% to 48%. VE estimates were similar for the various age groups included in this network. There were some variations by age, but a significant protective effect of the vaccine was observed in children and among those 50 through 64 years of age. Analysis of the remainder of the age groups did not show statistically significant effectiveness.

Looking at VE by subtype, the adjusted VE for all ages for A/H3N2 was significant at 34%. When stratified by age group, there was some variation with some estimates being statistically significant and others not. While there was limited A/H1N1pdm09 this season, there was enough to calculate an overall estimate for all ages combined of 54%. In terms of VE for the B lineage viruses, adjusted VE for all ages was 56% for all Influenza B, 55% for B/Yamagata, and 60% for B/Victoria.

The new platform, HAIVEN, was developed to learn more about the effectiveness of influenza vaccine against more severe influenza outcomes. This is a CDC-funded study to estimate the effectiveness of influenza vaccine specifically for prevention of influenza hospitalizations among adults. CDC has another platform that assesses hospitalizations in children, though this is not discussed during this session. The 2015-2016 season was the pilot season for the HAIVEN study, which included 7 hospitals. The 2016-2017 season included 10 hospitals and over 5000 acute care beds. The 4 enrolling sites and investigators include the following:

- ❑ Baylor Scott and White Health (Manju Gaglani)
- ❑ University of Michigan (Arnold Monto, Emily Martin)
- ❑ University of Pittsburgh (Rick Zimmerman, Fernanda Silveira, Don Middleton)
- ❑ Vanderbilt University (Keipp Talbot)

HAIVEN uses a similar design to the US Flu VE Network. Enrollees are comprised of adults aged 18 years of age and older who have been hospitalized for less than 72 hours with an ARI with cough ≤10 days duration. HAIVEN also uses the test-negative case-control design and estimates the odds of PCR-confirmed influenza among vaccinated compared to unvaccinated enrollees. The HAIVEN results presented during this session defined vaccination as receipt of at least one dose of 2016–2017 influenza vaccine 14 or more days prior to illness onset by patient or patient surrogate self-report. The analysis is similar to that of the US Flu VE Network with VE defined as 1 – adjusted odds ratio x 100% and also adjusted for a number of covariates (site, age, sex, race/ethnicity, days from onset to enrollment, calendar time of onset, number of hospitalizations in past year, frailty, and home oxygen use).

In 2016–2017, a little over 2200 patients were enrolled in the HAIVEN study. The pattern of influenza A and B enrollment was similar to that observed by the US Flu VE Network. This analysis includes data only for enrollees through April 14, 2017. However, enrollment continued through May 13, 2017. There were approximately 380 cases, which is quite lower than the number typically enrolled in a season in the US Flu VE Network. That makes stratification by certain subgroups tricky for HAIVEN. In terms of the distribution of the type of influenza infections in the HAIVEN study, approximately 70% were A/H3N2, 17% were B/Yamagata, and 4% were B/Victoria.

In terms of VE against any influenza A or B, for all ages included in this study, 62% of the influenza-positive cases were vaccinated and about 69% of the influenza-negative controls were vaccinated. That resulted in an unadjusted VE of 27% and an adjusted VE that was significant at 30%. When stratified by age groups, some of the VE estimates are less robust due to the sample size. However, a significant protective effect was observed in the oldest age group, 65 years of age and older, with a VE of 37%. Looking at the HAIVEN VE estimates by virus type among those 18 years of age and older, VE was 30% for influenza A and B, 20% for A/H3N2, and 53% for influenza B.

As mentioned earlier, one of the reasons for developing the new HAIVEN network was the interest in learning more about VE against more severe influenza outcomes and the desire to

assess these outcomes and VE against them over time similar to what is done with the outpatient network. There are data from HAIVEN from the 2015-2016 pilot season that have not previously been presented to ACIP. VE in HAIVEN during the 2015-2016 timeframe was 50%, suggesting that vaccination prevented half of influenza-associated hospitalizations among adults in that season.

CDC also is interested in understanding more about how VE against severe influenza disease relates or compares to VE among the milder influenza outcomes typically assessed in the US Flu VE network. In a direct side-by-side comparison of the VE estimates from the two networks for 2016-2017, the overall VE estimates from the inpatient and outpatient networks are similar with VE of 30% in both networks among all adults 18 years of age and over. Because HAIVEN did not enroll children, these VE estimates are restricted to adults.

In summary, vaccine reduced outpatient influenza visits by 42% for influenza A and B viruses and by 34% for influenza A/H3N2 viruses. VE was similar to previous A/H3N2 predominant seasons when vaccine was antigenically like circulating influenza viruses. Vaccine offered significant protection against influenza hospitalizations. Vaccine reduced influenza hospitalizations by 30% among all adults and by 37% among adults ≥65 years of age for influenza A and B viruses. It is important to note that these results are preliminary and may change when final datasets are available.

Discussion Points

Dr. Atmar asked whether VE information is available for trivalent versus quadrivalent vaccine for influenza B in particular.

Dr. Ferdinands replied that these data are not available yet because CDC is awaiting some final data that will provide details about vaccine type received; however, that is anticipated to come in later in the summer and will be evaluated.

Though the confidence intervals were wide, it appeared to Dr. Reingold that VE increased among people over the age of 65 compared to younger adults, which would be surprising. He wondered whether that was due to the use of higher potency vaccines, or if it mattered which vaccine people over 65 years of age received.

Dr. Ferdinands replied that there has been some suggestion regarding the 37% VE in the oldest age group that perhaps the point estimate may be somewhat higher for that age group. CDC will continue to examine this and will assess the uptake of high-dose vaccine in that age group, which potentially could be a contributing factor. However, this will not be known until more data are received on vaccine type later in the summer.

Dr. Bennett reminded everyone that this was the opposite in the outpatient setting in the US Flu VE Network.

Dr. Riley asked whether CDC has the ability to assess VE in pregnancy.

Dr. Ferdinands responded that unfortunately, the outpatient sample is small for pregnant women and is almost non-existent in the in-patient network because so few pregnant women are enrolled.

Knowing that adults do not shed virus as long as children do, Dr. Moore wondered what impact the HAIVEN data may have in terms of misclassifying people due to the 10-day window in which they may no longer be shedding virus and cannot be PCR-confirmed.

Dr. Ferdinands indicated that the case definition for HAIVEN was selected to include people who had been sick up to and including 10 days, given the smaller number of cases overall and the desire to enroll as many as possible to get as precise as possible VE estimate. However, the risk is losing accuracy on the outcome definition by doing that. A review of the literature suggested that there is not a lot of misclassification by extending out to the 10 days. Some additional analyses performed internally suggested that the bias from that in the estimates would be minimal by perhaps a couple of points at most.

Ms. Pellegrini asked whether HAIVEN can enroll pregnant women and if they anticipate expanding HAIVEN to enroll more hospitals.

Dr. Ferdinands indicated that they can enroll pregnant women, but that there are no plans at this point to expand. However, after the current 5-year study is over, this will be revaluated to determine what can be assessed with this number of hospitals.

Recognizing that an issue which would arise later is the differential efficacy in the older age group of the high-dose vaccines, Dr. Messonnier asked whether either study is robust enough in those 65 years of age and older to allow for more specific estimates around different vaccines.

Dr. Ferdinands replied that this was assessed in HAIVEN during the pilot year, which had a smaller sample size. However, there was a signal in the pilot year that high-dose had somewhat higher effectiveness. This will be considered carefully in the future.

Dr. Plotkin (Vaccine Consultant) pointed out that if they were honest about these data, the efficacy of the vaccine is only moderate. The question that arose in his mind was, “Why is that?” There is a putative correlate of protection. Generally speaking, 1:40 is considered to be an adequate response. However, the data suggest that that probably is only about 50% protective. It is known that titers wane after vaccination. He asked whether CDC could make serological measurements as well as PCR; that is, obtaining blood at the time influenza occurs to try to determine whether there is a correlate of protection whether it is hemagglutination inhibition (HAI) titer or microneutralization. This would be useful because perhaps the vaccines being used do not have sufficient antigen to elicit the type or size of responses desired over the period of the influenza outbreak. He wondered whether Dr. Belongia would like to comment on this.

Dr. Belongia agreed and emphasized that there is a need and opportunity to follow large community cohorts over multiple seasons with multiple episodes of vaccination. Studies like that were conducted in 1970s in Michigan and Seattle, but have not been conducted in any recent years to his knowledge. He thinks the virology, immunology, and vaccines have changed a lot and it is time to assess that again. However, the Flu VE Network is not really set up to do that because the investigators do not know who the people are until they present with a respiratory illness so it is not possible to identify them in advance to collect serum. It is potentially possible to collect a sample at the time people present, many of whom present within 2 to 3 days and are in the acute phase of illness.

Dr. Ferdinands added that during the pilot year and in the second year of HAIVEN, there will be the ability to collect residual clinical specimens from the patients who have been hospitalized.

Regarding the HAIVEN study, Dr. Whitley-Williams (NMA) requested that Dr. Ferdinands comment on the race and ethnicity data collected, whether there is any information on the comorbid conditions of the hospitalized patients, and whether the study hospitals are reflective of the US population.

Dr. Ferdinands replied that race and ethnicity data are collected similarly to the way in which the US Flu VE Network collects these data using the Census-based categories and self-report from the medical records. That sometimes has to be collapsed into a smaller number of categories if needed for analytic purposes. While she did not have the exact number readily available, she thought about 14% of the HAIVEN enrollees were non-white and will look it up to be certain. Data are collected on comorbid conditions in the HAIVEN study. Questions are posed about comorbid conditions and use of home oxygen and frailty in order to get at that. Data also are collected on the type of medical encounters enrollees had in the year prior to their enrollment. From that, it can be determined if they have a history of any number of chronic diseases. In this network, approximately 94% to 95% of enrollees do have a chronic condition. The 10 hospitals are located in 4 geographic sites, so it is difficult to say that this is completely representative. There is some geographic variation in influenza circulation, so that will be captured.

Dr. David Greenberg (Sanofi Pasteur) wondered if anything is known from the Flu VE Network and HAIVEN sites about what proportion of the cases and controls have received high-dose. Overall, it is about 60% nationally.

Dr. Ferdinands indicated that these data are not yet available from the 2016-2017 season on vaccine type for HIAVEN. It is known from the pilot season, 2015-2016, that about 40% of the vaccinees over 65 years of age had received high-dose vaccine. That is similar for the US Flu VE Network.

In terms of contemplating the suboptimal VE, Dr. Szilagyi requested a reminder of the extent to which there are data about vaccination in prior years and how many years this may go back in order to further explore the question regarding the potential impact of previous vaccine on VE.

Dr. Ferdinands responded that this is a tricky methodologic issue. Especially in HAIVEN in which two-thirds of enrollees are vaccinated, information is being collected about vaccination history. CDC would like to acquire at least 5 seasons' worth of vaccine information. The data quality becomes sketchier the further back it is collected, but an evaluation will be done for this first full year of enrollment to assess prior vaccination effects.

Dr. Sun (FDA) asked whether inter-center variability in the criteria for hospitalization is examined for the 10 hospitals in the 4 geographic areas.

Dr. Ferdinands replied that of the 10 hospitals, 5 or 6 are large tertiary care referral centers and the others are community hospitals. There are differences in the patient populations between those two groups. A standard case definition was used across the entire study, so each study site used exactly the same set of symptoms to determine which patients might be eligible. From that perspective, they should be fairly consistent. Perhaps there could be some differences in the types of patients who are hospitalized at the various facilities.

Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
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Dr. Shimabukuro provided the end of season updates for the 2016-2017 season influenza vaccine safety monitoring. He provided the following table of US influenza vaccine abbreviations, highlighting that high-dose trivalent and adjuvanted trivalent vaccines are approved for use in individuals 65 years of age and older, with some variability on the lower end of the age spectrum for the other vaccines:

Vaccine	Abbreviation
Trivalent inactivated influenza vaccine	IIV3
Quadrivalent inactivated influenza vaccine	IIV4
High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)	IIV3-HD
Intradermal trivalent and quadrivalent inactivated influenza vaccines	IIV3-ID IIV4-ID
Cell culture-based trivalent and quadrivalent inactivated influenza vaccine	ccIIV3 ccIIV4
Recombinant trivalent and quadrivalent inactivated influenza vaccine	RIV3 RIV4
Adjuvanted trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)	aIIV3

He reminded everyone that VAERS is a passive reporting system that is co-administered by the CDC and FDA. The strengths are that it includes national data, is good for rapid signal detection, and can detect rare AEs. The limitations include reporting bias, inconsistent data quality and completeness, and lack of an unvaccinated comparison group. Because of the limitations, whether a vaccine caused an AE generally cannot be assessed from VAERS data alone.

Included for this season were US influenza vaccine reports received in VAERS through May 26, 2017 for individuals vaccinated July 1, 2016 through May 1, 2017. Signs, symptoms, and diagnoses are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms. Clinical review of reports, which includes review of medical records when available, were performed for the following:

- ❑ All serious reports after IIV3, IIV3-HD, IIV4, IIV4-ID, ccIIV3, RIV3, aIIV3
- ❑ All anaphylaxis reports in persons with a history of egg allergy
- ❑ Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, and serious pregnancy reports

Serious reports are based on the Code of Federal Regulations and include death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability. Empirical Bayesian data mining is utilized to detect disproportional reporting for vaccine AE event pairings.

Following IIV3, IIV4, and IIV3-HD in 2016-2017, US serious reports ranged from 4% to 6% and correspondingly non-serious reports were 94% to 96%. Dr. Shimabukuro emphasized that this does not mean that 4% to 6% of people who got an influenza vaccination had an SAE. VAERS is a partial numerator system only, which means that of the VAERS reports for these products, 4% to 6% met the regulatory definition for serious. Guillain-Barré Syndrome (GBS) reports comprised a very small percentage of total reports from 0.9% to 1% for these products. Anaphylaxis reports are rare in VAERS, ranging from 0.2% to 0.6%. There were no data mining safety signals for GBS or anaphylaxis in association with trivalent, quadrivalent, or trivalent high-dose. Of the 27 IIV4 reports, 3 were in persons with a history of egg allergy. Following ccIIV4, RIV3, aIIV3-ID, and IIV4-ID, serious reports ranged from 4% to 7%. GBS was rarely reported and there were some anaphylaxis reports, but it is important to keep in mind that these small numbers can make big differences in percents. Importantly, there were no data mining signals for GBS or anaphylaxis for these influenza products either. One of the RIV3 anaphylaxis reports was in a person with a history of egg allergy. The breakdown for IIV3, IIV4, IIV3-HD, ccIIV4, RIV3, aIIV3-ID, and IIV4-ID is similar to previous seasons.

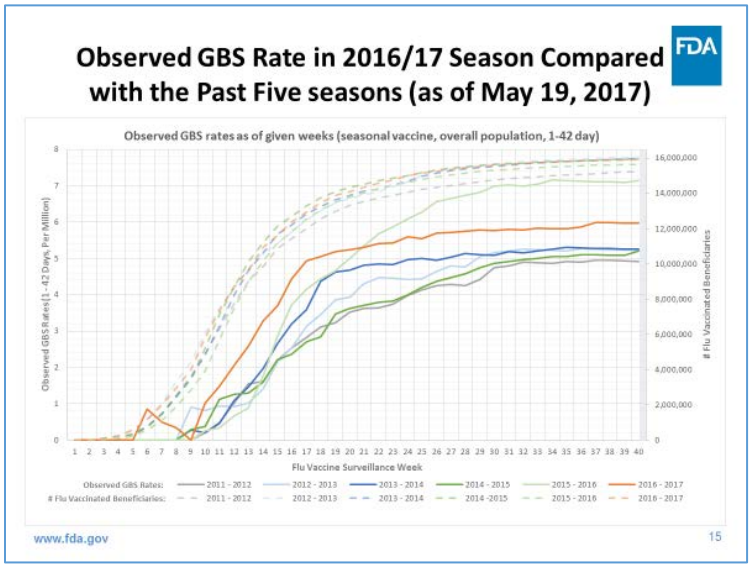
In terms of the anaphylaxis reports in persons with a history of egg allergy, one case was a 6-year-old female who received Fluzone® (IIV4) alone. Her medical history was significant for asthma, eczema, food allergies to eggs (signs symptoms not reported), peanuts, wheat, corn, and shellfish. The patient received "a flu shot" of unknown type 2 years prior, with no reported reactions. Symptom onset occurred within 30 to 35 minutes, including hives and tachycardia, but no wheezing. This was classified as a Brighton Level 3 anaphylaxis case. The Brighton classification ranges from 1 to 4, with Level 1 being the highest level of diagnostic certainty. The next case was a 37-year-old female who received Flublok® (RIV3) alone. As a reminder, Flublok® is egg-free. Her medical history was significant for hives to "flu shots" (unknown type) in the past and diarrhea and hives after eating eggs. Symptom onset occurred within minutes, including swelling of upper throat, difficulty swallowing, pruritus in tongue, throat, and chest and loss of consciousness. This case was classified as a Brighton Level 1.

The next case was in a 2-year-old female who received Fluzone® (IIV4) and HepA vaccine. Her medical history was significant for anaphylaxis with milk and a "positive" but unspecified reaction to eggs, although it was reported that the patient can eat eggs. She had previously received an IIV influenza vaccine of an unknown type and HepA vaccines without any problems. Symptom onset occurred within minutes, including vomiting, red rash on back, paleness, low responsiveness, and initial blood pressure (BP) of 84/40 that dropped to 70/30. This case was classified as a Brighton Level 1. The final report of anaphylaxis in a patient with egg allergy occurred in an 18-year-old female who received Afluria® (IIV4), inactivated polio vaccine (IPV), MCV, and Tdap in the same visit. She had a known history of egg allergy, but the signs and symptoms were not reported. This was known prior to receiving a "flu vaccine" of an unknown type in the past. The history is somewhat unclear, but that is what was in the report. No contra-indication to receiving IIV could be identified in the report. Symptom onset was within hours and included hives, severe respiratory distress with wheezing, and angioedema of face and throat swelling. This case was classified as a Brighton Level 1.

Of the 37 total pregnancy reports, 36 were with standard IIV3 or IIV4 and one was with ccIIV4. The median maternal age was 29 years. The median gestational age when reported was 21 weeks. The breakdown for trimester of vaccine was 5 (36%) in the first trimester, 4 (28%) in the second trimester, and 5 (36%) in the third trimester. Of the 37 reports, 7 (19%) included a pregnancy-specific outcome. Of these 7, 5 were spontaneous abortion and 2 were vaginal bleeding. Roughly half of the reports, 18 (49%), were non-pregnancy-specific AEs. This includes the one ccIIV4 report. There were 12 (32%) vaccination error reports. These vaccination error reports could be true error reports; reports in which a patient received an influenza vaccine and the person reporting it perceived this to be an error; and patients who received multiple vaccines, one of which may have been the vaccine given in error. To summarize VAERS surveillance for the 2016-2017 influenza season and plans for 2017-2018, no new safety concerns were detected for IIVs, ccIIV3, RIV3, or aIIV3 during the 2016-2017 influenza season. Surveillance for the 2017-2018 influenza season will include enhanced safety monitoring for aIIV3 (FLUAD™), IIV4-ID (Fluzone® Intradermal Quadrivalent), RIV4 (Flublok® Quadrivalent), pregnancy reports, and anaphylaxis reports in persons with history of egg allergy.

Moving on to FDA surveillance for GBS, FDA conducts near real-time surveillance for GBS after influenza vaccination every influenza season in collaboration with the Center for Medicare and Medicaid (CMS). About half of these beneficiaries receive influenza vaccination every season. The population under surveillance is about 15 to 16 million beneficiaries per season, almost 99% of whom are 65 years of age and older. FDA compares the current seasons' GBS rates with historic rates. Previously, this has been for three seasons. However, in the 2016-2017 season, FDA used the past five seasons to help with stability of data. FDA uses updated sequential probability ratio test (SPRT) to account for claims and clinical delays. If the observed rate exceeds a critical limit, that constitutes a statistical signal. CMS data are refreshed each week, although it takes up to 10 weeks for data to mature.

In week 17 of surveillance, which includes data as of December 9, 2016, the current GBS rate for the primary outcome was greater than the historical rate. By Week 20, the GBS rate in the current season declined and was very close to the historical rate. This is illustrated in the following graphic:



The current season is represented by the orange line, while the light green solid line is last season when there was a signal for GBS in FDA's GBS monitoring of the CMS data. As a reminder, there also was a signal detected in the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) for GBS as well. The spike in the orange line was an anomaly early in the season, which when looked into was resolved and is why there was a drop back down to zero. The GBS in the current season is very close to the average of the past five seasons. However, the GBS rate is lower than the GBS rate in the 2015-2016 season when it was 7.25 GBS cases/million vaccines. FDA plans to conduct an end-of-season self-controlled risk interval analysis. However, there are not sufficient data for 80% power yet, indicating that the number of GBS cases was quite small this season.

In week 40 of surveillance, GBS rate in a 6-week risk window was 5.96/million vaccinees, compared to an average of 5.70/million vaccinees for the prior five seasons. End-of-season analysis using a self-controlled design is to be conducted when 99% of the fee-for-service beneficiaries have been vaccinated. Limitations of surveillance include comparison to historical data, claims-based analysis, and no control for confounders.

Turning to VSD RCA for the current season, the VSD was established in 1990 as a collaboration between CDC and 9 integrated healthcare plans. It includes data on over 9 million persons per year (~3% of US population) and links vaccination data to health outcomes data (hospitalization, emergency department visits, outpatient visits). Patient characteristics are linked by unique identification (ID) numbers. Two methods are used to conduct RCA in VSD, self-controlled design and current versus historical design. In a self-controlled risk interval design, each patient serves as his/her own control, and events in the risk window and comparison window are assessed. In this particular case, vaccination occurs on Day 0, the risk window extends from Day 0 to Day 1, and the comparison window (control window) is Day 14 to Day 15. The time period in the risk window is considered exposed time and the time period in the comparison window is considered unexposed time. The current versus historical design assesses events in the risk window in patients in the current season versus patients during the historical comparison period.

The VSD RCA outcomes for the current season include acute disseminated encephalomyelitis (ADEM), anaphylaxis, Bell's palsy, encephalitis, GBS, seizures, and transverse myelitis. A total of 4,554,828 doses were administered in the VSD through April 29, 2017 broken down as follows: IIV3 (2,655,071), IIV4 (1,359,059), IIV High-Dose (456,043), ccIIV3 (78,002), IIV Intradermal (5,549), and RIV3 (1,104). IIV3 and IIV4 dominated, approaching 90% of all influenza vaccine doses administered in the VSD during the season.

Regarding the 2016-2017 VSD RCA results, it is important to note that the log-likelihood ratio (LLR) is the test statistic. If the LLR exceeds the critical value for any pre-specified outcome, there is a signal. To address this question in advance, that is not always a simple ratio for a self-controlled risk interval. There are different lengths of windows and adjustments have to be made for data lags. If the relative risk exceeds 1, there is a value for the LLR. None of the LLRs exceeded the critical value for IIV3 or IIV4 for any of the pre-specified endpoints, so there was no signal in the self-control design for IIV3 or IIV4 for this season. In the case of the current versus historical design, the relative risk is a simple ratio. None of the LLRs exceeded the critical values for any of the pre-specified outcomes for IIV3 or IIV4 in the current versus historical design, so there were no signals in this design either in the current season.

In summary of the 2016-2017 VSD influenza vaccine RCA, no RCA signals were identified in either the self-controlled risk interval or current versus historical designs for any of the pre-specified outcomes for IIV3 or IIV4. For IIV3 high-dose, a limited number of doses were administered in VSD for the 2016-2017 influenza season (n=450,242). There were no statistical signals or elevated relative risks for any pre-specified outcomes being monitored, which includes GBS, in either the self-controlled risk interval or current versus historical designs for high-dose. Data for ccIIV3, IIV Intradermal, and RIV3 are limited due to low use of these vaccines, but were generally reassuring.

A self-controlled risk interval and current versus historical RCA was conducted for the pre-specified conditions (anaphylaxis, Bell's palsy, encephalitis, GBS, seizures, transverse myelitis, acute disseminated encephalomyelitis) for the 2017-2018 influenza season. Work continues on a comprehensive analysis to evaluate the risk of GBS following pH1N1-containing seasonal influenza vaccines for the years 2010-2016. This study is a follow-up to the RCA signal in the self-controlled risk interval design for GBS following IIV3 detected during the 2015-2016 influenza season.

To summarize influenza vaccine safety monitoring for 2016-2017, no new safety concerns were detected in VAERS monitoring. There were reassuring results in FDA's near real-time monitoring for GBS following influenza vaccination in Medicare beneficiaries in CMS data. No signals were identified for any pre-specified outcomes being monitored in the VSD RCA.

Discussion Points

Dr. Romero asked whether Dr. Shimabukuro had information about the trimesters in which the 5 spontaneous abortions occurred in the 2016-2017 season. He also noted that no data were included on the RCA self-control results for IIV3 or IIV4.

Dr. Shimabukuro replied that the spontaneous abortions were clinically reviewed. They would have that information if it was included in the reports, which he will provide to Dr. Grohskopf. For the endpoint of ADEM, only the current versus historical design was used. ADEM is so rare, there were no meaningful data to present for the self-control risk interval design.

Dr. Lee asked whether the current versus historical comparisons actually accommodated for the transition between International Classification of Diseases (ICD-9) to ICD-10 that occurred during that historical period and whether that contributed to the elevated GBS risk observed in the 2015-2016 season. Related to that, she wondered whether it would be useful to consider a case-centered approach to account for seasonality and secular trend. This might result in a slightly different answer than what would be found with a self-controlled risk interval analysis.

Dr. Shimabukuro confirmed that the 2015-2016 season does span the ICD-9 to ICD-10 transition. His understanding from speaking with the statisticians and epidemiologists in VSD is that the problem, at least with GBS, is minimal. However, they cannot exclude that the transition from ICD-9 to ICD-10 may have played some role in what was seen in the data for that season. Multiple methods are being considered to analyze the data for that study, one of which is case-centered.

Kevin Ault (ACOG) noted that spontaneous abortion typically would occur in the first trimester up to 12 weeks or less than 20 weeks. Beyond those gestational ages, it would be referred to as stillbirth or pre-term delivery. There are good data showing that influenza vaccination during pregnancy prevents stillbirths and prematurity. He assumed that standard definitions of spontaneous abortion are being used.

Dr. Shimabukuro replied that they use the standard definition for spontaneous abortion. If there was a stillbirth, it would have been reported as such. Fetal demise is not being combined into one category. Those are spontaneous abortions based on the review of the report.

Flublok® in Pregnancy

Wayne E. Hachey, DO, MPH
Head Government and Clinical Services
Protein Sciences Corporation

Dr. Hachey indicated that Protein Sciences Corporation maintains a pregnancy registry, which includes all pregnancies reported during clinical trials and those reported voluntarily during seasonal use. Subject tracking during clinical trials is an active process, which ensures capture. However, for seasonal use, the package insert includes a request for notification of all Flublok® vaccine exposures during pregnancy. Again, this is voluntary and assumes that people are reading the package insert. There are some limited data from a vaccine coverage program conducted in Mongolia by the Center for Vaccine Equity (CVE).

Regarding pregnancies reported during clinical trials, Protein Sciences Corporation's first study was PSC 01 that was conducted in the 2004-2005 influenza season. For the 181 doses administered to women of childbearing age, there were 3 pregnancies. One subject received vaccine at 5 weeks gestation and had an uneventful term pregnancy. One subject became pregnant 3 months after receiving Flublok® and underwent an elective termination at 12 weeks. The third subject became pregnant 20 weeks following immunization and underwent an elective termination at 12 weeks.

The second study that involved women of childbearing age was PSC 04 that occurred in the 2007-2008 season. This involved 1371 doses to women of childbearing age, among whom there were 20 pregnancies. Of the 20, there were 12 uneventful live births. There was 1 spontaneous abortion in a woman who received vaccine 2 months prior to pregnancy and experienced the spontaneous abortion at 5 weeks. There were 2 elective terminations, 3 were lost to follow-up, and 2 withdrew from the study and would not provide pregnancy outcome data.

Study PSC 16 occurred during the 2013-2014 season. This involved 7 pregnancies among 675 women of childbearing age. Of these, 1 subject reported pregnancy 3 weeks following immunization and a spontaneous abortion 6 weeks later. The remaining 6 were uncomplicated live births.

In terms of pregnancies after routine seasonal influenza immunization, 5 pregnancies were reported. Of these, 4 were uneventful and 1 experienced a spontaneous abortion 2 days after immunization. At the time the pregnancy loss was reported to Protein Sciences Corporation, approximately 1,000,000 total doses had been administered.

The last data group comes from a vaccine coverage project in Mongolia. This program was conducted by CVE at the Task Force for Global Health. The goal was to increase influenza vaccine coverage in Mongolia. Protein Sciences Corporation donated 40,000 doses of Flublok® vaccine, which was given to 330 pregnant women. No serious AEs were reported; however, it is important to note that this was a passive surveillance network with a number of limitations. There was no active follow-up of pregnancies and the surveillance network capability to capture pregnancy-related AEs are uncertain. At best, these are somewhat reassuring data. However, it is hardly the same follow-up that would be experienced by someone reporting a pregnancy directly to Protein Sciences Corporation. With continued participation in this project, Protein Sciences Corporation hopes to include active follow up of individuals who received Flublok® during pregnancy in order to acquire better data.

In summary, excluding the Mongolia data, there were 35 Pregnancies. Of these, 23 resulted in normal outcomes, 3 ended in spontaneous abortions, 4 were electively terminated, 3 were lost to follow-up, and 2 withdrew from the study.

Influenza WG Considerations and Proposed Recommendations

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

Dr. Grohskopf provided an overview of the draft 2017-2018 ACIP influenza statement, which is anticipated to be published sometime in August 2017. It will be included in the *Morbidity and Mortality Weekly Report* (*MMWR*) *Recommendations and Reports* document.

One aspect of the statement not being proposed for change is the core recommendation. The draft statement re-iterates the core recommendation that annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications.

As is done each year, the statement will include the US influenza vaccine composition for 2017-2018:

Trivalent Vaccines
- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated)
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus (Victoria lineage)

Quadrivalent Vaccines
- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated)
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus (Victoria lineage)
- B/Phuket/3073/2013-like virus (Yamagata lineage)

This composition represents an update in the (H1N1)pdm09-like virus for 2017-2018.

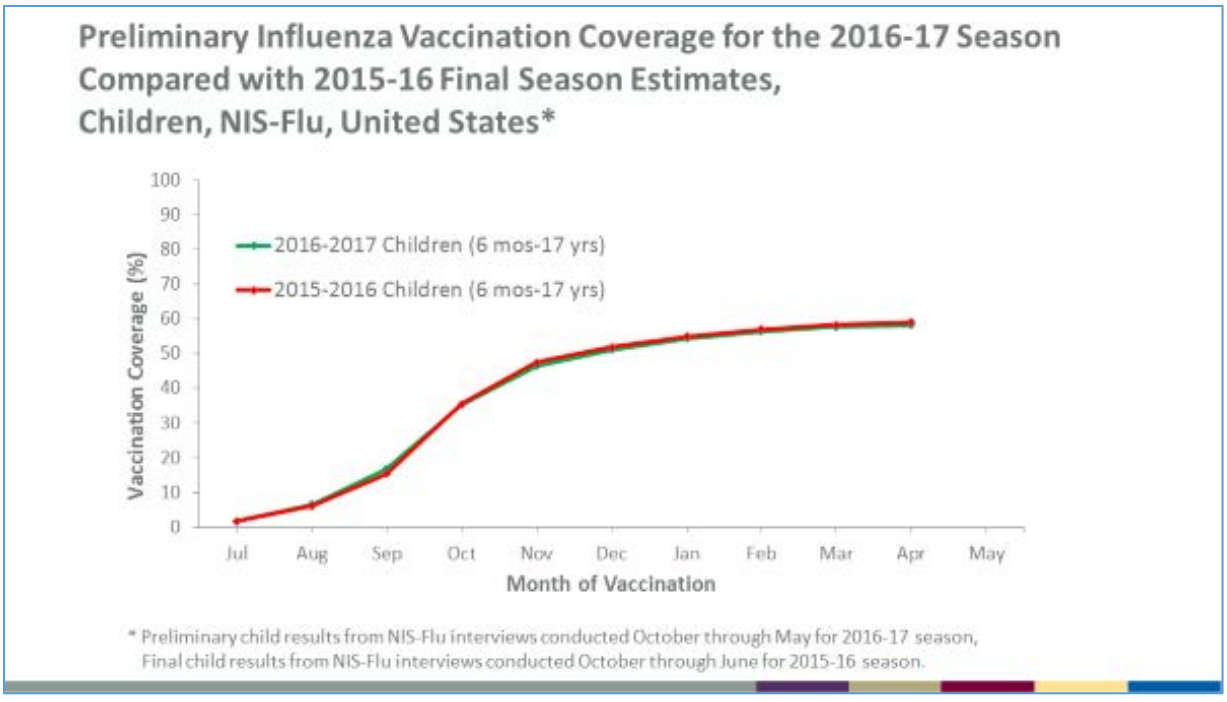
Next, there is a discussion of products licensed and changes in existing approval since publication of the last statement on August 26, 2016. These include:

- ❑ Afluria® Quadrivalent (IIV4, Seqirus), for persons aged ≥18 years
- ❑ Flublok® Quadrivalent (RIV4, Protein Sciences), for persons aged ≥18 years
- ❑ FluLaval® Quadrivalent (at 0.5cc dose) for children aged ≥6 months (previously licensed for ≥3 years)

Notably, prior to this licensure change for FluLaval®, the only influenza vaccine approved for 6- to 35-month-olds has been a 0.25cc dose of Fluzone® and Fluzone® Quadrivalent. That approval still exists, but there are now 2 options for children in the 6- to 35-month-old age group.

With regard to LAIV4 Flumist® Quadrivalent, during the June 2016 ACIP meeting, ACIP made the recommendation that LAIV not be used for the 2016-2017 season due to concerns about its effectiveness against (H1N1)pdm09-like viruses during the 2013-2014 and 2015-2016 seasons. The draft recommendation extends this recommendation that LAIV not be used into the 2017-2018 season while further data are awaited on LAIV4, which are anticipated to be presented to ACIP during the October 2017 meeting.

At the time the recommendation was made not to use LAIV for the 2016-2017 season, one question raised regarded whether this would adversely affect pediatric vaccine coverage rates for influenza. With that in mind, preliminary influenza vaccination coverage for the 2016-2017 season compared with 2015-2016 final season estimates are shown in the following graph, which shows considerable overlap and indicating that as the season progressed, coverage overall remained similar:



The following table summarizes data from the same source; however, this time there is stratification by age group within the pediatric population that shows similar coverage estimates for the two seasons:

Preliminary Influenza Vaccination Coverage for the 2016-17 Season Compared with 2015-16 Final Season Estimates by Age Group, Children, NIS-Flu, United States*

Age Group	2015-16 Season, Vaccinations received through April 2016 % (95% CI)†	2016-17 Season, Vaccinations received through April 2017 % (95% CI)†
All Children (6 months–17 years)	59.0 ± 0.8	58.2 ± 0.8
6 months–4 years	69.7 ± 1.3	69.4 ± 1.4
5–12 years	61.5 ± 1.2	59.2 ± 1.2§
13–17 years	46.6 ± 1.3	47.7 ± 1.5

* Preliminary child results from NIS-Flu interviews conducted October through May for 2016-17 season, Final child results from NIS-Flu interviews conducted October through June for 2015-16 season.
† % - Kaplan-Meier coverage estimate; 95% CI - confidence interval half-width.
§ Statistically significant decrease in preliminary 2016-17 coverage compared to 2015-16 final coverage.

Notably, there was a difference in the 5- through 12-year-old age group of 2.3% lower for 2016-2017 compared to 2015-2016. Though a small difference, it was statistically significant.

Returning to the content of the 2017-2018 statement, Dr. Grohskopf discussed the two areas for which language changes were proposed for consideration. The first of these related to Afluria® (IIV3). Afluria is licensed by FDA for persons aged 5 years and older. However, since the 2010-2011 influenza season, ACIP has recommended Afluria® only for persons aged 9 years and older following reports of febrile seizures and reactions that occurred in association with its use in Australia with the 2010 Southern Hemisphere formulation. The seizures were confined largely to those under 5 years of age; however, there were febrile reactions among children aged 5 through 8 years. In February 2017, ACIP heard a presentation from Seqirus™ that summarized the investigation into the root cause of these reactions and some manufacturing changes that were made as a result.

Because these data were presented several months ago, Dr. Grohskopf reviewed the main findings from the Seqirus™ presentation in February 2017. With the initial investigation into the happenings in Australia, CSL Biotherapies, the company at the time that held Afluria®, concluded that two factors probably in combination were associated with these events. One factor was that for the 2010-2011 season, the composition of the vaccine changed such that all three viruses in the seasonal vaccine changed. There was the introduction of the (H1N1)pdm09-like viruses, A/California/07/2009, into the seasonal vaccine. That had been the same virus in the monovalent vaccine. There also was the introduction of B/Brisbane/60/2008 for the B virus.

The second factor that was initially implicated pertained to residual lipid and ribonucleic acid (RNA) complexes that were in the vaccine product following splitting. This is an inactivated vaccine product. The viruses are split or disrupted. In this case, it is with a compound called taurodeoxycholate (TDOC). As presented to ACIP by Seqirus™ in February 2017, a study was conducted using an in vitro cell cytokine release model in which several different experimental settings altering the concentration of TDOC used on the various viruses was done. The original standard formulation used 0.9% for H1N1, 0.5% for B, and a higher concentration of 1.5% for H3N2. The take-home message is that raising the concentration of TDOC used to 1.5% for all viruses resulted in the greatest attenuation of the inflammatory signal. These data are also summarized in the paper by Rockman from *Vaccine* 2014 [Rockman S et al. / Vaccine 32 (2014) 3869-3876].

Also presented to ACIP in February 2017 were data from 2 studies in children 5 through 8 years of age. The first study compared a modified Afluria® trivalent in which the TDOC concentration was raised to 1.5% for the B strain to a licensed comparator quadrivalent vaccine. In this study, fever rates were similar. In addition, the fever prevalences were compared with historical fever data from previous formulations of trivalent CSL vaccine. In the new experimental Afluria® TIV, the fever prevalence was lower [https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000175-27/results].

A similar study was conducted in the same age group in which a quadrivalent Afluria® with a concentration of TDOC raised to 1.5% for all 4 viruses was compared with a licensed comparator quadrivalent. Again, there were similar fever rates and lower fever rates than were observed with the historical TIV fever data [Leong J, et al. file:///C:/Users/SU000044/Downloads/POSTER77_761.pdf].

As was summarized for ACIP by Seqirus™, it was felt that with the change in the TDOC content for use in treating the viruses, fever rates for children 5 through 8 years of age with the TIV and QIV were similar to comparator QIV and were less than observed historically with older TIV formulations of Afluria® IIV3. In consideration of discussion of these data that were presented to ACIP and also were discussed within the WG, the first proposed change is that Table 1, the large table that has been in the guidance for a number of years that summarizes information on all of the vaccine products anticipated to be available for the season, be modified to state that Afluria® is indicated for persons ≥5 years of age rather than ≥9 years of age as it currently states. In addition, the footnote that occurs that the bottom of that table stating ≥9 years of age and the reason why is recommended to be removed.

The second proposed modification relates to vaccination of pregnant women and choice of vaccine. Before going into the proposed language, Dr. Grohskopf presented a high-level summary of the recommendation for influenza vaccine in pregnant women. Pregnant women with risk factors for severe influenza illness have been recommended to receive influenza vaccine since the 1960s. Between that time and roughly the 1990s, vaccination was generally recommended for those who had another risk factor, for example, a chronic medical condition such as heart or lung disease that conferred a higher risk for severe influenza illness. Over time, it became increasingly recognized that pregnancy, particularly the second and third trimesters, were risk factors in and of themselves for severe illness and negative pregnancy outcomes in some studies. In 1995 and 1997, the third and second trimesters were added as risk factors themselves without regard to having another risk factors. Influenza vaccination has been recommended by ACIP for women who will be pregnant during influenza season without regard to trimester since 2004. Information that was considered for this recommendation included increased risk for severe influenza illness in pregnant women, particularly during

second and third trimesters; adverse pregnancy outcomes noted in some studies; and an association of some birth defects with maternal fever. Current language regarding pregnancy in the ACIP statement indicates that pregnant women should receive IIV specifically.

The WG discussed the information on pregnancy reports presented by Protein Sciences concerning Flublok® (RIV). The information on Mongolia was not available at the time, so that was not discussed. In addition, there have been three VAERS reports since 2013 of pregnant women who received Flublok®. In two of these reports, no AE was reported. In one report, a woman presented in clinic with vaginal bleeding and a suspected spontaneous abortion. In their discussions, the WG considered that there are relatively few data concerning the use of Flublok® in pregnancy. There is more experience and more data relating to IIVs. Although the evidence base consists largely of observational studies and safety surveillance data, it is overall reassuring on balance. There is a much longer clinical experience with the use of IIVs than with RIV. The WG also acknowledged that even for the inactivated vaccines, data are somewhat more limited for the first trimester and also for some newer inactivated vaccines, such as quadrivalents and cell-based vaccines.

While there are few data relating specific to the use of Flublok® in pregnancy, it was noted that the general overall safety profile of Flublok® in comparison to IIVs is reassuring. For example, one concern that arises is reactogenicity and inflammation. Overall, reactogenicity in the studies in which Flublok® inactivated vaccines have been compared, rates of most of the local and systemic AEs are similar to that observed with IIVs in clinical studies. Relatively few additives are listed in the RIV package insert (e.g., preservatives, antibiotics, gelatin, egg protein). However, not all inactivated vaccines contain these agents either. Flublok® does contain some residual insect cell and *Baculovirus* proteins in DNA, which is cited on the package insert. The inactivated vaccines do not contain these residuals. On initial licensure, Flublok® RIV3 received a Pregnancy Category B destination, which is similar to most of the other IIVs available. The Flublok® RIV4 was approved in fall 2016. That package insert incorporates the new FDA Pregnancy and Lactation Labeling language, so it is not quite directly comparable to the previous language.

Based on these considerations, the WG proposed the following recommendation for vaccination of pregnant women shown in comparison to the 2016-2017 language with the proposed changes underlined:

<u>2016-2017 Language</u>
"Because pregnant and postpartum women are at higher risk for severe illness and complications from influenza than women who are not pregnant, the ACIP recommends that all women who are pregnant or who might be pregnant in the upcoming influenza season receive IIV. Influenza vaccination can be administered at any time during pregnancy, before and during the influenza season."

<u>Proposed New Language for 2017-2018</u>
"Because pregnant and postpartum women are at higher risk for severe illness and complications from influenza than women who are not pregnant, the ACIP recommends that all women who are pregnant or who might be pregnant in the upcoming influenza season receive <u>influenza vaccine. Any licensed, recommended, and age-appropriate, trivalent or quadrivalent IIV or RIV may be used.</u> Influenza vaccination can be administered at any time during pregnancy, before and during the influenza season."

Discussion Points

Dr. Kempe requested clarity regarding whether the FDA licensure wording for the use of IIV3 and IIV4 influenza vaccines in pregnancy is exactly the same.

Dr. Grohskopf replied that the recommendations have not made a distinction with regard to pregnancy and IIV3 or IIV4, so either would be feasible.

Ms. Pellegrini observed a nuance that she wished to better understand. In general, most any vaccine may be used for any purpose for which it is licensed. These are licensed for use in anyone above a certain age. There is a subtle but important difference in the proposed language in making what would appear to be an affirmative statement that RIV is safe in pregnant women versus remaining silent on it or stating that ACIP is not saying it should not be used, but there are not enough data to affirmatively say it is safe. It seemed that they were heading there, and she wondered whether the rest of the group was comfortable with that.

Dr. Kempe said her understanding was that the FDA makes decisions about safety and that it is not necessarily ACIP's job, so she was somewhat confused about why the proposed language was calling this out.

Dr. Sun (FDA) clarified that in order for a vaccine to be indicated for pregnant women, it has to be in the package insert specifically for that population. When new vaccines were licensed for adults, which includes women who are pregnant, that is not considered to be inclusive of pregnant women. In other words, one would have to show safety for pregnant women in order for the label to state that it is safe in pregnant women. That is not to say that they are not safe. It is that there are not sufficient data to state that they are safe. The distinction here is that it is not in the label.

Dr. Bennett clarified that this change is simply to make Flublok® consistent with all of the other vaccines, because essentially there are not a lot of data, but there are no safety signals to distinguish Flublok® from the other vaccines that ACIP recommends.

Dr. Lee agreed with Ms. Pellegrini in that the proposed language makes an affirmative statement as opposed to the absence of a clear statement for it. It seemed that the sentence could be moved to a generic section to state that ACIP would be in favor of any of the influenza vaccines period for any people. However, because it was in this section, it seemed to implicate that ACIP has a certainty of the benefits, risks, and balance of that. However, only 1000 doses have been administered. It felt like they did not have enough information. It was not that it should not be used, but calling it out specifically seemed to indicate its use in the particular population.

Dr. Walter thought part of it had to do with the way the rest of the recommendations read. They do mention all of these vaccine products. It was meant to be inclusive and not give an endorsement of safety.

Dr. Belongia agreed and thought it was a matter of being equivalent to IIV. Especially in the first trimester, there is a relative paucity of data for IIV as well. Flublok® is a recombinant vaccine. Theoretically, it should not be any worse than IIV in terms of the potential to cause harm because it is theoretically pure HA, recognizing with any manufacturing process nothing is 100% pure. Afluria® is a split vaccine with RNA, lipids, and other things that Flublok® does not have.

Based on that, he would not penalize Flublok® and it would be at least equivalent to IIV in the absence of any evidence.

Dr. Hunter asked whether the WG acknowledged the implications of a lack of preference between vaccines, based on the fact that there is a ratio of 2:1 trivalent to quadrivalent being used. Because the trivalent is less expensive than the quadrivalent and large systems often will purchase only one or the other, clinicians often do not get to choose what, in their opinion, is necessarily appropriate for particular patients because of the health system in which they practice. That decision feeds into the manufacturing process of what is produced.

Dr. Walter said he thought the intent of the WG was to allow use of whatever product was available.

Dr. Bennett thought it was implicit in the proposed recommendation language that the WG did not choose to make any preferential recommendations.

Dr. Walter confirmed that this was correct.

Dr. Lee asked if put into the context of the reset of the recommendations, the intent of the proposed language reflected the differential uncertainty in the different vaccines, but ACIP would not be making any preference statement.

Dr. Walter said he thought the pregnancy section discussed experience. The proposed language just puts it into context with the rest of the recommendations as outlined.

Dr. Grohskopf clarified that the draft recommendations are divided into two sections, the Recommendation Summary and the Background. The Background discusses in some detail what literature base is available for each vaccine.

Ms. Pellegrini remained uncomfortable with the new pregnancy language and wondered whether there was an option to separate it out as a distinct issue or vote.

Dr. Bennett pointed out that because there was no motion on the floor, Ms. Pellegrini could propose any option she liked.

Ms. Pellegrini made a motion to separate the proposed pregnancy language for an individual vote from the rest of the recommendations. Dr. Hunter seconded the motion for the purpose of further discussion.

Dr. Messonnier clarified that if there is a motion on the floor, it would be permissible in the context of that motion to make a recommended change to the language.

Dr. Bennett called for discussion on separating the pregnancy language and voting on it separately from the full statement.

Dr. Kempe wondered whether if the proposed language simply stated, “a recommended influenza vaccine product may be used” and did not single anything out it would make it more comfortable. The safety issues are FDA’s not ACIP’s decisions. That is true for any vaccine during pregnancy.

Dr. Hunter asked whether the suggestion was to remove “trivalent or quadrivalent IIV or RIV” and retaining “Any licensed, recommended, and age appropriate vaccine may be used.”

Dr. Kempe thought that would take it out of the realm of suggesting that they have carefully looked at all of these different products.

Dr. Grohskopf pointed out that the one complication is that she would need to insert language about LAIV. This past season, LAIV was not recommended but was available, so language had to be included referencing previous recommendations for its use or not use. So, to say “any licensed, recommended . . .” is probably okay, but there should probably be a sentence stating that LAIV should not be used in pregnancy because of the general recommendation to not use live virus vaccines.

Dr. Belongia thought it would be acceptable alternative wording to say “Any licensed, recommended, age-appropriate vaccine may be used. LAIV should not be used in pregnancy.”

As an obstetrician, Dr. Riley interpreted the language to mean that she could use anything that is available in pregnancy other than LAIV. She read it as more choices and that more women would get vaccinated. The materials sent to ACIP members go through the limits to the data available.

Dr. Atmar did not see that the proposed language change really changed anything. The proposed language is more specific about which types of vaccines would be age- and pregnancy-appropriate. The other language required the addition of another sentence to state specifically that LAIV should not be used. The statement did not address the relative paucity of data in either choice. Therefore, he saw no reason to change the language as originally proposed.

Dr. Fryhofer (ACP) said that as a clinician who sees patients, she does not have the knowledge base that the researchers have. Therefore, she tries to think of the recommendations in terms of what clinicians will think when they read them. She thinks clinicians appreciate as much detail as possible. Looking at the proposed language, it was not clear to her whether ccIIV would be included.

Ms. Hayes (ACNM) agreed that it is helpful for clinicians if more data are provided on what drug or vaccine is or is not appropriate to give. She also thought they must remind people that live vaccine is not to be given during pregnancy. To her, the exclusion was almost more important than the inclusion.

Dr. Grohskopf clarified that the sentence about the exclusion falls immediately after this material and will be there regardless.

It seemed to Dr. Thompson (NVAC) that the full sentence proposed for revision was adding complexity. The sentence above it states that all pregnant women should receive influenza vaccine and her inference is that it should be licensed, age-appropriate, and recommended. It was not clear to her why there was an extra sentence or what it added.

Dr. Belongia thought the WG's issue with the 2016-2017 recommendation was that it stated "IIV." The goal was to get away from that. He thought stating "any licensed influenza vaccine and not LAIV" pretty much said the same thing.

Dr. Messonnier thought they were back to a problem that ACIP discussed generically in the past, which regarded how most providers make their decisions. While she completely understood the detail-orientation of ACIP, which is what it should be, in the end most providers are not reading these recommendations at the level ACIP is reading them. What matters equally is what is in the schedule, and hopefully the eventual maternal schedule that will be created and how things are articulated. The current schedule states, "Pregnant women should receive IIV." In some ways, it seemed that the request was for ACIP's intensions to be clearer in the materials being used. Perhaps more importantly is how the intent is communicated rather than what it actually says.

Dr. Bennett agreed. In an effort to move forward, she asked Ms. Pellegrini to make a motion for the wording she would like, determine whether others agreed, and then move forward with the vote.

Following additional discussion, Ms. Pellegrini withdrew the original motion and Dr. Hunter seconded the withdrawal.

Dr. Atmar made a new motion to approve the 2017-2018 Influenza Vaccine Recommendations as presented.

Dr. Kempe recommended that the more general statement be made to read, "Any licensed, recommended and age-appropriate vaccine. LAIV should not be used."

Dr. Lee pointed out that intent was clearer in the preliminary information provided to ACIP and she wondered whether that could be posted. Dr. Bennett indicated that they did not have it to put up on the screen, but that the wordsmithing could be done post hoc and sent to all members to ensure that everyone is comfortable with it.

Public Comment

The following letters were submitted by Alachua County Board of County Commissioners prior to the meeting for consideration by ACIP:

Alachua County
Board of County Commissioners

April 10, 2017

Ms. Carolyn Bridges MD Associate Director for Adult Immunization, Immunization Services Division,
National Center for Immunization and Respiratory Diseases,
Centers for Disease Control CDC
1600 Clifton Road, NE
Atlanta, GA 30329-4027

Advisory Committee on Immunization Practices (ACIP)
ACIP Secretariat Amanda Cohn, MD
ACIP Chair Nancy Bennett, MD, MS
CDC
1600 Clifton Road, NE
Mailstop A27
Atlanta, GA 30329-4027

RE: Alachua County Florida School Located Influenza Vaccination Program

Dear Colleagues:

At the March 28, 2017 Alachua County Board of County Commissioners meeting, the Commission received a report from the Alachua County Health Department's Administrator, Paul Myers. His annual update on the Control Flu Program revealed a concerning inference that associated the mandated use of flu shots during this year's campaign, instead of the usual intranasal spray, with a 40% reduction in program participation.

This significant reduction in doses administered has resulted in thousands of children, mostly from socioeconomically challenged neighborhoods, lacking the protection that they have been provided in the previous 8 years of the program. The flu shot is not only more traumatic for children, but does not, according to many studies, impart substantially greater protection from influenza disease than the intranasal spray.

It is the Commission's understanding that the CDC's current language regarding the intranasal spray states that it "should not be used". We urge the CDC to reconsider this language and provide a softening of its position. At a minimum, permissive language for school based programs is strongly recommended. Vaccinating significantly less children with a shot that *might* be more effective versus immunizing many more children with the intranasal spray that *may* be less effective is a questionable strategy at best, and ignores a large body of scientific evidence that supports the vaccine effectiveness of the intranasal spray. What is certain is that requiring shots lowers vaccine uptake and therefore renders large numbers of children, and those they come into contact with, unprotected from influenza.

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Alachua County has long supported the School Located Influenza Vaccination Program that has, until this year, utilized FluMist. We strongly encourage the CDC to re-evaluate its position on FluMist by mid-June 2017 at the latest, so that our program can utilize FluMist for the upcoming 2017/2018 campaign. The intranasal spray has proven to decrease influenza associated morbidity, school and work absenteeism, in addition to saving millions of dollars in direct and indirect healthcare costs.

Thank you for your immediate attention to this matter. Please contact me should you have any questions or require additional information.

Sincerely,

Ken Cornell, Chair
Alachua County Commission
Chr17.076

KC/GP/lg

cc: Board of County Commissioners
Lee A. Niblock, County Manager
Michele Lieberman, County Attorney
Gina Peebles, Assistant County Manager
Paul Myers, Alachua County Health Department

Alachua County
Board of County Commissioners

June 15, 2017

Advisory Committee on Immunization Practices (ACIP)
ACIP Secretariat Amanda Cohn, MD
ACIP Chair Nancy Bennett, MD, MS
CDC
1600 Clifton Road, NE
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Atlanta, GA 30329-4027
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Ms. Carolyn Bridges MD Associate Director for Adult Immunization, Immunization Services Division, National Center for Immunization and Respiratory Diseases,
Centers for Disease Control CDC
1600 Clifton Road, NE
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RE: Alachua County Florida School Located Influenza Vaccination Program

Dear Dr. Cohn,

Thank you for the opportunity to speak with you on May 15, 2017, regarding Alachua County's School Located Influenza Vaccination Program. This call was a follow-up to my letter dated March 29, 2017 referencing the 40% reduction in overall program participation (K-12) that we directly attribute to the requirement to use shots versus the intranasal spray.

As you requested, we have further analyzed this year's program data to answer the 4 questions listed below. We utilized school rosters, further denoted by program vaccinated/non-vaccinated students, compared to the State of Florida's immunization registry, FLSHOTS. It should be noted that all pediatric providers in Alachua County utilize FLSHOTS.

1. What was the change in program participation for the primary target group (K-5) as compared to last year (2015 vs. 2016)?
    a. Of the 6081 K-5 students immunized by the program in 2015, 2293 were immunized by the program in 2016; a reduction of 62.3%.

2. Of those K-5 students who participated in the 2015 school program, but not in 2016, how many received the immunization from a different provider?

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a. 529 K-5 students who participated in the school program in 2015, but not in 2016, received the vaccination from a non-school program provider.

3. What demographic was impacted and by how much?
   a. In 2015, 6081 K-5 students participated in the program. In 2016, 3259 of them were not vaccinated at all; a reduction of 53.6%. Of those, 1699 were VFC eligible for a reduction in VFC students of 52.2%

4. What was the impact of lower vaccination coverage on morbidity?
   a. K-12 students presenting to school health clinics with Influenza like illness increased from 2015 to 2016 in Alachua County Schools.

Clearly, Alachua County, relying on hard data, experienced a significant reduction in immunization coverage for the target group of K-5 grades. This group we affectionately label "the super-spreaders". Disproportionately affected were the social-economically challenged demographic; one that can least afford to become ill and one that suffers worse health outcomes from doing so. Our data does not mirror that of the referenced NIS that indicated a reduction in immunization coverage of 1%-2% from 2015 to 2016.

Thank you for the opportunity to provide additional input. I hope you find these data compelling and serve as a basis to consider a softening of the ACIP's language regarding the utilization of the intranasal influenza vaccine that currently states that the spray "should not be used". I would reiterate my previous request that the Alachua County Program be supported by the ACIP in utilizing the intranasal spray to maximize immunization rates, reduce influenza associated morbidity and provide in-US data for further policy considerations. I look forward to the results of the ACIP meeting on June 21, 2017 and am available at your convenience for continued dialogue.

Sincerely,

Ken Cornell, Chair
Alachua County Commission
Chr17.114

KC/PM/lg

cc: Board of County Commissioners
Dr. Lee A. Niblock, County Manager
Michele Lieberman, County Attorney
Gina Peebles, Assistant County Manager
Paul Myers, Alachua County Health Department
David Kim MD, Adult Immunization, Immunization, Services Division

Pam Rockwell
Parent of a Child with Autism
Presented During the Meeting

I want to encourage the ACIP to change the recommendation for flu vaccine to add a contraindication for the first trimester of pregnancy. Most studies of flu vaccine safety in pregnancy only follow the child for first year of life, but you can't tell if someone has a developmental disability until they are at least 2 two years old. Last November, researchers at Kaiser Permanente published a study that showed and increased risk of autism in children whose mothers were vaccinated during the first trimester of pregnancy. It was 4/1000 increase. It's about 20% of the regular risk for autism. This is the only published data that you have to make recommendations on. The FDA has not tested any vaccines for flu after 1 year, so whether that's Flublok® or any other vaccine, no one knows what happens after 1 year right now, except for this study. I would really like you to make your recommendations on actual data and not on wishful thinking. I know you think there is probably no chance that autism could be caused by a maternal vaccine, but autism experts will tell you that the genetics alone can't explain why autism develops, that there is an environment component, and that early pregnancy an extremely vulnerable time. A human fetus does not develop a blood brain barrier (BBB) until the second trimester, so it is more vulnerable to toxins and infections. There are studies that link fever during pregnancy with autism. There are studies that link maternal infections with autism, including influenza infections. Individuals with autism tend to have biomarkers of inflammation and have more activated glial cells in their brains, indicating more immune activity. Women who have had children with regressive autism even have antibodies in their blood that bind human brain cells. These antibodies have been used to make animal models of autism. Pregnant moneys or mice that have been exposed to these antibodies in early pregnancy have mostly male offspring that show autistic-like behaviors. Even the genetics of autism point to immune dysfunction. Female relatives of autistic people are more likely to have autoimmune disorders like rheumatoid arthritis (RA), multiple sclerosis (MS), lupus, or thyroid disease.

I'm not an anti-vaxer, but infections could cause an autoimmune version of autism, then the vaccines for those infections could also potentially trigger that. But, if you picked the right antigen, something that didn't cause autoantibodies or cause a fever at the wrong time, you might actually end up with a vaccine that not only prevents influenza, but it prevents the autism that is caused by influenza. But, if you're not actually tracking which vaccines cause these secondary autoimmune disorders like autism or lupus, then you're not ever going to find out which ones could be used to prevent those secondary endpoints. I'm a housewife. I am not a doctor or a scientist. I have a 17-year old autistic son. He was diagnosed at 20 months old. He is not a vaccine injury. They were not vaccinating pregnant women 17 years ago. But, the drug that made the biggest difference in his life when he was 7 years old was amantadine, which is used to treat influenza, and it wasn't used because he had influenza. It was used because it also binds human N-methyl-D-aspartate (NMDA) receptors. This circuit, the NMDA receptor circuit, is a really well-studied circuit that is a problem in autism. It's also a problem in Alzheimer's disease. Memantine is a very close cousin of amantadine. If you had an antibody that was shaped like amantadine that bound M2 proton-selective ion channels, you could fight the flu really well and you make great antibodies to the flu, but you also have a risk of an autoimmune disorder. So, this is one of those cases that's actually bad news for you, because that would mean that functionally, you would have a good vaccine—if you actually got rid of the autoimmune problems, you would reduce the effectiveness of your vaccine.

So, I'm going to point out that the H1N1 vaccine, when it came out in 2009, it was 75% effective. These days, it's only around 50% effective—maybe less than that. But, there have been a lot of vaccine changes in the meantime. There have been HA concentrations so that you don't have as many of the M2 protons pumps in the vaccine, and there have been innovations like Flublok® that don't even have the M2 pumps in the first place. It's possible that those vaccines actually already reduce the risk of autism, but you really need to look. In the meantime, the only thing you have on the table right now is that you have data that says in the first trimester of pregnancy if you use a flu vaccine, you have a much higher risk of autism. Really, if you just made it second trimester and third trimester only, maybe you could actually improve some people's lives. Thank you.

Discussion Points

Dr. Bennett indicated that Ms. Rockwell's full comments will be available to the committee.

Regarding the letters submitted from Alachua County for public comment, Ms. Pellegrini emphasized that this county has gone through a lot of work to provide ACIP with some disparities data. There was a significant reduction in their school-based immunization program because they could not use LAIV.

Motion/Vote: 2017-2018 Influenza Vaccine Recommendations

The Motion for the 2017-2018 Influenza Vaccine Recommendations had a number of nuances raised during the discussion before the final vote was cast. The progression follows:

- Ms. Pellegrini initially made a motion to separate the proposed pregnancy language for an individual vote from the rest of the recommendations. Dr. Hunter seconded the motion for the purpose of further discussion.
- Following additional discussion, Ms. Pellegrini withdrew the original motion and Dr. Hunter seconded the withdrawal.
- Dr. Atmar made a new motion to approve the 2017-2018 Influenza Vaccine Recommendations as presented. Dr. Riley seconded the new motion.
- Dr. Kempe recommended that a more general statement be made to the pregnancy component to read, "Any licensed, recommended and age-appropriate vaccine may be used. LAIV should not be used."
- Dr. Bennett indicated that precise language to reflect the sentiment of the vote would be crafted post-hoc and sent to all members to ensure that everyone is comfortable with it.

Following public comment, a vote was taken and the new motion to include the suggested revision carried unanimously with 15 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

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

VFC Resolution Update: Influenza Vaccines

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: 1) update the Recommended Vaccination Schedule section with the addition of a table of age-indications for currently available influenza vaccines covered under this resolution; and 2) update the information in the Contraindications and Precautions section.

Eligible groups include all children aged 6 months through 18 years. The recommended vaccination schedule for children 6 months through 8 years of age to receive 1 or 2 doses and children 9 through 18 years of age to receive 1 dose. The following table has been added to list the currently approved influenza vaccines in the VFC program, including the age indications for each vaccine:

Brand Name	Presentation	Age Indication
Afluria (Trivalent)	0.5 mL pre-filled syringe	>= 5 years
Afluria (Trivalent)	5.0mL multidose vial	>= 5 years
Fluarix (Quadrivalent)	0.5 mL pre-filled syringe	>= 36 months
Flucelvax (Quadrivalent)	0.5 mL pre-filled syringe	>= 4 years
Flulaval (Quadrivalent)	0.5 mL pre-filled syringe	>= 6 months
Flulaval (Quadrivalent)	5.0 mL multidose vial	>= 6 months
Fluvirin (Trivalent)	0.5 mL pre-filled syringe	>= 4 years
Fluvirin (Trivalent)	5.0 mL multidose vial	>= 4 years
Fluzone (Quadrivalent)	0.25mL pre-filled syringe	>= 6 through 35 months
Fluzone (Quadrivalent)	0.5mL prefilled syringe/vial	>= 36 months
Fluzone (Quadrivalent)	5.0mL multidose vial	>= 6 months

The brand names are listed in the table in alphabetical order. The first two rows for Afluria® vaccine now have an age indication of ≥5 years of age to reflect the discussion that just occurred. In addition, a note will be added to indicate that the use of brand names is not meant to preclude the use of other comparable licensed vaccines.

The recommended intervals and doses language follows and will not change:

Recommended Intervals

- ❑ Minimum Age: 6 months
- ❑ Minimum interval between dose 1 and dose 2 (where applicable): 4 weeks

Recommended Dosage

- Refer to product package insert.

The Contraindications and Precautions section previously pointed to the most recent influenza recommendation. However, because that recommendation includes the information about Afluria®, which is not current now that a new recommendation has been passed, there is not a published reference that can be pointed to. When that occurs, the language is included. The following is the language for the Contraindications and Precautions section that is taken from the existing ACIP recommendation for the 2016-2017 season, which will not necessarily be changed. However, a statement also is included that when a recommendation is published by ACIP within 6 months of the passing of this resolution, that language is included by reference:

Contraindications:

- History of severe allergic reaction to any component of the vaccine or after previous dose of any influenza vaccine. However, ACIP makes specific recommendations for the use of influenza vaccine in persons with egg allergy (see Influenza Vaccination of Persons with a History of Egg Allergy, in www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm)

Precautions:

- Moderate or severe acute illness with or without fever
- GBS within 6 weeks following a previous dose of influenza vaccine

[If an ACIP recommendation regarding influenza vaccination is published within 6 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 URL].

Motion/Vote: VFC Resolution for the 2017-2018 Influenza Vaccine Recommendations

Dr. Hunter motioned to approve the VFC Resolution for the 2017-2018 Influenza Vaccine Recommendations. Dr. Moore seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

15 Favored:	Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Moore, Pellegrini, Reingold, 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
Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation

Dr. Belongia reminded everyone that the primary objective of the Herpes Zoster (HZ) WG is to develop evidence-informed vaccine policy for the use of HZ vaccines. The WG will:

- Consider vaccine and programmatic performance of the currently licensed live attenuated vaccine by Merck, which is trade-named Zostavax® and also is referred to as ZLV
- Consider the efficacy, safety, and duration of protection of the adjuvanted HZ subunit vaccine by GSK, which is trade-named Shingrix and also is known as HZ/su vaccine that is currently under FDA review, with a decision expected by this fall
- Identify programmatic options for both vaccines that incorporate cost-effectiveness analyses and the potential impact on disease burden in the US

The WG has convened 28 conference calls since August 2015 and received a variety of presentations by manufactures and researchers on the effectiveness, safety, immunogenicity, cost-effectiveness, and programmatic barriers of HZ vaccines. The WG has considered the body of evidence regarding both vaccines, and has identified key zoster vaccine policy questions and discussed options. In addition, there will be upcoming presentations and data for discussions on the CDC cost-effectiveness analysis and GSK plans regarding program implementation, including vaccine price, efforts to assure completion for this 2-dose vaccine, efforts to inform and prepare vaccine providers and patients regarding reactogenicity, and efforts to minimize disparities.

ACIP received presentations during the October 2016 meeting on HZ epidemiology and Zostavax® performance and coverage and Phase III efficacy studies of HZ/su vaccine (ZOE-50 & ZOE-70). In February 2017, ACIP heard presentations on the safety summary of HZ/su, the GRADE evaluation of HZ/su, and considerations for policy by CDC. During this meeting, presentations were provided on Zostavax® Phase IV effectiveness studies, the GRADE evaluation of Zostavax®, immunogenicity of HZ/su in prior Zostavax® recipients, a cost-effectiveness analysis summary, and considerations for policy. A vote is planned for the October 2017 ACIP meeting.

Zostavax® Phase IV Study

Nicola Klein, MD, PhD
Director, Kaiser Permanente Vaccine Study Center
Kaiser Permanent Northern California

Dr. Klein presented the first results on up to 8 years of follow-up (2007-2014) from Kaiser Permanente's long-term effectiveness study for Zostavax® funded by Merck. This study is a post-licensure commitment to FDA and the European Medicines Agency (EMA). The primary objective of the study is to estimate VE against HZ by age at vaccination and time since vaccination, while the secondary objective is to estimate VE against PHN by age at vaccination and time since vaccination. The study is being conducted within Kaiser Permanente Northern California (KPNC). KPNC has more than 1 million members 50 years of age or older, as well as complete electronic healthcare records (EHRs). KPNC has offered Zostavax® vaccine, or ZVL, free of charge since mid-2006. Since July 2013, KPNC has had a database health prompt for vaccination for persons 60 years of age and above.

The study design is a continuous accrual of people as they become age-eligible for ZVL, starting in January 2007. That includes May 2006 for those 60 years of age and above and March 2011 for those 50 through 59 years of age. The study cohort is updated annually to include newly eligible members. The members are unvaccinated at study entry, and then switch to vaccinated status after they receive ZVL. Vaccinated and unvaccinated individuals in the study are followed for the occurrence of HZ and PHN.

In terms of the statistical analysis plan, VE is estimated against incident HZ or PHN using Cox regression. VE is calculated by 1 – the hazard ratio. The Cox regression is on a calendar timeline and is stratified by birth year. Models also were adjusted for demographic characteristics, time-varying comorbidities, immunocompromised status, and use of health services. VE was estimated for vaccines for the following analyses: overall, by time since vaccination, by age at vaccination, by age at vaccination and time since vaccination, and by immunocompromised status at the time of vaccination. In terms of age and time since vaccination, KPNC hypothesized that both age at vaccination and time since vaccination matter to VE.

Regarding uptake of ZVL from 2007 through 2014, there was a reasonably steady increase in uptake until the database health prompt in July 2013 for those 60 years of age and older when there was a much sharper increase. There continues to be very low uptake amongst individuals 50 through 59 years of age. For the study population, from January 2007 to December 2014, 1.3 million persons ≥ 50 years contributed approximately 5.8 million person-years of follow-up. The average duration of follow-up was 4.3 years, while the average duration of vaccinated follow-up was 2.6 years. Of the 1.3 million people, 29% received ZVL. Of the nearly 400,000 people vaccinated, most (222,517) were 60 through 69 years of age.

For the primary objective of VE against HZ, for the case definition, an HZ diagnosis code was used accompanied by a prescription for an antiviral medication or a laboratory test positive for varicella zoster virus. Nearly 49,000 incident cases of HZ were identified. A random sample of charts was reviewed to verify the definition, and there was a very high positive predictive value (PPV) of 98%. These are the cases included in the primary analysis. Also identified were just over 5,900 less-certain HZ cases. These were primary HZ diagnosis without an antiviral prescription. PPV for these cases was 86%. These cases were included only in the sensitivity analyses and did not contribute to the primary analysis.

Regarding HZ incidence by age group and vaccine status, there was an increase by age and quite clearly incidence was less in vaccinated versus unvaccinated. The incidence of HZ is consistent with other population-based studies. Overall VE of ZVL against HZ was 49.1% with confidence intervals of 47.5% to 50.6% and a significant P-value. These models were adjusted for calendar time, age, sex, race/ethnic group, influenza vaccination, immunocompromised status during follow-up, outpatient visits, and comorbid conditions. They were not adjusted for age at vaccination or time since vaccination.

Looking at VE of ZVL against HZ by time since vaccination, there was high VE in the first year, a drop in the second year, and then gradual decreases through the course of study. By 7 to 8 years out, VE is still statistically significant but the confidence intervals are wide due to the smaller number of cases. In every age group, VE of ZVL is similarly high in the first year, drops substantially in the second year, and then decreases more gradually after the first year. For those 65 years of age and above, the VE is between 45% and 50%. Combining VE against HZ by age at vaccination and time since vaccination, most notable is that every age group starts off with high VE, with VE dropping fairly dramatically in the second year and then decreasing more gradually thereafter. For those 50 through 59 years of age, there was not enough time to trace the trajectory of waning with precision more than 3 years.

For VE of ZVL against HZ by immunocompromised status at the time of vaccination, it is important to note that KPNC does not advocate administering ZVL to persons who are immunocompromised because it is contraindicated. However, this is a study conducted with real-world data and people who are immunocompromised do receive vaccination on occasion for a variety of reasons. Regardless of low (mild) or high (more serious) immunocompromised status, there is substantial protection against HZ following ZVL. In addition, protection is similar to that of persons who are not immunocompromised at the time of vaccination.

For the second objective, VE against PHN, the PHN case definition began with the nearly 49,000 incident HZ cases and identified those with a PHN diagnosis based on ICD and internal Kaiser codes. Codes were included that were associated with a visit and/or prescription, and that occurred 90 days to 1 year after the HZ case index date. A total of 3,316 PHN cases (6.8%) were identified. Cases with a PHN code for both a visit and a prescription were accepted electronically (N=1551). A sample of charts was reviewed to verify that algorithm, with a very high confirmation rate of 96%. For cases with a PHN code for only a visit or a prescription (N=1987), all of the charts were reviewed and 89% (1765) of those were confirmed and were included in the analysis.

Incidence of PHN by age group and vaccination status was similar to the HZ story in that the vaccinated appeared to have a lower incidence than the unvaccinated. There is an increase in PHN for each age group as well. The overall VE of ZVL against PHN is 68.7%, which is higher than the overall VE of 49.1% for HZ. Again, this model is not adjusted for age at vaccination or time since vaccination but is adjusted for all of the other covariates, including: calendar time, age, sex, race/ethnic group, influenza vaccination, immunocompromised status during follow-up, outpatient visits, and comorbid conditions.

In terms of time since vaccination for VE of ZVL against PHN, like HZ, there is a similar pattern for PHN. The VE against PHN is highest in the first year and drops after the first year. After the second year, there is less evidence of waning for PHN than HZ. Currently, the case numbers are much fewer for PHN. More will be learned as the study continues over time and this information can be updated. Like HZ, the VE against PHN by age at vaccination shows a similar pattern with similar protection levels across all age groups 50 years of age and above at 60% to 70%.

It is important to note the overall VE estimate includes all of the cases in the study, but the average is the best approximation to crudely estimate the average VE over 3 or 5 years if everyone in the study can be followed for 3 or 5 years. For HZ across the age groups and certainly for 65 years of age and above, VE averages 45% to 50% for 3 and 5 years. For PHN, VE averages 60% to 70% for 3 and 5 years.

In conclusion, these results are consistent with clinical trials and other real-world studies. VE against HZ was greater than 60% in all age groups in the first year after vaccination, wanes in the second year in all age groups, and decreases gradually thereafter. By year 7 or 8, VE is about half as effective as during year 1, but is still clinically important and statistically significant. There is no clear timepoint when protection ends; that is, there is no clear point at which there is an obvious increase in risk that may suggest an obvious time to revaccinate. Average VE for HZ over 5 years following vaccination was approximately 45% to 50% in all age groups 60 years of age and above, and for PHN was approximately 60% to 70% in all age groups 60 years of age and above. There is less evidence for waning against PHN than against HZ. There may be waning, but more time may be needed to see it. Persons vaccinated at 80 years and older have similar protection against HZ and PHN to younger vaccinees. In this study of routine use, persons immunocompromised at the time of vaccination have similar levels of protection against HZ and PHN. For time reasons, the 80 and above data were not presented but were provided in the ACIP members' packets.

Zostavax® GRADE

Angela Guo, MPH
Oak Ridge Institute for Science and Education (ORISE) Fellow
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Guo presented the results from the GRADE analysis of live attenuated HZ vaccine, ZVL. She reminded everyone that the GRADE process is used to develop policy questions, consider critical outcomes, review and summarize evidence of benefits and harms, and evaluate the quality of evidence. The remaining steps to assess population benefit, evaluate values and preferences, review health economic data, consider formulating recommendations, and ACIP recommendation and GRADE category will be presented during a future meeting.

The policy question for consideration is, "Is the live attenuated herpes zoster vaccine (ZVL) safe and effective at preventing herpes zoster?" The population of interest is immunocompetent adults aged 50 years and older. The intervention of interest is one dose of ZVL. The WG looked for studies that compared this intervention to placebo or no vaccine. The outcomes the WG considered most important were HZ, PHN, duration of protection against HZ defined as protection four or more years post vaccination, SAEs, and reactogenicity. Outcomes included in the evidence profile can be divided into benefits and harms. The benefits of prevention of HZ

and PHN were deemed critical and duration of protection considered important. In the harm category, SAEs were deemed critical and reactogenicity was considered important.

The WG completed a systematic review of studies in any language from PubMed, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, Scopus, and clinicaltrials.gov. Efforts also were made to obtain unpublished or other relevant data. Initial search terms included "zostavax", or "zoster" and "vaccine ADJ2 live", or "zoster" and "attenuated ADJ2 live", or "zoster" and "vaccine ADJ2 attenuated", or "zoster vaccine live", or "zoster vaccine attenuated." Articles were included if they presented data on ZVL and involved immunocompetent adults aged 50 years or older, included data for relevant intervention (ZVL, one dose, minimum of 19,400 PFU), included data relevant to the outcome measures being assessed, and reported primary data. Working with an expert in Library Sciences, the WG identified 1113 references via database searches. An additional 158 references were identified from clinicaltrials.gov. Another 8 references were identified from searching reference lists and reviewing conference abstracts. Title and abstracts were then screened for all 1279 references, and records were excluded if there was no primary data reported or if the study did not include the population or intervention of interest. Following that step, the WG conducted full text screenings of 159 articles of which 119 were excluded because the study did not report data for the intervention or outcomes of interest, was ongoing, had results reported in another study that was reviewed, or were case reports of individual AEs.

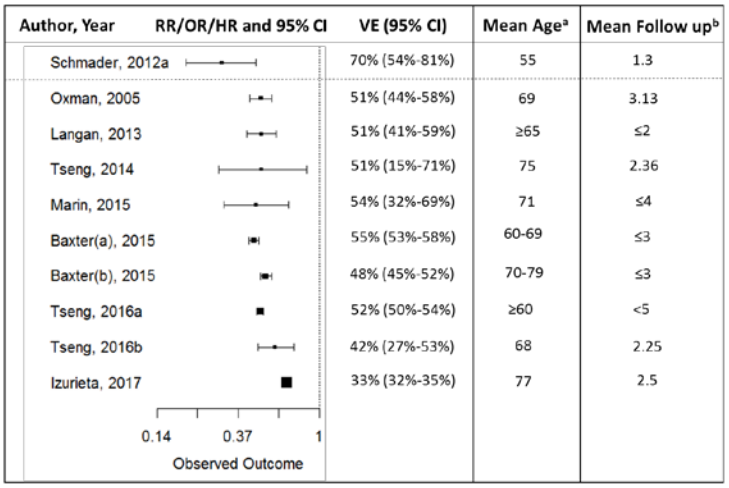
For reference, the evidence types outlined in the GRADE process are as follows:

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Regarding the GRADEing of evidence of ZVL starting with potential benefits, Outcome #1 is vaccine efficacy or effectiveness against herpes zoster. There were two randomized controlled trials (RCTs) included for assessment. Oxman et al reported an RCT in adults 60 years of age and older, also known as the Shingles Prevention Study (SPS). Schmader et al reported an RCT in adults aged 50 through 59 years of age, also known as the ZOSTAVAX® Efficacy and Safety Trial (ZEST). There were an additional 7 observational studies included in the assessment, which looked at real-world effectiveness of ZVL. These studies were mainly conducted in managed care settings or using Medicare administrative data.

This forest plot demonstrates the varying estimates of effect from the studies included in the analysis for this outcome:

Figure 1. Comparative VE of Zostavax for the prevention of herpes zoster



Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;
[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.
[b]If mean follow up no available, length of study follow-up period post zoster vaccination in years was reported.

The x-axis represents the risk, odds, or hazards ratios and their 95% confidence intervals that were either reported directly from the study or calculated based on the reported VE. Also included on this figure are the VE estimates from each study and their 95% confidence intervals, the mean age of study participants, and the mean follow-up time post vaccination. Schmader 2012a was an RCT in adults aged 50 through 59 years of age. It is important to note that this age group is younger than the rest of the studies which looked at adults aged 60 and older. Overall, the estimates were relatively consistent among studies and demonstrated the vaccine to be protective against herpes zoster.

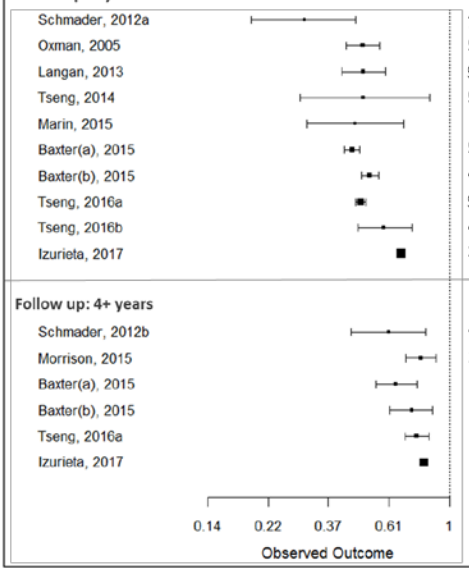
The type of evidence supporting the prevention of herpes zoster is type 1. For the two RCTs, there were no serious risk of bias concerns and no concerns of inconsistency, given that the study population for Schmader 2012a was younger than the other studies. There also were no concerns of indirectness and imprecision. This led to an evidence type 1 for the RCTs. The observational studies were downgraded for risk of bias because outcomes assessors were likely aware of the intervention received by participants. There were no concerns related to inconsistency, indirectness, and imprecision. This led to an evidence type of 4 for observational studies. The overall evidence type for this outcome was 1, following ACIP GRADE guidelines in which the overall evidence type for each outcome is based on the strongest evidence within that outcome.

Moving on to Outcome #2, duration of protection against HZ looking specifically at 4 or more years post-vaccination, there were two RCTs included for assessment. Schmader et al reported follow-up data from participants in the SPS 3 to 8 years post-vaccination in the Short-Term Persistence Substudy (STPS). Morrison et al reported follow-up data from the participants of the SPS 4 to 12 years post-vaccination in the Long-Term Persistence Study (LTPS). Both studies had important limitations regarding their comparison groups. In the STPS, participants were un-blinded during the study period and placebo recipients were eligible to receive the vaccine. Once placebo participants received ZVL, they were no longer able to serve as controls, limiting the placebo group available for follow-up. In the LTPS, there were no placebo controls since participants already had been un-blinded. Instead, a comparison group was

modeled using data from the placebo groups in the SPS and STP. There were an additional 3 observational studies included in this assessment.

This forest plot demonstrates the varying estimates of effect from the studies included in the analysis for this outcome, by years since vaccination:

Figure 2. Comparative VE of Zostavax for the prevention of herpes zoster, by length of follow up time post-vaccination



Author, Year	RR/OR/HR and 95% CI	VE (95% CI)	Mean Age[a]	Mean Follow up[b]
Follow up: 4 years or fewer				
Schmader, 2012a		70% (54%-81%)	55	1.3
Oxman, 2005		51% (44%-58%)	69	3.13
Langan, 2013		51% (41%-59%)	≥65	≤2
Tseng, 2014		51% (15%-71%)	75	2.36
Marin, 2015		54% (32%-69%)	71	≤4
Baxter(a), 2015		55% (53%-58%)	60-69	≤3
Baxter(b), 2015		48% (45%-52%)	70-79	≤3
Tseng, 2016a		52% (50%-54%)	≥60	<5
Tseng, 2016b		42% (27%-53%)	68	2.25
Izurieta, 2017		33% (32%-35%)	77	2.5
Follow up: 4+ years				
Schmader, 2012b		40% (18%-56%)	73	3.3 - 7.8
Morrison, 2015		21% (11%-30%)	74	4.7 - 11.6
Baxter(a), 2015		36% (24%-46%)	60-69	5 - 6
Baxter(b), 2015		27% (13%-39%)	70-79	5 - 6
Tseng, 2016a		24% (16%-31%)	≥60	5 - 8
Izurieta, 2017		19% (17%-22%)	77	4 - 7

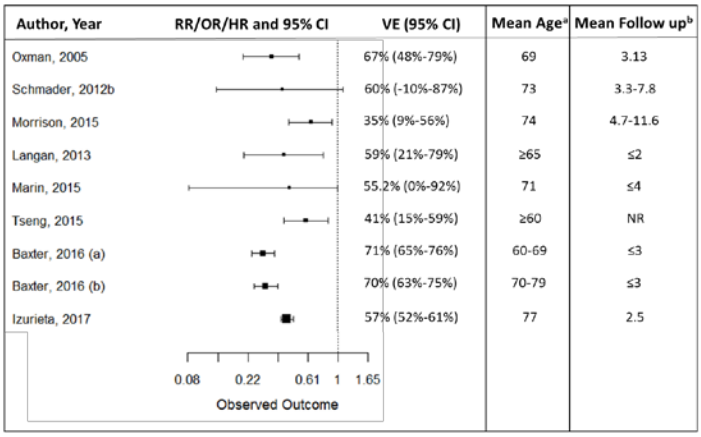
Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;;
[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.
[b]Length of study follow-up period post zoster vaccination in years.

The top half of the forest plot includes studies that looked at VE during the first four years post vaccination. This is what was presented earlier for Outcome #1. The bottom half of the forest plot includes studies that looked at VE four or more years post vaccination. These studies that looked at long-term protection were included in GRADE analysis for this outcome. Overall, the WG found that the estimates for protection 4 or more years post-vaccination to be relatively consistent among studies and to demonstrate that the vaccine was still protective against HZ after four years, although not as protective as during the first four years post-vaccination.

While the SPS, STPS, and LTPS were conducted in different time periods and among different study populations with different age structures, overall, they are consistent in showing a decline in VE over time. The WG determined that the 2 RCTs had serious limitations in regard to their comparison groups as discussed previously, and thus were given an initial evidence level of 2. The observational studies were downgraded for risk of bias, because outcome assessors were likely aware of the intervention received by participants. The WG found no other serious concerns and found that the evidence type for this outcome is 2.

Moving on to Outcome #3, VE against PHN, there were 8 studies that reported estimates for VE against PHN. There were 3 RCTs included for assessment: SPS, STPS, and LTPS, discussed previously. There were an additional 5 observational studies included for assessment. This forest plot demonstrates the varying estimates of effect from the studies included in the analysis for the prevention of PHN:

Figure 3. Comparative VE of Zostavax for the prevention of post-herpetic neuralgia



Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;
[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.
[b]If mean follow up no available, length of study follow-up period post zoster vaccination in years was reported.

The first 3 studies on the figure are experimental, and the remaining studies observational. Overall, the WG found that the estimates for prevention of PHN to be relatively consistent among studies, although some studies had large confidence intervals.

The WG deemed Oxman 2005, SPS, as the only RCT without major limitations. The STPS and LTPS were graded as RCTs with serious limitations given concerns around their comparison groups, and thus were given an initial evidence level of 2. These studies also had large 95% confidence intervals and were downgraded for imprecision. Observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants, and because PHN was likely underreported because PHN diagnosis was often based on healthcare encounters and not self-report. The WG found the overall evidence type for this outcome to be 1.

For the two harm outcomes, SAEs and reactogenicity, there were 11 studies that directly met the WG's PICO (population, intervention, comparison, outcomes) question and had a comparison group that was either placebo or no vaccine. Of these studies, 9 were RCTs and 2 were large observational studies. There were 10 studies with comparison groups that reported data on SAEs related to vaccination. In 8 placebo-controlled RCTs with over 36,000 participants receiving ZVL, there were no imbalances in SAEs between vaccine and placebo groups. The 2 large observation studies found no increased risk post-vaccination for cardiovascular, neurologic, or infectious conditions studied among over 222,000 participants receiving ZVL. Overall, the WG found no SAEs associated with ZVL.

There were additional studies that reported SAEs related to ZVL live that did not have comparison groups. However, the WG included these studies in the GRADE analysis since they had at least one study arm that received the vaccine. There were an additional 7 RCTs, 6 non-randomized clinical trials, and 5 observational studies. Overall, the findings are consistent

with findings from the placebo-controlled studies, with no SAEs found to be associated with zoster vaccine live. Overall, there were 28 studies included in the GRADE analysis for SAEs related to vaccination. The 8 RCTs with comparison groups were given an evidence type 1. The 13 RCTs with limitations included randomized trials with no comparison group and non-randomized clinical trials as mentioned earlier. These were given an initial evidence level of 2. The trials with limitations and observational studies were downgraded for risk of bias because outcome assessors were likely aware of the intervention received by participants. The overall evidence type for this outcome is 1.

There was additional safety data from case reports related to SAEs and Oka-caused AEs. Merck's 10-year post-marketing review reported 13 cases of PCR-confirmed VZV rash caused by the Oka vaccine strain. In clinical trials, 2 subjects with varicella-like rashes and zoster-like rashes had PCR-confirmed Oka strain varicella. An additional 7 case reports of SAEs related to ZVL were not included in the GRADE analysis. None of these events have been substantiated as a safety signal for ZVL through additional research or reporting through VAERS.

For Outcome #5, reactogenicity, there were 25 studies that reported data on reactogenicity, defined as injection-site reactions or systemic reactions related to vaccination. Injection-site reactions were the most common AEs related to vaccination. One large RCT in adults 60 years and older reported injection-site reactions among 48% of vaccine recipients compared to 17% among placebo. One large RCT in adults aged 50 through 59 reported injection-site reactions among 64% of vaccine recipients compared to 14% among placebo. The range of injection-site reactions reported among the remaining studies was 8% to 62%, with the large variation likely due to the large differences in sample sizes among the remaining studies. However, the majority of studies reported an estimate between 35% and 55%. There were 4 studies that reported moderate/severe (grade 3) injection-site reactions that ranged between 0% to 4% of vaccine recipients. This includes a post-hoc analysis of the SPS that found that <1% of participants reported grade 3 reactions post vaccination. There were 7 studies that reported vaccine-related systemic AEs, with reactions reported among 0% to 8% of vaccine recipients.

There were 25 studies included in the assessment for reactogenicity. The 15 RCTs were given an evidence type of 1. Non-RCT and observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants. This lead to an evidence type 3 for non-randomized trials and an evidence type 4 for observational studies. The overall evidence type for this outcome was 1.

In summary, first to provide some context of how to interpret the different evidence types:

- Evidence Type 1: The WG is very confident that the true effect lies close to that of the estimate of effect.
- Evidence Type 2: The WG is moderately confident in the effect estimate.
- Evidence Type 3: The WG's confidence in the effect estimate is limited.
- Evidence Type 4: The WG has very little confidence in the effect estimate.

As a reminder, the WG is not measuring how good the intervention is, but rather how much confidence they have in the estimates of effect.

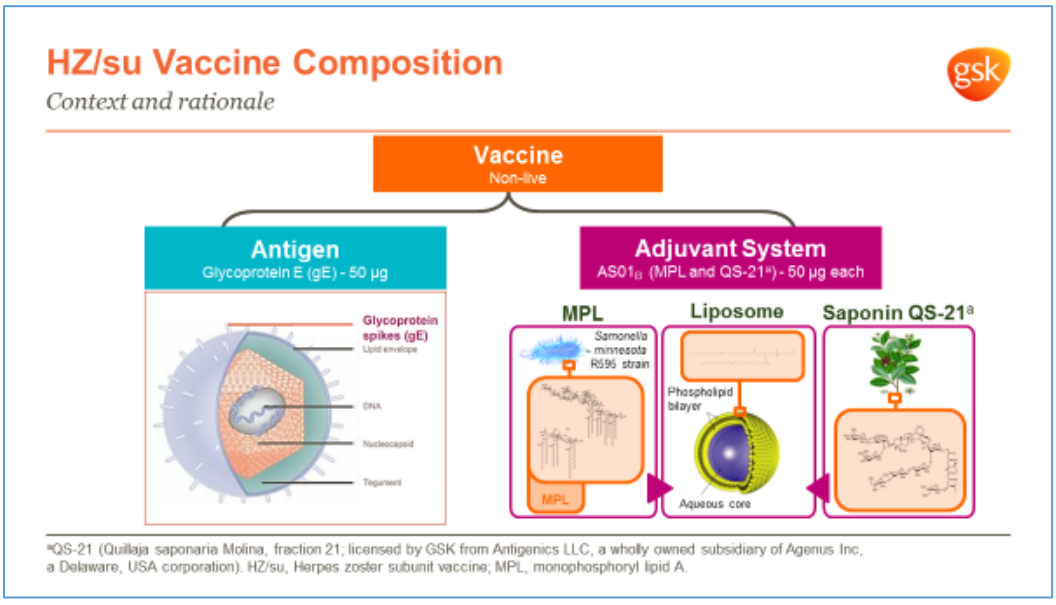
In terms of the GRADE summary for one dose of ZVL compared to placebo or no vaccine in adults aged 50 and older, the critical outcomes of HZ, PHN, and SAEs related to vaccination are all supported by at least one good quality large RCT and were given an evidence type 1. For these critical outcomes, the overall evidence type is 1. In other words, the WG's level of confidence in the estimate of effect of these outcomes is high. For important outcomes, reactogenicity and duration of protection were assigned an evidence type of 1 and 2, respectively. To recap, the findings were that ZVL is effective in preventing herpes zoster and PHN and no safety concerns of SAEs related to the vaccine were observed in real-world or clinical settings.

Herpes Zoster Vaccine Revaccination Data

Romulo Colindres, MD, MPH
Global Medical Affairs Lead
Zoster Vaccine Program
Glaxo/Smith/Kline

Dr. Colindres noted that he would be presenting to ACIP on behalf of a very large team at GSK and many study investigators on the immunogenicity and safety of Shingrix in adults previously vaccinated with ZVL. To place this presentation into context, he reminded everyone that the ZOE-50 and ZOE-70 Phase III clinical trials were previously presented at the June 2015 and October 2016 ACIP meetings. In February 2017, a broad overview of HZ/su safety was presented to ACIP with no major safety concerns today. The presentation for this June 2017 session focused on the Zoster-048 study evaluating revaccination with HZ/su in terms of the context and rationale for why the revaccination study was conducted, the objectives and study design, results, and important conclusions and key take-away messages.

The following graphic illustrates the composition of the non-live, HZ/su vaccine candidate:



On the left in turquois 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 immune response. On the right is the adjuvant system $ASO1_B$, which serves to enhance the glycoprotein E (gE)-specific immune response. $ASO1_B$ is a liposome-based adjuvant system containing the immunostimulants MPL and QS-21. Synergistically, MPL and QS-21 induce a stronger and long-lasting both humoral and cell-mediated immune response.

To begin, some context and rationale for why the ZVL revaccination study was conducted. ZVL has been licensed in the US since 2006. Approximately 31% of US adults ≥60 years of age have received ZVL[1]. Vaccination with ZVL, the current standard, offers protection against HZ with a VE of 51% in adults ≥60 years of age[2]. However, as has been published in the literature and was presented by Dr. Klein earlier, this protection wanes over time[3]. Therefore, revaccination with a different HZ vaccine may be required to attain optimal and sustained protection against shingles. The Zoster-048 study was designed to generate immunogenicity and safety data in persons who received ZVL at least 5 years prior [[1]CDC. Vaccination coverage among adults in the United States, NHIS, 2015. www.cdc.gov/vaccines. Accessed June 7, 2017; [2]2016 Zostavax PI; [3]Morrison VA, et al. *Clin Infect Dis*. 2015;60:900-999].

Moving on to the objectives and study design, Zoster-048 is a Phase III, prospective, non-randomized, group-matched study conducted in the US. Subjects ≥65 years of age were enrolled in parallel in two groups, the previous ZVL or no previous ZVL groups. As the name implies, previous ZVLs were subjects who received the ZVL live ≥5 years prior and the no previous ZVL were those who did not receive the live vaccine. There were two co-primary objectives. The first was to compare anti-gE antibody concentrations 1 month post-dose 2 of HZ/su between the two groups, and the second was to evaluate safety and reactogenicity up to 1 month post-dose 2. There were also secondary objectives, which were to assess humoral and cell-mediated immune responses at different time points, as well as an ongoing safety assessment up to 12 months post-dose 2.

Prior to vaccination, potential subjects went to a screening visit for eligibility, ZVL history, and matching variables. Based on this information, 215 subjects each were enrolled in the previous ZVL group and the no previous ZVL group. Subsequently, all subjects received HZ/su at Month 0 and Month 2. In order to assess humoral and cellular immune responses, blood samples were taken at baseline or pre-vaccination, 1 month post-dose 1, and 1 month post-dose 2. There also will be a blood sample taken at the end of the study 12 months post the second dose. As the study is ongoing, the results presented during this meeting were through the Active Phase or through Visit 4, Month 3.

For participant enrollment, 822 participants were screened for eligibility, ZVL vaccination, and matching variables. The matching variables include age (65-69, 70-79, ≥80), gender, race, and medical condition as appropriate (in hierarchical order: immune mediated diseases, diabetes mellitus, depression, pulmonary conditions, heart conditions, and none of the above). The result was that out of 822 participants screened, 430 subjects (215 in each group) were matched and vaccinated. There were 213 subjects who received Dose 2 and completed the Active Phase of the study in the previous ZVL group versus 212 in the no previous ZVL group.

Turning to the study results, the mean age of subjects upon receipt of the first dose of HZ/su was 70.9 years. There was nearly an equivalent number of males and females enrolled in the study, all subjects were Caucasian. The mean time since previous ZVL vaccination was 6.7 years.

In terms of the primary endpoint, non-inferiority of previous ZVL to no previous ZVL in terms of humoral immune response 1 month post the second dose of HZ/su, the GMCs of approximately 48,000 for the previous ZVL group compared to the GMCs of approximately 50,000 in the no previous ZVL group, the GMC ratio total value was 1.04 with an upper limit of the 95% confidence interval of 1.17. This is well below the preset criterion of 1.5 for non-inferiority. Clearly, the primary endpoint of this study was met.

Next, there were secondary objectives pertaining to the humoral immune response at separate time points. There was virtually no difference between the two groups for any of the timepoints. Furthermore, the GMC results from the ZOE-50 and ZOE-70 clinical studies for both time points (pre-vaccination or baseline, and 1-month post-dose 2) are remarkably similar to those of the Zoster-048 study.

Cellular immune responses also were assessed by measuring gE-specific CD4 T-cell frequencies. Similar to the patterns that were seen for the humoral immune responses, the T-cell frequencies are similar between the groups at all of the time points studied in the Zoster-048 study. In the ZOE-50 study, the cell-mediated immune responses are similar to those in the Zoster-048 study.

Transitioning to the safety results, solicited local and systemic symptoms were collected for 7 days after each dose, while unsolicited AEs were collected for 30 days after each dose. SAEs and potential immune-mediated diseases (pIMDs) are being collected and followed through the entire study period or 12 months post the second dose. Again, as this is an ongoing study, the results presented during this meeting were through Month 3 analysis or 30 days post the second dose.

In terms of SAEs and unsolicited AEs up to 30 days post last vaccination, there appeared to be a higher point estimate in the previous ZVL group compared to the no previous ZVL group. Although there was some overlap in the confidence intervals, the investigators looked more closely into these unsolicited AEs, and there are two points to make. The first is that the absolute number of AEs was relatively small, and these AEs were widely dispersed over more than 20 system organ classes with no apparent clustering or biologic plausibility. Lastly and of note, there were no pIMDs or related SAEs reported from first vaccination up to 30 days post last vaccination.

Regarding the local or injection site symptoms within 7 days post-vaccination of any grade, the results are consistent with the Phase III clinical trials with pain being the most commonly reported injection site symptom in both groups. All symptoms were of a duration of 2 to 3 days, and the majority were mild to moderate in intensity. Looking specifically at Grade 3 injection site symptoms, again pain was the most common solicited injection site symptom for both groups and all groups showed similar reporting for all symptoms. The median duration for these Grade 3 symptoms was 1 day.

For solicited systemic symptoms of any grade, the most commonly reported symptoms were fatigue, headache, and myalgia all of which were reported similarly between both groups and all had a duration between 1 and 2 days. These results also are consistent with the Phase III clinical trials. For Grade 3 solicited systemic systems, the two most commonly reported symptoms were fatigue and myalgia and they were transient with a median duration of 1 to 1.5 days.

Regarding the conclusions, Shingrix induced a strong humoral and cellular immune response consistent with Phase III ZOE trials, regardless of previous vaccination with ZVL. There were no clinically significant safety differences observed between the study groups within 30 days post-dose 2 of Shingrix. Solicited local and systemic symptoms also were similar between the two groups.

In summary, the results of Shingrix Phase III clinical trials ZOE-50 and ZOE-70 demonstrated unprecedented age-independent efficacy of > 90% even in those above 70 and above 80 years of age. This high vaccine efficacy has been shown to persist through at least 4 years post-vaccination. Earlier in 2017, GSK presented the well-characterized safety profile of Shingrix with no concerns to date. Although solicited local and systemic symptoms are more common in the vaccine than the placebo group, the majority were mild to moderate in intensity and of short duration. In addition, there were reassuring immune persistence data going up to 9 years, which was presented in February 2017. The results of the Zoster-048 revaccination study have demonstrated that having been previously vaccinated with ZVL does not negatively impact the immunogenicity or safety of Shingrix. Given that the immunogenicity and safety results of this study are consistent with the ZOE clinical trials, GSK is encouraged that Shingrix may become an option for individuals who have previously received ZVL and may benefit from the high vaccine efficacy of Shingrix observed in previous trials.

Discussion Points

Dr. Reingold asked whether any of the people enrolled in the study had a history of HZ before they were enrolled and, if so, what the effects of the vaccine were in people with a history versus no history of HZ.

Dr. Colindres replied that in the GSK study, a history of HZ was an exclusion criterion and they would not have been included in the study.

Dr. Klein responded that Merck also excluded people with a history of HZ.

With respect to the Kaiser study, Dr. Moore recalled that Dr. Klein mentioned 5900 cases that were borderline that had an 86% PPV and were excluded, but were included in the sensitivity analysis. She inquired as to how they impacted the sensitivity analyses.

Dr. Klein replied that the findings were essentially the same in those cases as with the primary analysis.

Dr. Hunter asked whether the Kaiser study really had only 29% uptake of the ZVL vaccine in people over 50 who did not have to pay anything for the vaccine.

Dr. Klein confirmed that this was correct even though it is a free vaccine. Uptake definitely increased when the database prompt was implemented for those 65 years of age and above. All of Kaiser's vaccines are free, but reminding physicians and patients with the prompt is important to increasing uptake.

Dr. Hunter observed that the national data on HZ vaccine uptake is based on 60 years and older, not 50 years and older. He wondered if Kaiser reanalyzed the data for 60 and older it would be higher than 30%.

Dr. Klein acknowledged that it is much higher than 29% for those 60 years of age and older, although she did not have the exact percentage.

Cost-Effectiveness Models

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Dr. Leidner described two cost-effectiveness models, which were developed by two different teams, Merck and GSK. Each of these models was described in a report submitted to the ACIP HZ WG, as well as in a presentation given to the ACIP HZ WG. Both reports went through the CDC economic review following the ACIP Guidance for Health Economics Studies. An earlier draft of these slides circulated to Merck and GSK for review. A cost-effectiveness analysis by the CDC team is forthcoming in October 2017.

A cost-effectiveness ratio (CER) can be considered a price paid per unit of health gained. In some models, health gained is thought of as a cost per case avoided. Outcomes considered in this presentation are quality-adjusted life-years (QALYs). A QALY is suitable for HZ because QALY accounts for morbidity loss and the main disease burden of HZ is in pain, which is a morbidity outcome. CERs always compare two potential strategies, for example, vaccination versus no vaccination. Dr. Leidner explained that throughout the presentation, he would be using the notation of Strategy 1 versus Strategy 2 to define the scenarios.

The CER is the result of calculations based on several assumptions, or parameters, or inputs. The assumptions, combined with how they are calculated, is the cost-effectiveness model. The output of that model is the CER. Parameters can include intervention (i.e., vaccine) effectiveness, costs of intervention, costs of disease outcomes, and many others. An important aspect of these two things is that the availability of relevant data varies by parameter. As a quick concrete example of how CERs work, imagine Intervention A having a CER of $1 million/QALY and Intervention B having a CER of $10,000/QALY. If this were the case, one would say that if $CER_A > CER_B$, then intervention A is *less* cost-effective than B.

Regarding the background of the model and base case results, the current vaccine, ZVL or Zostavax® by Merck, is licensed and recommended. Zostavax® is a 1-dose vaccine that has been received by 20 to 25 million people. The candidate vaccine is a HZ/su vaccine, Shingrix, by GSK. Shingrix is a 2-dose vaccine. The GSK model and Merck model cost-effectiveness research objectives were to assess adults 60 years of age and older who have never received a vaccine for HZ in terms of the cost-effectiveness of ZVL versus no vaccine, HZ/su versus no vaccine, and HZ/su versus ZVL (head-to-head). Both models contain several additional sub-analyses that were not included in this presentation due to time restrictions.

In terms of the base case scenario, the findings for ZVL versus no vaccine were a cost of $120,000/QALY for GSK and $125,000/QALY for Merck. This is a fairly close finding for two separately made cost-effectiveness models. Regarding the HZ/su versus no vaccine, the Merck model identified a CER for the HZ/su vaccine of $74,000/QALY. This is greater than the GSK model finding of $12,000/QALY. The next step was to determine exactly why these two values differed.

Regarding initial VE for HZ/su, the GSK model assumes a single dose of the HZ/su confers 90% VE initially and the Merck model assumes 73%. That difference is contrasted with how similar these are in the 2-dose assumption. In terms of VE through time, the GSK model starts at 90% and then declines gradually to 0% by Year 16. By contrast, the Merck model starts at 73% and declines to 0% after 1 year. For 2 doses of the HZ/su vaccine, the models are very similar for the first 5 years and then both decline, with the GSK model declining at a more gradual rate.

As a reminder for the HZ/su versus no vaccine scenario, the GSK model base case result is $12,000/QALY and the Merck model result is $74,000/QALY as seen earlier. If in the GSK model a sensitivity analysis is produced, the parameters would be affected by lowering of the second dose compliance rate, lowering the first dose efficacy, and increasing the rate of waning following a single dose of the HZ/su vaccine. Changing these inputs results in an increase in the CER bringing it much closer to the Merck base case results. To foreshadow the discussion later, this type of sensitivity analysis is pretty common in these models.

In terms of the vaccine cost assumptions, vaccine costs are very important for cost-effectiveness in general. For ZVL, both models assume a comparable cost about $200 per single dose (GSK $197; Merck $213). For the HZ/su vaccine, the GSK model assumes that a single dose costs $140 and the Merck model assumes that a single dose costs $106. Accounting for the fact that there are 2 doses of the HZ/su vaccine and vaccine administration fees, the total 2-dose cost of the HZ/su vaccine is $320 for the GSK model and $250 for the Merck model.

Regarding cost-effectiveness in general, the scenario comparing HZ/su vaccine to no vaccine includes the base case model at $12,000/QALY for GSK and $74,000 for Merck. For the sensitivity analyses, the extreme values were identified. The two takeaways from this are that the error bars overlap and all extreme points are lower than $150,000/QALY.

Moving to the head-to-head comparison of the HZ/su vaccine to ZVL, in both base cases in both models the HZ/su vaccine was found to be cost-saving relative to ZVL. The only case in which ZVL was found to be cost-saving relative to the HZ/su vaccine was in the scenario in the Merck model that favored ZVL.

In summary, for the HZ/su versus no vaccine scenario, the base case ranged from $12,000 to $74,000 per QALY gained. The sensitivity analyses brought this from cost-saving to $150,000 per QALY gained. In the ZVL versus no vaccine scenario, the base case cost-effectives ranged from $120,000 to $125,000 per QALY gained. In the sensitivity analyses, the range was from $60,000 to $260,000 per QALY gained. In the HZ/su versus ZVL scenario, the base case of both models found that HZ/su is cost-saving relative to ZVL. In one case, ZVL was cost-saving relative to the HZ/su, which was in the Merck model with parameters that favored ZVL. Important factors influencing the observed range in values between the two models include efficacy and waning immunity for the first dose of HZ/su vaccine and long-term waning immunity for 2doses of HZ/su vaccine. Important factors influencing the observed range in overall cost-effectiveness include the HZ/su vaccine cost, HZ/su regimen completion, HZ incidence, cost to treat a case of HZ with and without PHN, initial efficacy of a single dose of HZ/su, and rate of waning immunity from HZ/su.

The limitations of the study are uncertainty around several key parameters, including limited empirical data for efficacy and waning immunity for the first dose of HZ/su vaccine, 2-dose regimen completion of HZ/su outside of clinical trials, and long-term waning immunity for 2 doses of HZ/su vaccine. In addition, the price for the HZ/su vaccine has not been published.

Discussion Points

Dr. Kempe observed that the Merck base case assumed only one immunization. The rationale for that was not clear to her, given that the vaccine license application is as a 2-dose vaccine.

Dr. Leidner replied that both models account for the fact that regimen completion may not be 100% and what the immunity would be for the portion who did not complete the series.

Dr. Hunter asked whether there were criteria in the sensitivity analyses for various levels of completion (e.g., 0%, 50%, 100% of the population finished the second dose).

Dr. Leidner indicated that there were such criteria in the sensitivity analyses. The base case assumption for second dose completion for the Merck model was 73% and for the GSK model it was 68%. The lower bounds for both were about 45% and the upper bounds were 90% plus or minus 1% or 2%.

Dr. Thompson (NVAC) wondered whether Dr. Leidner could offer some intuition behind the different assumptions on the waning, and the logic and evidence behind why the two companies appear to be looking at this very differently.

Dr. Leidner replied that in terms of the literature on a single dose of HZ/su, there are no data on what that efficacy would be. GSK based their results on some internal data and Merck based their results on an assumption. He deferred to the manufacturers to respond regarding the motivation of their selection of particular wane rates.

Dr. Bresnitz (Merck) confirmed that there are no data published for the 1-dose subunit vaccine, so they basically have to guess or try to come up with some estimate not only in terms of 1-dose efficacy, but also the durability of that dose. The waning immunity shown was based on the Phase II study results on the immunogenicity data published by GSK, which led them to conduct their pivotal trials with the 2-dose vaccine. GSK's Phase II study showed that after 1 dose, they did not reach what the peak was after 2 doses, and after 3 years it basically returned to close to baseline. That is what Merck used to assess what they thought might be efficacy and durability.

Dr. Friedland (GSK) replied that when they reviewed their data, they needed to come up with an assumption for what VE would be for 1 dose even though this is a 2-dose vaccine, and what the waning rates would be. For Phase II, GSK conducted a study that assessed 1 dose and showed that immunity was maintained above baseline out to 3 years for cellular and humoral immunity. In addition, the rate of waning was assessed. The assumption regarded why the rate of waning would be any different for the subunit versus the live vaccine. The live vaccine wanes at approximately 5.1% to 5.4% per year, which was the rate included in the GSK model for 1 dose.

Dr. Lee asked what types of models were built for the two different analyses, what the time horizon was, and whether discounting was used. Related to that, the estimates for ZVL versus no vaccine were quite similar for the two, which was reassuring on one hand, but also because the functions might be different that go into those models, she wondered whether they looked

further to determine if the same assumptions were used, or if the results were the same because they just happened to get to the same results. She thought it would be helpful to understand the price assumptions, the range of the sensitivity analyses, and whether a probabilistic sensitivity analysis (PSA) would be typically used in this situation or these types of models or if there would be reliance on one way to help understand the robustness of these analyses.

Dr. Leidner replied that both were lifetime models, both included discounting, and they were Markov models. A lot of the assumptions were very comparable between the two models. There were very similar costs per case, waning immunity and efficacy assumptions for ZVL were extremely close. To him, it appeared that the two manufacturers relied on the published evidence and used the same or very similar parameters. While he did not present any PSA results, both models did produce PSA results. The error bars he presented contained 80% to 90% of the PSA results. In terms of price, the Merck model assumed a price parity of the HZ/su vaccine with ZVL. Around that price parity, they expanded plus or minus 20%. For the GSK model, a base case was assumed of $145 [$140] with an upper bound of $175 and lower bound of $125 [per dose]. He deferred to the manufacturers to discuss the motivation behind those ranges.

Regarding the pattern of waning after vaccination and assuming a constant rate of waning, it seemed to Dr. Reingold that the data Dr. Klein presented showed that there is a dramatic decrease in the first year that remains relative constant after that. From a clinical protection point of view, that seemed to be a better model of what is going to occur than constant waning.

In terms of the 2-dose waning, Dr. Bresnitz (Merck) reminded ACIP that data were presented during the February 2017 ACIP meeting that were based on a Phase II study of immunologic data involving a group of 70 people in the Phase II trial that was homogenous from Europe. That is not representative of what was in the ZOE-50 and ZOE-70 studies, which he thought was the basis of the model for the durability of the vaccine that goes out to 30 years. There is about a 4-fold decrease from the response immediately after 2 doses to what is observed at 9 years. The bottom quartile of the point estimate at 9 years overlaps with the top quartile of the estimate at baseline. Given that there is no correlate of protection, he did not know whether they could say anything about the real durability or effectiveness of those data, but it does decline over time. This information is available on the ACIP website. He also noted that the cost-effectiveness model was for those 60 years of age and older, but the policy question addressed in the GRADE analysis presented earlier in the session for Zostavax® and for Shingrix during the last ACIP meeting was for persons 50 years of age and over.

For the waning assumptions in the model, Dr. Friedland (GSK) noted that everyone had the full report submitted and reviewed by the CDC Economic Team. The data for waning came from the ZOE-50 and Zoe-70 studies, so the actual numbers are that the rate of waning for the first 4 years for people 50 through 70 years of age was 1%, and then was 2.3% in years 5 and beyond. For individuals over 70 years of age, the rate of waning was 3.6% throughout the model. Those data come from the Phase III RCT vaccine efficacy studies.

Dr. Bennett observed that it will be interesting to see the CDC model having seen these two models, and to see how the decisions are made about the data to use in the new model.

Consideration for the Use of HZ Vaccines

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Dr. Dooling began with a review of HZ and PHN epidemiology in the US. The annual rate of HZ is approximately 4 cases of HZ per 1000 population or roughly 1 million cases annually[1,2]. Incidence increases with age, ranging from about 1 case/1000 children to about 15 cases/1000 population 80 years and older.[2,3] For adults 50 years and older with HZ, about 10% to 18% will go on to develop PHN. Similar to HZ, incidence increases with age[3]. For many, the pain of HZ and the unrelenting persistence of PHN can be debilitating [[1]Jumaan et al., JID, 2005, 191:2002-7; [2]Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9; and [3]Insinga et al., J Gen Intern Med. 2005, 20:748-53].

In terms of vaccination coverage for ZVL among adults 60 years of age and older in the US between 2007-2015, starting from FDA licensure in 2006, ZVL has shown a slow and steady increase in trend in coverage to approximately 31% by 2015. Dr. Dooling indicated that she would not review safety and efficacy as they were discussed in previous presentations.

Regarding the GRADE evaluation of HZ/su that was presented to ACIP in February 2017, the vaccine was significantly efficacious in preventing both HZ and PHN. The estimates for VE against HZ were 97% for individuals 50 through 69 years of age and 91% for individuals 70 years of age and older. The estimates for VE in preventing PHN were 91% for those 50 years of age and older and 89% for those 70 years of age and older. The protection against HZ was at least 85% in the 4 years study. Regarding SAEs, no difference was detected between vaccinated and comparison population. However, Grade 3 reactions were reported more commonly in vaccinated groups compared to placebo. All of the outcomes examined were supported by Type 1 evidence.

The following are key HZ vaccine policy questions before the ACIP:

- ❑ Should ACIP recommend HZ/su for vaccination of immunocompetent adults either as a Category A or a Category B?
- ❑ At what age should HZ/su age-based recommendations start: 50 years of age or 60 years of age?
- ❑ Should ACIP recommend a preference for HZ/su over ZVL?
- ❑ Should ACIP recommend that individuals previously vaccinated with ZVL receive HZ/su?

In order to address these policy questions, Dr. Dooling presented the WG's interpretation of the data, the WG's deliberations, and the WG's current perspective on the policy. However, the WG is awaiting a final price for HZ/su in order to complete final cost-effectiveness analyses, as well as strategies to achieve high 2-dose adherence for HZ/su. Therefore, the interim work group perspective was expressed during this session.

With respect to the first policy question regarding whether ACIP should recommend HZ/su for vaccination of immunocompetent adults, the WG interpretation of the data is as follows. Based on 1 large Phase III RCT, HZ/su demonstrated high VE against HZ of 97% and 91% for 50 through 69 year olds and ≥70 year olds, respectively; high vaccine efficacy against PHN at 91% for >50 year olds; and maintenance of efficacy above 85% for 4 years following vaccination in ≥ 70 year olds. Based on 1 large Phase III RCT and additional small studies, HZ/su demonstrated no differences detected between vaccinated and comparison populations for SAEs and more commonly reported Grade 3 reactions in vaccinated groups (17%) compared to placebo (3%).

What does all of this mean in terms of the burden of disease that can be expected to be prevented through the use of HZ/su vaccine? In terms of health outcomes comparing HZ/su to no vaccine in a cohort of 10,000 60-year-olds over 4 years, simplifying assumptions were made that VE is stable over 4 years at 97% for HZ and 93% for PHN, disease incidence is stable over 4 years (HZ= 8:1000, PHN= 0.9:1000), and all vaccinees completed 2 doses of HZ/su. In 4 years under these parameters, approximately 320 cases of HZ and 36 cases of PHN would be expected in an unvaccinated cohort of 10,000. If vaccinated with HZ/su, cases expected would decrease to 10 for HZ and 3 for PHN thus preventing 310 cases of HZ and 33 cases of PHN over 4 years. Under these simplistic parameters, the number needed to vaccinate (NNV) to prevent 1 case of HZ in 4 years would be 32 and NNV to prevent 1 case of PHN in 4 years would be 303.

Looking at the same health outcomes in the same cohort with the expected cases of HZ and PHN modeled over the lifespan, a number of assumptions were made regarding 2-dose compliance and 1-dose effectiveness of HZ/su and rates of waning of the vaccination. Those assumptions were introduced in the previous cost-effectiveness analysis presentation. The estimates were derived from the Merck and GSK models. Estimates for HZ cases expected over the lifespan in an unvaccinated cohort range from 1961 to 2020. Estimates of PHN cases expected range from 200 to 226. Estimates of disease in the HZ/su vaccinated group range from 925 to 1250 for HZ and 114 to 130 for PHN. The number of HZ cases expected to be prevented over the lifespan through HZ/su ranges from 780 to 1036, and the number of PHN cases expected to be prevented over the lifespan ranges from 70 to 112. Therefore, over the lifespan, the NNV to prevent 1 cases of HZ is 10 to 13 and the NNV to prevent 1 case of PHN is 89 to 142.

Returning the focus to the first policy question regarding whether ACIP should recommend HZ/su for vaccination of immunocompetent adults, based on review and GRADE assessment of the evidence for critical and important outcomes, the WG is confident that the vaccine is safe, efficacious, and maintains high protection against HZ 4 years following vaccination. WG members acknowledged the importance of clear ACIP recommendations. Under most assumptions, HZ/su demonstrates NNV and cost-effectiveness similar to or more favorable than other adult vaccines. The WG is favorable to vaccinating immunocompetent adults with HZ/su as a Category A.

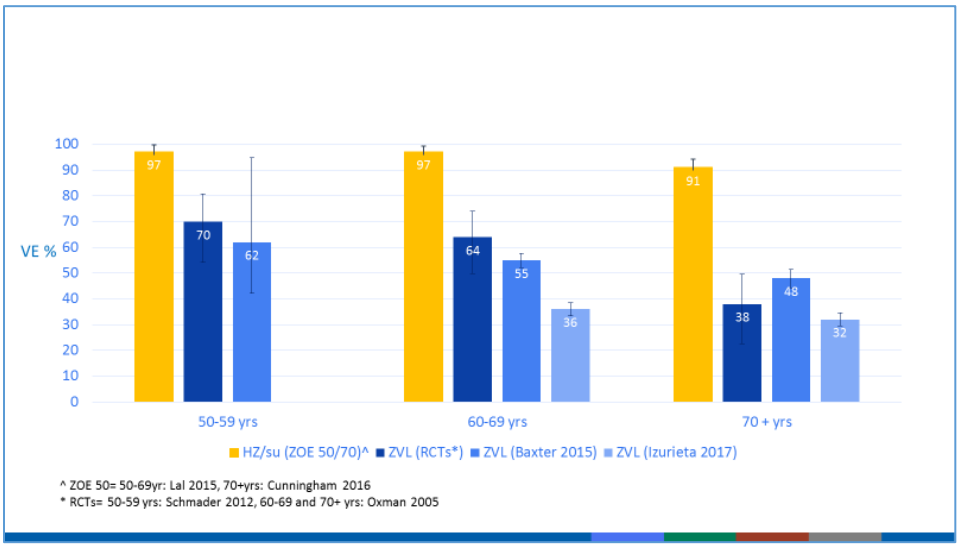
In terms of the second question regarding whether the HZ/su age-based recommendations should start at 50 or 60 years of age, the WG interpretation of the data was that HZ/su efficacy is very high in the 50 through 59-year-old group at 97%. There is minimal waning in the first 4 years following vaccine receipt. Waning beyond 4 years is unknown. In a small Phase II study of participants 60 years of age and older, immunogenicity data at years 4, 6, and 9 years following HZ/su vaccination shows similar CD4+ T-cell response with a >3-fold rise above

baseline. These data were presented to ACIP in February 2017. However, there is no established correlate of protection.

WG deliberations on this question included a number of points. HZ and PHN incidence increases with age. In 2011, ACIP did not recommend ZVL for 50 through 59-year-olds because there was evidence of waning in the first 4 years and beyond. HZ/su VE is very high in this age group (97%) with minimal waning in the first 4 years. The degree of waning beyond 4 years is uncertain. However, durability has been demonstrated for cellular and humoral immunological outcomes at 6 and 9 years. There are about 42 million people who are 50 through 59 years of age in this country, and about 21% of all HZ episodes occur in this age group annually. The WG is favorable toward an age-based recommendation starting at 50 years old; however, policy proposals are awaiting a final price for HZ/su and accompanying cost-effectiveness analyses for this subgroup.

The next question considered regarded whether ACIP should recommend a preference for HZ/su over ZVL. In terms of the WG interpretation of the data, it is important to note that these vaccines have not been studied in a head-to-head efficacy trial. HZ/su estimates of efficacy are higher than ZVL estimates across all age groups. HZ/su appears to wane at a slower rate than ZVL over the first 4 years. With respect to safety outcomes, it should be noted that HZ/su vaccine has been studied in approximately 16,000 participants in clinical trials; whereas, ZVL has been administered to more than 20 million people in the US following its clinical trials. Neither vaccine is associated with SAEs in immunocompetent persons. HZ/su is more reactogenic than ZVL. ZVL is a live-attenuated virus, which can cause HZ in rare circumstances. In terms of economics, HZ/su is more cost-effective than ZVL under most assumptions.

This graph depicts VE and effectiveness against HZ for HZ/su and ZVL by age group during the first 4 years following vaccination:



As shown on the graph, the HZ/su vaccine is more efficacious in each age category and the difference is larger amongst older recipients.

Returning to the simple cohort of 10,000 people 60 years of age and older followed over 4 years comparing no vaccine, ZVL, and HZ/su, the same simplifying assumptions were made that VE is stable over 4 years, disease incidence is stable over 4 years, and HZ/su recipients completed 2 doses. Already presented was what would be expected for the unvaccinated and HZ/su cohorts. After 4 years in the cohort vaccinated with ZVL, approximately 150 cases of HZ and 12 cases of PHN would be expected. Therefore, for every 10,000 people vaccinated, HZ/su is expected to prevent an additional 105 cases of HZ and 9 cases of PHN compared to ZVL over 4 years.

Looking at those same 3 cohorts modeled over the lifespan, a number of assumptions have been made regarding 2-dose compliance and 1-dose effectiveness of HZ/su, as well as the rates of waning of both vaccines. Again, these were discussed in the previous presentation. The following estimates are derived from Merck and GSK analyses. The number of cases expected was presented for the no vaccination and HZ/su cohorts. Over the lifetime in the ZVL cohort, estimates of HZ cases expected ranged from 1600 to 1640 and expected cases of PHN ranged from 140 to 177. Therefore, for every 10,000 people vaccinated, HZ/su is expected to prevent an additional 360 to 715 cases of HZ and 10 to 63 cases of PHN compared to ZVL over the lifespan.

The two policies under consideration by the WG were a preference for HZ/su vaccine or no preference for either vaccine. Dr. Dooling reviewed the pros and cons of each of these options as deliberated by the WG.

Under a preference for HZ/su, the pros would be substantially more prevention of HZ, PHN, and other complications. This is a particularly important issue for seniors 80 years and older who are most vulnerable and at highest risk for HZ and PHN. HZ/su is more cost-effective than ZVL under most assumptions. However, the price has not been finalized and a cost-effectiveness analysis is pending. HZ/su is refrigerator-stable, which may decrease provider barriers. Cons of a preferential recommendation are that HZ/su vaccine may be removed from the market if an unexpected safety signal is observed with HZ/su. This policy may lead to more Grade 3 reactions following vaccination. HZ/su requires 2 doses, which will likely increase programmatic barriers.

In terms of a no preference policy, this would support competition and safeguard a stable vaccine supply in the event of an unexpected safety signal. On the con side, large difference in VE will result in thousands of preventable HZ cases and hundreds of PHN cases. Additionally, some insurers or delivery systems may choose to cover only the less expensive vaccine if no preference is stated. Finally, a non-preferential policy places the onus on providers to compare safety and efficacy.

Ultimately, there are a number of unknowns in this decision analysis. There is always a possibility that an unexpected safety event with HZ/su may occur. The VE of HZ/su beyond 4 years is unknown. The real-world 2-dose compliance of HZ/su is unknown, and the VE and durability of 1 dose of HZ/su are both unknown. With regard to programmatic and implementation factors, price, insurance coverage details, and healthcare seeking among vaccinees with reactions are all unknown.

In terms of how long it will take to answer the unknowns, assuming that HZ vaccine uptake continues at its current pace of about 3 to 4 million doses annually, a 1- to 2-year period may be sufficient to accumulate real-world safety data of HZ/su vaccine for surveillance for rare AEs. For 2-dose compliance of HZ/su, again a 1- to 2-year period probably will be needed as compliance will likely change as the program matures and providers become familiar with the HZ/su reactogenicity profile. For VE, a 4- to 8-year period beyond licensure would be necessary to study and report on long-term effectiveness. VE of 1 dose of HZ/su would require at least a 2- to 3-year period for an observational study in, for example, a large health maintenance organization (HMO) with at least 1 million unvaccinated adults to accumulate sufficient 1-dose HZ/su recipients. At least 4 years would be required for age-specific estimates and duration of protection. During this period, preventable cases of HZ and PHN may continue to occur if a less effective vaccine is used.

To recap the WG deliberations regarding a preference for HZ/su vaccine over ZVL, HZ/su can prevent significantly more HZ and PHN than ZVL. HZ/su is more cost-effective than ZVL under most assumptions. A preference would safeguard access to the more efficacious vaccine; whereas, insurers or delivery systems may choose to carry only the less expensive vaccine if no preference is stated. An equivalent recommendation puts the onus on clinicians to review the literature on both vaccines to compare safety and efficacy. However, there are a number of key unknowns, including 2-dose compliance, VE of 1 dose, long-term waning, and the possibility of an unexpected safety signal. The majority of WG member favored that a preference be stated for HZ/su over ZVL. A minority of WG members thought no preference should be stated at this time. The WG is awaiting a final price for HZ/su and accompanying cost-effectiveness analyses.

In terms of the final policy question regarding whether individuals previously vaccinated with ZVL should receive HZ/su, the WG's interpretation of the data was as follows. HZ/su is more efficacious than ZVL in all age categories. Experimental and observational studies indicate significant waning of protection from ZVL. VE drops the first year after receipt by 15% to 25%. By 6 years post-vaccination, most studies estimate that VE is less than 35%. There may be negligible protection by 10 years post-vaccination. HZ/su is significantly more efficacious over 4 years with a VE of greater than 97% in the first year, which is maintained above 85% in the subsequent 3 years for all ages. In a small study presented to ACIP earlier in this session, vaccination with HZ/su 5 years following ZVL did not alter the safety or immunogenicity of HZ/su. There is a significant gap in HZ protection between that provided by HZ/su and that provided by ZVL.

The WG deliberations on this policy question were as follows. Prior ZVL receipt should not be a contraindication to receiving HZ/su. For prior ZVL recipients, HZ/su is a new vaccine. A substantial amount of HZ and PHN could be prevented by vaccinating this population with HZ/su. Prior ZVL did not alter the safety or immunogenicity of HZ/su. Of the US population, 31% of individuals 60 years of age and older have already followed ACIP recommendations and received ZVL. A significant fraction of ZVL recipients now have very low vaccine protection for HZ and PHN. The WG's perspective was that HZ/su should be considered for people who have already received ZVL. The WG is awaiting a final price for HZ/su and accompanying cost-effectiveness analyses.

Looking forward, the WG will review a summary of the GRADE analyses of both vaccines, the CDC cost-effectiveness model, and considerations for policy during the October 2017 ACIP meeting. In addition, and FDA licensure decision for HZ/su vaccine is expected prior to the ACIP October 2017 meeting. At the ACIP's discretion, a vote on HZ vaccine recommendations

may be taken in October 2017. In closing, Dr. Dooling requested feedback on whether there are additional data that would help ACIP develop policy for the use of HZ vaccines in adults.

Discussion Points

Dr. Atmar recalled that a question was raised during the meeting in February regarding the racial make-up of the ZOE trials, which included only 1% African Americans. The revaccination study presented during this session included 100% Caucasians. This remains a major gap in terms of understanding whether the vaccine will perform similarly in all groups.

Dr. Dooling replied that the data presented represented all of the data accumulated up to this point.

Dr. Kempe pointed out that many of the analyses presented during this session were helpful and straightforward, but these analyses assumed that everyone would receive 2 doses. The previous analyses heard earlier were based on 1 dose. She would like to see these data with 25% and 50% of individuals receiving 2 doses.

Dr. Dooling clarified that she presented the cohort based over 4 years in which everybody received 2 doses, which she referred to as the simplified cohort. The subsequent cohorts, which were modeled by both GSK and Merck did assume real-world estimates of what they expect to be 2-dose compliance. As Dr. Leidner previously presented, for GSK the estimate was 69% 2-dose compliance and for Merck was 72% 2-dose compliance. Some sensitivity analyses were performed for those as well, which were not presented.

Dr. Bennett noted that in the simplified cohort, the 60 year and above age group was used. She wondered why this did not begin at 50 years of age and above, given that the recommendation of the WG was to begin at 50 years of age.

Dr. Dooling replied that they wanted to use as much current real-world data as possible, so the current recommendation was modeled. The 50 through 59-year-old cohort will be modeled, included a cost-effectiveness analysis, to be presented during the October 2017 ACIP meeting.

Dr. Kempe said she would like to see it lower than 75%, because that is potentially unrealistic.

Dr. Walter inquired as to whether there would be any costing for a revaccination scenario.

Dr. Dooling indicated that revaccination costing would be done as well. It was provided by one of the manufacturers, but was not presented during this session due to time constraints. This also will be done in the CDC cost-effectiveness model.

Dr. Lee asked whether they would be able to see if Dr. Klein's data, presented during this session, would make any difference in the outcomes of the models, which she thought would be very helpful. To follow up on the disparities issue, she inquired as to whether there are currently any disparities occurring with regard to HZ and PHN. As they are making considerations about preferences, she worried that there may be some unintended consequences, particularly if there are underinsured adults who have to pay out-of-pocket. She wants to make sure that they think through considerations such as this to understand whether cost does make a difference, and if it is Medicare D versus B how that might impact the implementation of a program.

Dr. Dooling replied that ZVL is currently covered under Part D as part of Medicare, and no indication has been received that this would change if a new vaccine is licensed for that indication. Regarding the question about the Phase IV studies from KPNC, those data were used to inform the longer-term waning of Zostavax® in the Merck model.

Referring to a slide, Ms. Pellegrini observed that Dr. Dooling noted that the rate of HZ among those 50 through 59 year of age represents 21% of the cases. She wondered whether similar data are available on PHN.

Dr. Dooling replied that less than 21% of PHN will occur in those 50 through 59 years of age.

Dr. Harpaz added that the rates of PHN accelerate at the age of 60. The rates of PHN among those 50 through 59 years of age is considerably lower than the rates among older adults.

Dr. Schmader (AGS) added that he did not have any specifics, but agreed that the PHN rate among persons 50 through 59 years of age is much lower.

Regarding Dr. Kempe's point about 2-dose coverage, Dr. Moore reported that the WG discussed extensively what constitutes realistic 2-dose coverage. They look at HepB coverage and completion of the series. There are some encouraging aspects to think about in terms of 2-dose coverage in this population. Those 50 years of age and older see their pharmacists a lot, and pharmacies are a source of immunization for that group. She Googled how many people over 50 years of age have a regular daily prescription. Based on data from 2005, she found that 76% of people over 50 years of age take a daily prescription, which means they see their pharmacists very regularly. The average number of prescriptions was 4, and it is probably higher now than it was in 2005. In other words, there are many opportunities for encounters with the healthcare community where immunizations can be given. This is in stark contrast to younger adults who may be at high risk for pneumococcal disease or younger adults who are getting HPV vaccine for whom there are harder challenges in terms of getting them in. She is hopeful that if there is a preference, programmatically people can be coached and helped with programmatic opportunities to increase the numbers.

Dr. Foster (APhA) observed that one of the major problems with getting people vaccinated with Zostavax® currently is the fact that the ages 60 through 65 are not covered under Medicare. Many pharmacies have difficulty billing for people in that age group. If this is lowered to age 50, unless insurance mechanisms are developed along with this, it is still going to be a very difficult process for pharmacists.

Dr. Hunter inquired as to what the likelihood would be during the first 1 to 4 years after a recommendation is made, if it is preferential, they would be "burning a bridge" and would not be able to reverse that and still have live vaccine available if something goes wrong from an implementation and market share point of view.

Dr. Dooling responded that this remains an unknown as well. From some of the informal qualitative outreach CDC has done and input from partners, many clinicians will still want to give the vaccine with which they are most familiar and have experience. The intent is for Zostavax® to retain its Category A recommendation and clinicians would continue to have access to that vaccine. She stated that she could not predict the distribution of market share under the case of a preferential vaccine recommendation.

Dr. Reingold thought surely there must be observational data on the rates and VE in groups other than Caucasians. Instead of controlling for race and ethnicity, perhaps they could produce race- and ethnicity-specific VE estimates even if they have wide confidence intervals.

Dr. Bennett noted that this would be difficult with HZ/su because the numbers are so small, but it would be possible with the live vaccine.

Regarding the framing of the cost-effectiveness analyses, Dr. Thompson (NVAC) observed that in the evolution of HZ vaccines, there was first the introduction of ZVL and to her, that is currently the status quo. She thought if ACIP was considering a change in the recommendation, the way to frame the economic analysis would be to consider the new vaccine relative to the status quo. She thought that was done to some extent in the head-to-head comparison, but it would be better to do this much more directly. In that regard, some of the uncertainty lies in the unknowns mentioned that potentially would be significant factors. She thought some sensitivity or uncertainty analyses could be performed around some of those with input from members of the WG to explore how that changes the preferential option based on a comparison of the current status quo to a subunit vaccine. Regarding the challenges with the uncertainty about how people will receive the vaccine and whether there are issues with side effects, adjuvant irritation, or anything that could change how people respond to the vaccination, that is obviously a major uncertainty that is difficult to guess at. One thing that triggers for her is that if it is known that the vaccine feels different or behaves differently, that would be a very important opportunity to communicate this to people to head off some of the potential issues.

Dr. Dooling agreed that 2-dose compliance will be affected by many factors, one of which is the ability to communicate with clinicians and the public about what will be expected in terms of reactogenicity. The WG is aware of that issue and will be working on it before the October 2017 ACIP meeting.

Regarding programmatic, implementation, and preferential issues, Dr. Bresnitz (Merck) pointed out that ACIP rarely makes a preferential recommendation. They have not done so for influenza, never did it for the HPV vaccine, and the last time it was done for LAIV, they had to go back on that for different reasons that had nothing to do with AEs. The safety database for Shingrix with about 16,000 people is very similar to when Zostavax® was licensed following the SPS, so the Shingrix safety database is probably adequate for licensure, though he left that to FDA to decide. Zostavax® has had experience with 20 to 25 million people over the last 10 plus years in the US and 36 million individuals globally. It is unknown with a vaccine that has a novel adjuvant in terms of the target population, comorbidities, and doses being used, the long-term SAEs remain unknown. Clearly, in the pivotal trials, there have been no differences with the placebo. There has been reactogenicity, which is probably because of the adjuvant. One of the first things he had to deal with when he was the State Epidemiologist in New Jersey was RotaShield® where it went to market, and after a couple of million doses it had to be taken off of the market due to an acute event immediately post-vaccination. There was not another vaccine at the time to replace it. He said he could speculate on the answer to the question of what would happen if there is a preferential to Merck's vaccine, demand clearly will go down. When demand goes down, production will go down. Live attenuated vaccine cannot be ramped up that quickly. Over time, if an SAE presents a year or two later, it would be hard to ramp up if production has been reduced.

He clarified that Merck was asked to include the 73% completion rate in its model. They do not think it is going to be 73%, but in deference to CDC who wanted to have a more comparable rate to what GSK was developing, Merck included this in its model as the base case. At that time, it was based on data from the Nelson paper that examined series completion for HepA and HepB that was more than 10 years old. Since then, there have been two publications. One was by GSK that was presented in May 2017 on this particular issue with Truven data and Merck did the same analysis, which showed that completion rates are less than 73%. He urged the WG to use the more recent data that has been validated by two separate analyses sponsored by two separate manufacturers. While he thought the pros and cons statement was great and agreed with most of them, with the exception of the insurance issue. He did not think that the insurance statement was accurate. He suggested that Zostavax® should be divided into 3 categories (commercial, Medicaid, Medicare), given that these are different in terms of reimbursement. His understanding under ACA is that when a vaccine is recommended by ACIP, it has to be covered by commercial insurance. There is not a preference for one over the other. It has to be covered. Medicaid is not an issue because most states do not cover Zostavax®. They have to include it in their formulary, but they tier it. He emphasized that a preferential recommendation would make a difference, and that ACIP has not done this previously. These two vaccines have different attributes and the market should be allowed to determine what is going to happen. There are advantages for one and there are advantages for the other that are obvious. That is what happened with the HPV vaccine. They let the market dictate and Cervarix® is no longer on the market.

Dr. Friedland (GSK) reported that in the model presented during this session, there were a wide range of sensitivity analyses, varying second dose compliance and many other variables. Across all of the various sensitivity analyses pertaining to compliance, cost-effectiveness is generally maintained. Regarding compliance and preparing the patient for the experience of the vaccination in terms of reactogenicity, second dose compliance will be great if they all work together. GSK will be discussing with the WG its plans to help bring education to providers, pharmacists, and patients so that there is a benefit from the full vaccination series that this vaccine provides. While they have to put something into a model for compliance rates, they can aim higher to achieve very high compliance rates for a vaccine that has great potential to offer very high efficacy for people of all ages.

Dr. Netoskie (AHIP) concurred with the comment about payers and whether they can prefer one over another. If Shingrix is approved, it would be covered. The confusion in the marketplace is that there may be variability in the year following approval in terms of which plans may adopt sooner versus later. He also thinks when physicians are evaluating their choices as far as physician preference, they also may choose to take a “wait and see” approach. That also may limit access to patients who may wish to receive the newer vaccine. He thinks there will be a lot of variability in the marketplace as this vaccine enters it, but health insurance plans would provide both options. In those 50 through 60 years of age, only the new vaccine would be covered if approved. Grandfather plans still exist and may fall outside of this process.

Dr. Belongia added that his understanding is that large healthcare systems could choose one product for a variety of cost and logistical reasons.

Dr. Moore added that those healthcare delivery systems with so many quality measures might, in the absence of a preferential recommendation for a 2-dose product, prefer to use a 1-dose product because it is easier to achieve quality benchmarks with 1 dose than with 2. There may be pressure because of the way they are measured nowadays to do the easier rather than the more efficacious thing.

Dr. Bennett observed that there have been some difficulties with pneumococcal vaccine in nursing homes because pneumococcal polysaccharide vaccine (PPSV) is considerably less expensive than PCV. Despite the recommendations, people are receiving pneumococcal polysaccharide vaccine (PPSV23) first.

Varicella Vaccines

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Dr. Harpaz reported on the impact of the US varicella vaccination program on the incidence of HZ. In terms of background, Dr. Edgar Hope-Simpson was a brilliant clinician and researcher in the United Kingdom (UK) during the post-war era. He developed a particular interest in varicella and HZ. While he had no formal training in epidemiology, he was a keen observer and he drew many conclusions regarding the complex natural history of varicella that still hold true today. Some 50 years ago, Dr. Hope-Simpson published his hypothesis regarding the interaction of varicella and HZ. By 1965, there was evidence that HZ was caused by reactivation of varicella zoster virus (VZV) present in latent form in dorsal root ganglia. Dr. Hope-Simpson postulated that VZV reactivation occurred years to decades after initial varicella infection, and that reactivation and subsequent development of HZ were under immunological control. He speculated that that control is maintained by two processes, endogenous boosting of immunity due to subclinical VZV reactivation without the development of HZ and/or by exogenous boosting due to exposure to children with chickenpox.

Decades later in the early 1990s, as ACIP and FDA deliberated about varicella vaccination, they considered that if Dr. Hope-Simpson was correct, the program would reduce VZV circulation and thus exposure, and the decline in exogenous boosting might then plausibly lead to an increase in the risk of HZ. The same concern continues to make vaccine policy-makers in Europe and elsewhere cautious about introducing varicella vaccination even today. An early influential infectious disease model to evaluate the implications of the Hope-Simpson hypothesis by Brisson et al published in *Vaccine* in 2002 stated in the abstract, ". . . Mass varicella vaccination is expected to cause a major epidemic of herpes-zoster, affecting more than 50% of those aged 10-44 years at the introduction of vaccination [M. Bisson, et al, *Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox*, *Vaccine* 20 (2002) 2500-2507]. The following is a key figure from the Brisson et al analysis illustrating the predictive incidence of zoster in the general population following the introduction of routine varicella vaccination:

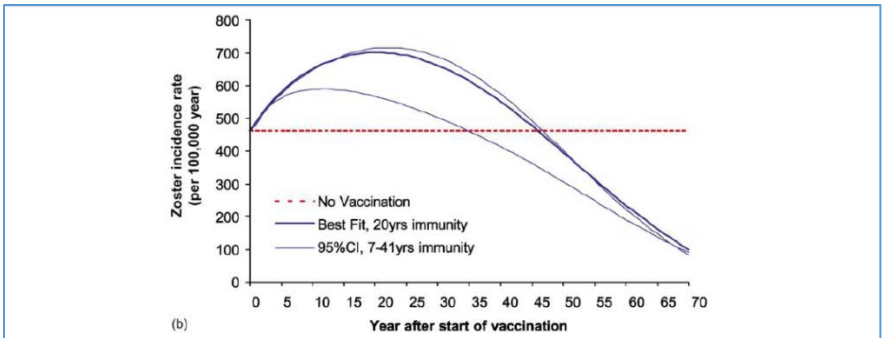


Fig. 4. Prediction of post-vaccination incidence of herpes-zoster. (a) Lifetime risk of zoster among unvaccinated individuals of different ages at the start of vaccination by different durations of immunity to zoster after exposure to varicella. (b) Incidence of zoster over time after the introduction of vaccination for the 'best-fit' model ($1/\sigma = 20$ years) and the 95% confidence bounds of $1/\sigma$ (7 and 41 years). The no vaccination scenario is represented by the dotted line.

An immediate decline in varicella rates is assumed in the above model. The dashed horizontal line shows zoster rates assuming no varicella vaccination, the violet curve representing the base case assumes zoster risk is reduced for 20 years following exposure to varicella. The two gray lines representing sensitivity analyses assume that zoster risk is reduced for either 7 or 41 years following varicella exposure. The base case model predicts that zoster rates will increase for the first 20 years after launch of varicella vaccination, peaking at levels about 50% higher than during the pre-vaccine era. Rates increase immediately and most rapidly immediately upon introduction of vaccination. Incidence then declines as fewer and fewer individuals remain latently infected with wild-type VZV. Numerous models have been published over the last two decades to evaluate the implications of the Hope-Simpson model. Most show that the results are qualitatively similar to these, with rapid increases in zoster rates immediately following introduction of varicella vaccination and peaking between 20 and 30 years later.

It has now been just over 20 years since ACIP first recommended varicella vaccine in 1996. Having framed the issues, Dr. Harpaz went on to discuss: 1) the background of varicella in the US in terms of the burden, introduction of varicella vaccination, and the impact on VZV circulation; 2) HZ in the US with regard to the epidemiology and risk factors, including baseline rates, and the introduction of zoster vaccination and vaccine uptake; and 3) the impact of the US varicella program on HZ trends. He discussed zoster in adults only since there has been no speculation that varicella vaccination would increase zoster rates among children born after launch of the program. However, he indicated that he would be happy to answer questions about this during the discussion period.

Regarding the burden of varicella during the pre-vaccine era, by young adulthood almost all persons in the US had evidence of prior infection. This is an indication that at that time averaged over several years in the entire US birth cohort of 4 million experienced varicella infection annually. Aside from service as a source of exogenous boosting, these cases translated to the large burden of disease annually, including approximately 11,000 to 13,500 hospitalizations and approximately 100 to 150 deaths. The greatest disease burden was in children who experienced greater than 90% of cases, 70% of hospitalizations, and 50% of deaths. There also were approximately 44 cases of congenital varicella syndrome annually. The large burden of disease was the rationale for introduction of varicella vaccine to begin with [Refs: Wharton ID Clin N Am 1996; Galil PIDJ 2002; Davis Pediatrics 2004; Meyer JID 2000; Nguyen NEJM 2005; Enders G & Miller E (2000) Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM and Gershon AA (eds) Varicella-zoster virus].

The varicella vaccines used in the US are Merck's VARIVAX® and ProQuad® licensed in 1995 and 2005, respectively. Both are comprised of live-attenuated VZV. In 1996, ACIP recommended 1 dose of varicella vaccine for all children 12 through 18 months of age[1]. The 1-dose program effectively prevented severe varicella, but school-based outbreaks persisted, so ACIP added a second dose recommendation in 2006 for all children 4 through 6 years of age[2] [[1]*MMWR* 1996;45(RR-11); [2]*MMWR* 2007;56(RR-4):1-39].

Regarding varicella vaccine coverage with 1-dose uptake in children 19 through 35 months of age in the US for the years 1996 to 2015, by 2006 or so uptake approached 90% in this cohort and was considerably higher at the age of school entry. By 2012, uptake for the second dose reached 88% among 7-year old children and subsequently reached 94% [http://www.cdc.gov].

In terms of how all of this vaccination has affected varicella circulation, four states have engaged in continuous varicella reporting (Illinois, Michigan, Texas, West Virginia) from 1990 or earlier. Incidence declined by an average of 97% (range 93%-98%) between 1993 to 2014. This reduction obviously translated to huge reductions in the total burden of varicella disease, including hospitalizations, deaths, and outbreaks [Lopez et al. MMWR 2016].

In 1995, CDC established Varicella Active Surveillance Projects (VASP) to more carefully monitor the impacts of the varicella vaccine program. This table shows the aggregated data for sites stratified by age group:

Age Group	Antelope Valley, CA (%)	West Philadelphia (%)
<1	-97	-94
1-4	-98	-97
5-9	-99	-99
10-14	-93	-99
15-19	-86	-94
20+	-94	-91
Total	-97.5	-98

Both sites reported 98% declines. Indeed, circulation already was down by about 90% at the beginning of the last decade. There were huge declines in all age groups, including infants under 1 year of age. Since infants are not eligible for varicella vaccine, the reduction in this age group is presumably due to the reduction in VZV infection resulting in herd protection.

Moving on to HZ in the US, prior to licensure of zoster vaccine, HZ incidence was about 4 per 1000 population annually with an annual risk of about 30%)[1]. There were approximately 1 million cases of HZ annually, approximately 110,000 cases of post-herpetic neuralgia of 90 days in duration, approximately 10,000 to 30,000 hospitalizations, and about 90,000 eye complications[2]. Risk factors include age, immunosuppression, gender, race, and genetics/family history[1]. Age is the key risk factor for zoster. Risk varies by an order of magnitude across the age spectrum, and age affects everybody. Those who are immunocompromised bear a substantial portion of the total zoster burden in the US at up to 20-fold for some conditions. Women are at a 25% to 35% increased risk of zoster compared to men regardless of age, though it is unclear why. Caucasians are at 40% to 50% higher risk of

zoster compared to African Americans, which is presumed to be related to genetics. Though family history appears to be a risk factor for zoster, the fold increase in risk varies widely across different studies from 2-fold to about 20-fold. A key point regarding zoster risk is that just as there is not a mechanistic explanation for why VZV suddenly reactivates after decades of latency, what distinguishes most of the approximately 1/3 individuals who develop HZ from the approximately 2/3 individuals who do not also is unkown[1] [[1]Harpaz et al., MMWR Recomm Rep. 2008; [2]Yawn et al. Mayo Clin Proc 2013].

There is another major unknown about HZ. The incidence of HZ has been increasing from years to decades preceding the availability of varicella vaccine. This has been noted in 5 of 6 US studies[1] and involves all adult age groups. The obvious causes have been ruled-out for these increases and there are no explanations [1,2]. Comparable increases have been seen prior to varicella vaccination in most studies conducted in Canada, the UK, Spain, Taiwan, Japan, Australia, Czech Republic, and S. Korea[3]. This phenomenon obviously makes it a lot harder to interpret the impacts of varicella vaccination on HZ rates [[1]Ragozzino MW, Medicine (Baltimore), 61(1982):310-6; Kawai K, CID, 63(2016):221-6; Singleton J, 41ST Annual Meeting IDSA 2003, Abstract 899; Leung J, CID, 52(2011):332-40; Hales CM, Ann Intern Med 160(2014):582-3; Hales CM (unpublished thesis, 2015, http://scholarworks.gsu.edu/ math theses/149/); Jumaan AO, JID 191(2005):2002-7; [2]Joesoef RM, Mayo Clin Proc. 87(2012):961-7; and Kawai K, BMJ Open. 4(2014):e004833; Park SY, Korean J Dermatol, 42(2004):1531-5 (in Korean); Smetana J, Epidemiol Mikrobiol Imunol, 59(2010):138-146 (in Czech)].

Another factor that can complicate this determination is HZ vaccine itself. Merck's ZOSTAVAX® was licensed in 2006 and was recommended by ACIP for adults 60 years of age and older in 2008. In 2010, FDA extended the ZOSTAVAX® license to persons 50 through 59 years of age based on additional clinical trial data. ACIP has maintained the age-based at 60 years of age and older. It is believed that to date, ZOSTAVAX® has not had a substantial impact on population-wide HZ incidence for several reasons. First, uptake has been modest. Uptake reached 31% in 2015 amongst persons 60 years of age and older. In addition, VE for prevention of HZ is 51% for persons 60 years of age and older and is much lower for the oldest cohorts. Also, that protection appears to wane to baseline levels at about 10 years [Lu P, Vaccine, 2009; Lu P, AJPM, 2011; Williams W, MMWR, 2012; Williams W, MMWR, 2014; Lu P, Vaccine, 2015; Williams W, MMWR, 2016; Williams W, MMWR, 2017].

From a policy perspective, the key question for decision makers is not whether exogenous boosting controls HZ risk within certain households or in certain subgroups, but instead whether varicella vaccination leads to increases in HZ in the population at large. The US, with a population of 320 million, an effective national varicella vaccination program lasting over 20 years, and several sources of data regarding HZ incidence is the ideal setting to test this question. In terms of the information regarding the impact of varicella vaccine on HZ rates in the US, there have been 7 US studies showing HZ trends following availability of varicella vaccine that include an adequate number of years of data following introduction of varicella vaccination to be informative. None of these 7 studies shows evidence of an accelerating trend following introduction of varicella vaccination[1], and 5 of the 7 studies suggest a deceleration, at least in certain age groups[2] [[1]Kawai K, CID, 63(2016):221-6; Jumaan AO, JID 191(2005):2002-7; Leung J, CID, 52(2011):332-40; Harpaz R, OFID 2015:2 (suppl_1): 1052; Hales CM, Ann Intern Med 160(2014):582-3; Zhang J (unpublished); Izurieta HS, CID, 64(2017):785-793; Moanna A, OFID 2016: 3 (suppl_1): 628; Yih WK, BMC Public Health. 5(2005):68; Mass DPH (unpublished); Tseng HF, JID, 213(2016):1872-5; [2]Leung J, CID, 52(2011):332-40; Harpaz R, OFID 2015:2 (suppl_1): 1052; Hales CM, Ann Intern Med 160(2014):582-3; Zhang J (unpublished); Izurieta HS, CID, 64(2017):785-793; Moanna A, OFID 2016: 3 (suppl_1): 628;

Yih WK, BMC Public Health. 5(2005):68; Mass DPH (unpublished); Tseng HF, JID, 213(2016):1872-5].

Data on incidence in adults 35 years of age and older for the years 1993-2014 were updated through 2006 in 2011. The results for the last 8 years have not yet been published. These data are from MarketScan® databases, which contain health insurance claims data on 230 million unique patients since the early 1990s acquired from over 100 self-insured employers, state governments, hospitals, health insurance plans, and Medicare in all states and represent current and former employees, retirees, and beneficiaries. The data covers ages 35 years and older with ages stratified into 30-44 years, 45-54 years, 55-64 years, and 65 years and older. There was a significant upward trend in HZ incidence in all age strata from the very start of the observation time to several years before varicella vaccine was introduced. While these data are not adjusted, earlier published analyses showing almost identical patterns were adjusted for sex, region, urban versus rural, and immunosuppression status. A series of negative controls were used to assure that the results were not due to secular changes in health-seeing behavior or in case finding. Not only has there been no evidence of varicella vaccination in plummeting varicella rates contributed to increasing HZ incidence, but also rates appear to have plateaued for persons 65 years of age and older beginning around 2007. As mentioned earlier, it is not really feasible that this plateauing could be attributable to ZOSTAVAX®. There are two other points. First, in the 2011 paper to look for varicella vaccine impact on HZ incidence, the 50 states were stratified into those with high varicella vaccine coverage and low varicella vaccine coverage. There were no differences in HZ rates in these two groupings of states. Second, mean age at occurrence of HZ did not change over time. If exogenous boosting was important, one might speculate or predict that mean age would have declined in the absence of exposure to varicella, but that did not happen. The age stayed stable [Harpaz R, IDWEEK 2015].

The results of analysis of HZ incidence from 1992-2010 amongst Medicare beneficiaries 65 years of age and older were published in 2013. All key variables were adjusted for and negative controls were used to look for secular changes in health-seeking or case finding. These results amongst older adults are very similar to the MarketScan® results, with a large increase in incidence amongst all age strata from the very beginning of the study starting several years before licensure of varicella vaccine. These results also provided no evidence that varicella vaccination has contributed to an increase in HZ incidence, and also show the plateauing phenomenon beginning in 2007. Also in this study, HZ rates did not vary in states with high versus low varicella vaccination uptake and median age at the development of HZ remained stable throughout the entire observation period[1]. The Medicare analysis was recently extended to 2014, though the results have not yet been published. In these unadjusted aggregated data for Medicare beneficiaries 65 years of age and older, the plateauing continues and rates appear to be declining. As noted earlier, it is not feasible that uptake of ZOSTAVAX® could be bending the curve so abruptly in 2007[2] [[1]Hales C. et al., Ann Intern Med. 2013;159:739-745; [2]CDC, Unpublished].

From data presented at IDWEEK in October 2016 on age-specific HZ rates 2000-2014 amongst the 5 to 6 million veterans who received their healthcare in the Veterans Administration (VA) system, the authors reported that by 2015, ZOSTAVAX® uptake was just 6% in persons 60 years of age and older and just 5% in persons 50 through 59 years of age. The authors noted that HZ rates stabilized in recent years after years of increase, and even decreased significantly in persons 60 through 69 years of age. Once again, there is no indication from this analysis that varicella vaccination has led to an increase in the incidence of HZ in this population [Moanna A, IDWEEK, 2016]. The VA population and healthcare system are quite different from those of

MarketScan® and Medicare, so the consistency of the findings across these different platforms suggests that they are very robust.

In summary, there has not been any evidence that varicella vaccination has led to a noticeable increase in HZ rates in the general US population. There are several potential explanations. Frist, Hope-Simpson's hypothesis may be incorrect. VZV exposure has little to no impact on HZ control, or any impact may be of short duration. Perhaps subclinical VZV reactivation and endogenous boosting compensate when exogenous boosting declines. Second, perhaps there were too few sufficiently-intense VZV exposures during the pre-vaccine era to noticeably alter HZ rates at the population level. The effects may have been limited to smaller subgroups such as parents of young children or occupational groups. Or, perhaps the population base for HZ is concentrated in older adults who have fewer VZV contacts and who also may respond less robustly due to immune senescence. Third, perhaps Hope-Simpson's hypothesis partially manifests as a reduction in the mean age of development of HZ due to less exogenous boosting. HZ tends to be milder in younger adults, so they may be less inclined to seek care, masking the effect. It would be hard to rule out that possibility, but there is also no evidence to support that it is true and there is soft evidence to suggest that it is not likely. Fourth, some might suggest that it is too early to see an impact of the varicella vaccination program. One could argue that it has only been 12 to 13 years since rates of varicella have declined by 80% or more and more years are needed to see an effect. However, most models predicted an effect much sooner than 20 years. In household studies suggesting that exogenous boosting reduces the risk of HZ, the effect is immediate. Finally, perhaps all of the US studies are wrong and true HZ incidence is being missed due to overriding artifacts across all sites and all study designs. Data on HZ rates after introduction of varicella vaccination have also been published for Australia and Canada. To date, the Australia data are somewhat hard to interpret because of a lack of data on baseline trends and because public varicella vaccine programs in Australia were introduced more recently in 2005. Regarding Canada, varicella vaccine was marketed starting in 1998 to 1999. However, publicly funded programs were launched much later on a province-by-province basis, so the duration of follow-up is still not that long. Studies have been published for 4 provinces, 3 of which have shown no evidence of acceleration of HZ rates. A study was published two weeks ago from Manitoba that does suggest an abrupt increase in recent years.

In conclusion, varicella incidence, outbreaks, and severe disease have declined to low levels in all age groups. Among children, HZ rates have declined to very low levels though data were not presented during this session on this aspect. In terms of HZ amongst adults, there is no specific evidence that the varicella program has increased HZ rates in the general population. The epidemiology does seem to be changing and cannot be explained, just as what distinguishes persons who experience HZ from those who do not, cannot be explained. In theory, it is possible that the US data have not revealed an increase either because it is not powered to see a small increase or because more time is needed to see an effect for some reason. This seems unlikely, but at a minimum, models can be updated and constrained using the US data to allow for more realistic assumptions regarding varicella vaccine impact. Finally, the US experience can provide reassurance for countries considering adoption of varicella vaccination.

Discussion Points

Dr. Thompson (NVPO) requested clarification regarding the VA data, specifically about the portion of VA patients that had received the zoster vaccine.

Dr. Harpaz clarified that the authors presented that in the VA population, only 6% of individuals 60 years of age and older and only 5% of those 50 through 59 years of age had received ZOSTAVAX®. Thus, this is essentially an unvaccinated population.

Dr. Plotkin (Vaccine Consultant) said that for amusement, he wanted to mention that a French friend of his conducted a study in sequestered monks in which he showed that there was no increase in HZ in those sequestered monks who had never seen children by and large. Perhaps that should remind ACIP that modeling is supposition and epidemiology is fact.

Dr. Harpaz thanked Dr. Plotkin and, in jest, noted that the sequestered monk population had a very low rate of genital herpes as well.

Anthrax Vaccine

Dr. Kate Hendricks
Medical Officer, Bacterial Special Pathogens Branch
Division of High Consequence Pathogens and Pathology
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Hendrix discussed updating recommendations for use of anthrax vaccine in the US. In terms of background, she briefly discussed the disease anthrax, the vaccine, the current recommendations, and approval of two antitoxins for PEP. She then discussed the rationale for reconvening the Anthrax Vaccine WG and the WG's terms of reference, as well as a new formulation of anthrax vaccine adsorbed (AVA).

With regard to background, *Bacillus anthracis* is the causative agent of anthrax. It is a Gram-positive spore-forming bacterium. Spores are the infective form and are similar in size (3-5 micrometers in length) to the tuberculosis bacilli (2-4 micrometers in length), which makes them respirable. The vegetative form produces two major toxins, lethal toxin and edema toxin. In nature, anthrax is primarily a disease of herbivores. In the late 19th and early 20th Centuries, it was an important occupational disease in humans. Since then, it has occurred primarily among people who have butchered and /or eaten diseased animals and very sporadically among people who incidentally inhale the spores during the course of their work or hobby.

In terms of the natural cycle, herbivores graze on land contaminated with spores, which germinate and cause anthrax. They then die, exsanguinate, and further contaminate the grazing land. As just mentioned, humans are infected by butchering and or eating the dead or dying animals. Biting flies can also carry the bacterium from carcasses to healthy animals.

Spores introduced through the skin lead to cutaneous anthrax; those that are swallowed lead to ingestion anthrax; those introduced through the lungs to inhalation anthrax; and those introduced in a percutaneous manner to injection anthrax. Meningitis may also complicate primary anthrax infections of the skin, gastrointestinal tract, and soft tissue. In addition, a substantial number of cases (32 from 1900-2005) occurred in patients with systemic anthrax without a recognized port of entry (i.e., primary anthrax meningitis). After gaining entry, *B. anthracis* spores are thought to either germinate locally or to be transported by phagocytic cells

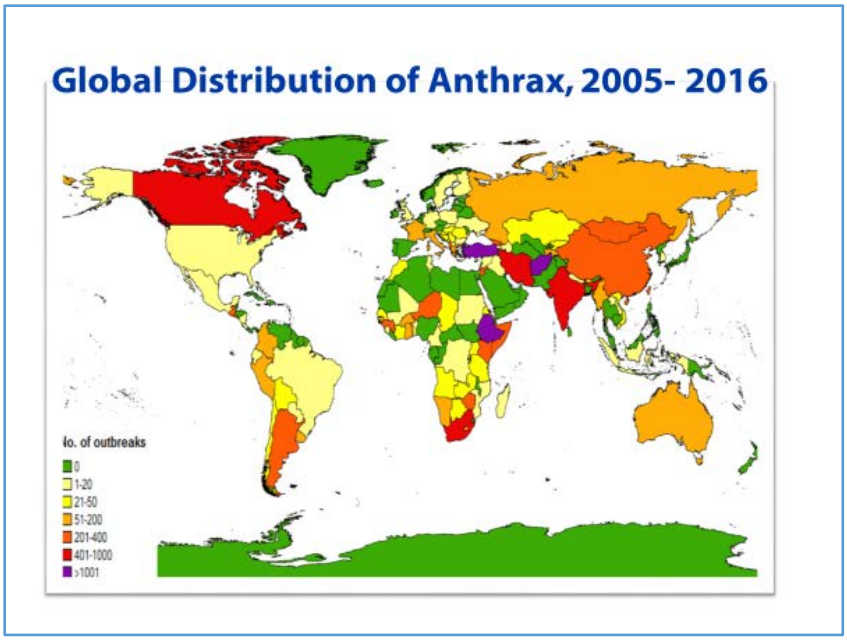
to the lymphatics and regional lymph nodes, where they can germinate. Bacteria begin producing toxin within hours of germination.

Cutaneous anthrax is by far the most common form of anthrax. Spores are introduced through the skin, usually but not always through pre-existing abrasions. Infections can remain local or can lead to systemic illness in about a third of the cases. Germination occurs 1 to 3 hours after inoculation, while incubation takes 1 to 17 days. In the early 1900s, the case fatality rate without treatment was 24%. With treatment, less than 2% of patients with cutaneous anthrax die. Ingestion anthrax is the second most common form of naturally occurring anthrax. Following a 1- to 14-day incubation, the infection can manifest either in the oropharynx or lower in the gastrointestinal system. The case fatality rate is 40%, but may be higher in children.

Inhalation of aerosolized spores from hair, hides, animals or biowarfare (BW)- or bioterrorism (BT)-related events leads to inhalation anthrax. Most of the cases described in the medical literature are either occupational or BW- or BT-related. The range for the observed incubation period in humans is longer than those observed for other forms of anthrax. In 1979, there was an anthrax outbreak that occurred following an accidental release of *B. anthracis* from a biowarfare program in Sverdlovsk, Union of Soviet Socialist Republics (USSR). The incubation period there ranged from 2 to 43 days. In 2001, there were anthrax letter incidents in the US in which incubations ranged from 5 to 13 days. Data from non-human primates are consistent with slightly longer incubations. The case fatality rate has improved somewhat with modern critical care, but is still very high. In the 20th Century, the case fatality rate exceeded 90%. Since then, with modern critical care that includes combination antimicrobials and drainage of pleural fluid, it has still approached 50%.

A new type of anthrax has been identified in the last decade or two in heroin-injecting drug users in northern Europe. These are severe soft tissue infections that are deep under the skin or in the muscle where the drug was injected. It is not uncommon for these to present with meningeal or abdominal symptoms. This type of anthrax has never been reported in the US. Transmission is from injection of contaminated heroin. The incubation is from 2 to 10 days, and the case fatality rate with treatment approaches 40%. Meningitis is a very common complication of inhalation, ingestion, injection, and systemic cutaneous anthrax. More than half of the autopsies done on patients who died with inhalation anthrax in Sverdlosk showed hemorrhagic meningitis. Meningitis can also occur as a primary manifestation of anthrax (i.e., no other route of transmission) and it is thought to be a form of inhalation anthrax. Based on data for 1900-2005, the case fatality rate for inhalation anthrax with meningitis was 100% versus about 80% for inhalation anthrax without meningitis.

This distribution map color codes countries by numbers of outbreaks reported during the 2005-2016 time period and includes livestock, wildlife, and human data. Purple and red countries have the most reported outbreaks; green and yellow countries have the fewest reported outbreaks. The data come from the Food and Agriculture Organization (FAO) of the United Nations (UN). The map likely under-represents the true disease distribution:

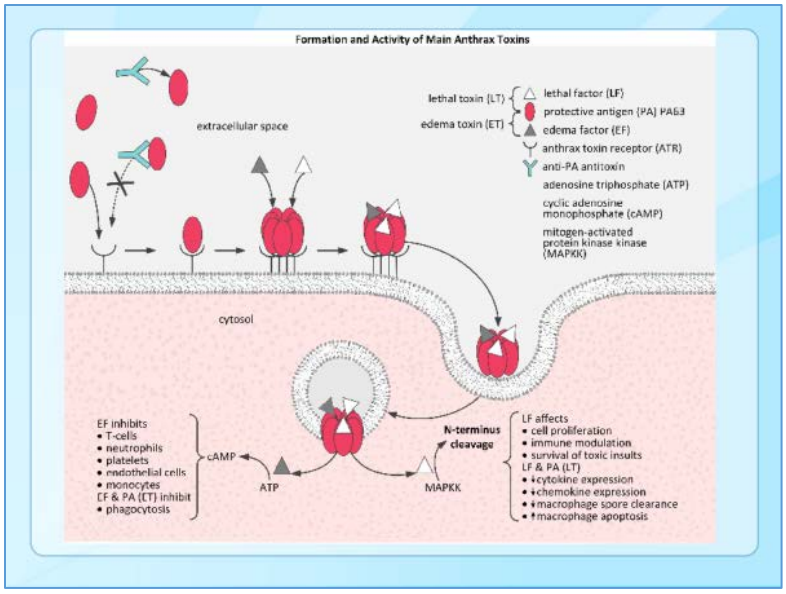


In terms of human anthrax cases reported in the US in the latter half of the 20th Century, a large epizootic outbreak in Oklahoma in 1957 sparked national annual vaccination of livestock against anthrax. Only 5 cases occurred from 1980 through 1999. The anthrax letter incident occurred in 2001, and there have been no cases from 2014-2017.

For a variety of reasons, anthrax spores are the most likely bioweapon. Anthrax spores are relatively easy to produce; can be stored for a long time; can be dispersed in the air through a variety of means; and are odorless, colorless, tasteless, and difficult to detect. The resulting disease, inhalation anthrax, is highly lethal. The spores may survive for greater than 40 years. An aerosol release can cause widespread illness and death among unprotected persons. A 1979 release of anthrax spores from a laboratory in Sverdlosk led to least 77 cases of anthrax and 66 deaths in the nearby community. The 2001 US mail incident led to 22 cases of anthrax, 11 of which were inhalation anthrax, with 5 deaths. In a simulated unmitigated wide area anthrax release in a subway system, it is estimated that there would be 100,000 or more casualties.

AVA (BioThrax®), was manufactured for a few decades by the Michigan Department of Health and Human Resources (MDHHR). However, it is now manufactured by Emergent Biosolutions. AVA is a sterile, cell-free filtrate made from an avirulent (toxigenic, but non-encapsulated) strain of *B. anthracis**. The final product contains 1.2 mg/ml of aluminum for an adjuvant and benzethonium chloride and formaldehyde as preservatives [*http://www.biothrax.com/].

The formation and activity of main anthrax toxins are depicted in the following graphic:



The two main toxins produced by *Bacillus anthracis* each come in two parts. One of the parts is protective antigen, depicted in the above graphic as a red oval. For either toxin to enter the cell, protective antigen needs to bind to the anthrax toxin receptor, then form a heptamer, and have the toxins attached. The cell surface invaginates and protective antigen forms a pore through which the edema factor and lethal factor escape to wreak havoc. If an antibody interferes with protective antigen and keeps it from binding to the anthrax toxin receptor, this whole cascade can be stopped.

The vaccine under discussion during this session, AVA, primes the immune system to recognize and block protective antigen (PA), which is common to all anthrax strains. Vaccine efficacy against numerous anthrax strains has been demonstrated in many animal studies. This vaccine has a long history. In the mid-1950s, there was the Ft. Detrick formulation. This first US product was a cell-free filtrate from an aerobic culture of the Vollum strain of *B. anthracis*, precipitated with alum. This vaccine provided protection in monkeys, caused minimal reactivity and short-term adverse events in humans, and was used in Dr. Brachman's efficacy study of human vaccination against anthrax in millworkers. In the 1960s, the manufacturing process was improved, resulting in increased PA concentration and increased purity and potency. This new formulation was referred to as the "Lansing" formulation. In the 1970s, the "Lansing" formulation was licensed by NIH using data from the Brachman studies. The vaccine was recommended for those at high risk of exposure to anthrax. AVA was reapproved for licensure by FDA in 1985. Immunogenicity and reactogenicity data on AVA were reviewed by ACIP in 2007-2009, and the current guidelines were published in 2010.

New data are available for post-exposure use of AVA plus CPG 7909, aka Nuthrax®. Synthetic oligonucleotides (ODN) with "CpG motifs" trigger cells with toll-like receptors (TLRs). TLRs are a type of pathogen recognition receptor that are expressed primarily on immune cells. The utility of CpG oligonucleotides as vaccine adjuvants has been evaluated in a number of clinical trials. Results indicate that CpG ODN improve antigen presentation and the generation of vaccine-specific cellular and humoral responses. Compared with AVA, AVA plus CPG 7909 is expected to achieve an accelerated immune response, necessitating fewer injections and a reduced amount of antigen to confer protection.

Referring to the graphic of the formation and activity of main anthrax toxins shown earlier, antibodies that interfere with protective antigen binding to the anthrax receptor, whether they are from vaccination or passive transfer, keep the two main toxins from being released. Three antitoxins are approved for treatment of inhalation anthrax in combination with antimicrobials: Raxibacumab, Anthim, and Anthrax Immune Globulin Intravenous (AIGIV). AIGIV is polyclonal and the other two are monoclonal.

Anthrax vaccine adsorbed has two uses. It is used for pre-exposure prophylaxis (PrEP), which used to be called general use prophylaxis (GUP), in person with occupational risk of exposure to *Bacillus anthracis*. It is also used for PEP for persons potentially exposed to *Bacillus anthracis*. For PrEP, AVA is recommended for the prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age at high risk of exposure. For this indication, it is administered intramuscularly at a 0.5ml dose at 0, 1, and 6 months for the primary series, and at 12 and 18 months after the start of the primary series and at 1-years intervals thereafter for persons at continued risk of infection.

Groups considered to be at high risk of infection include: 1) persons handling potentially infected animals in research settings or in areas with a high incidence of enzootic anthrax, or when standards and restrictions are insufficient to prevent exposure to *B. anthracis;* 2) persons who perform certain types of laboratory work involving *B. anthracis*; 3) persons involved in anthrax environmental investigations or remediation efforts; 4) certain military personnel; and 5) may be offered to persons involved in emergency response activities. For PEP, AVA is recommended for unvaccinated persons after exposure to aerosolized *B. anthracis* spores. For this indication, it is administered subcutaneously at a 0.5ml dose at 0, 2, and 4 weeks in combination with 60 days of oral antimicrobials. This series results in rapid anti-PA antibody production and augments the antimicrobial portion of PEP. By combining vaccine and antimicrobials, the individual is protected from the germinating spores and vegetative cells of B. anthracis while their immune system is being “primed” and developing anamnestic capability.

As previously mentioned, three antitoxins are approved for treatment of inhalation anthrax in combination with antimicrobials: Raxibacumab, Anthim, and AIGIV. Two of the three antitoxins that are approved for treatment are also FDA-approved for prophylaxis. When alternatives are not available or inappropriate, Raxibacumab and Anthim are recommended.

The WG is being asked to discuss a number of issues related to mass vaccination following a wide-area release of *B. anthracis* spores. A variety of new data have become available since publication of the last set of ACIP recommendations for AVA. These include data on increased intervals between booster doses for PrEP, an alternative administration route for PEP, and modeling for an adequate immune response in humans based on non-human primate studies. Additionally, there are data for a new formulation of AVA that is currently being developed in pursuit of eventual FDA licensure. The WG also would like ACIP to review and advise on using anthrax antitoxins for PEP. The ACIP Anthrax Vaccine WG was reconvened in the spring of 2017. The WG’s terms of reference are to review the following:

- ❑ AVA data on a reduced booster schedule for pre-exposure prophylaxis
- ❑ Immunogenicity, safety, and logistical considerations for providing AVA via intramuscular versus a subcutaneous route and to provide evidence-based recommendations for administration as a post-exposure prophylaxis

- ❑ AVA with CPG 7909 Adjuvant data and to provide evidence-based recommendations for post-exposure prophylaxis

- ❑ Efficacy and immunogenicity data on a reduced schedule and half-dose AVA use for post-exposure prophylaxis to prepare for a potential emergency meeting for a mass casualty incident when AVA is a limited resource

- ❑ Review and advise on the use of AVA and antitoxin for post-exposure prophylaxis when no effective antimicrobials are available or have an absolute contraindication

Discussion Points

Dr. Belongia requested information regarding the current use of AVA in the US Military.

Dr. Yacovone (DoD) replied that the DoD currently uses AVA in the protocol for certain identified people who are considered at high risk for certain geographic locations, and also in certain groups that respond to incidents.

Dr. Reingold inquired as to where the efficacy data would come from.

Dr. Messonnier responded that efficacy will be based on correlates of protection.

Dr. Plotkin (Vaccine Consultant) indicated that he worked with Dr. Philip Brachman. The efficacy study was conducted on workers receiving goat hair, basically, and the efficacy was quite high. Although, there were not enough inhalation cases for statistical power, it did appear that it did work against both cutaneous and pulmonary exposure.
Dr. Messonnier said she thought what Dr. Reingold was asking referred to the future since natural experiences will not be occurring. The answer to that is the WG is reviewing immunological studies and correlates of protection in animal challenge studies.

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 HepB vaccine supply. She reported that Merck is not currently distributing its adult HepB vaccine and will not be distributing vaccine through the end of 2017. The dialysis formulation of HepB vaccine is not affected. GSK has sufficient supplies of adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply; however, preferences for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time.

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

Day 1: Public Comment

Andrea Woodruff
Sales Director
Optimized Financial System

I am here to request that all de-identified data as well as models, and I mean full models, not models referred to in part in a paper or partially presented, but that the full models along with corresponding data be publicly available, and that you ensure that the statistics presented here at these meetings are statistically significant with widely accepted statistical methods. Essentially, I am asking that you ensure that you are not using snapshot data, but full picture data. Formerly, I worked for one of the largest vaccine manufacturers selling vaccines. Afterwards, I interned at the US Senate Committee on Health, Education, Labor, and Pensions (HELP) following vaccine legislation. Additionally, I worked for the Council on Foreign Relations (CRF) doing corporate fundraising that included vaccine manufacturers.

I am not anti-vaccine. I couldn't be better trained to be pro-vaccine. However, it became impossible to ignore that the current vaccine vetting process hurt me and my family. While I am pro the concept of vaccination, I believe in transparency of data, models, and statistically significant information and presentations. I now own a company that does applied analytics, specifically operations research. I wanted answers to questions that were not adequately provided. In order to start getting used to the data, I started by asking, "Do increased vaccination rates decrease vaccine-preventable disease?" I thought this would be easy. Surely the data would be publicly available and prove that this is so.

Everyone I spoke to at the CDC seemed to think that this is available. But when I went to go look for the data, I essentially found snapshot reports with incomplete data and it was not downloadable. Nothing was convincing when I looked at it critically. We wrote 7 models on GitHub. GitHub is a public repository for models and data that uses linear regressions, auto regressions, and Bayesian Hierarchical models. I have no financial interest here. I provided the work at no cost publicly to be criticized publicly to ensure common understanding and to get some answers for myself and my family.

We had problems accessing *MMWR* data, so we used WHO data. My tax dollars were used to gather *MMWR* data, and to collect all of the data actually that the CDC uses. So, why don't I have access to it? Please listen to me. Nothing showing that the higher the vaccination rate, the lower the disease incidence were statistically significant in the United States—nothing that we've run so far. If you are making recommendations, you should have downloadable data that is publicly available to anyone to check the work that is being done here. Thank you.

Discussion Points

Dr. Bennett thanked Ms. Woodruff, acknowledging that the CDC has been working with her and will continue to do so. She expressed ACIP's appreciation for Ms. Woodruff's comments.

Ms. Woodruff also submitted the following letter to ACIP:

Dear ACIP Members,

I appreciate you taking the time and thank you for reading. My goal is to bring the medical community, public health, the vaccine injured, and the vaccine choice advocates together to a common understanding. I know that will not be easy, but I feel that it is vital to bring various opinions together so we can move forward. I am deeply concerned about the bubbles I see being formed around the pro-vaccine movement and the vaccine choice groups. I believe that there are huge strides in medicine that can be achieved if we can learn to understand each other's prospective. I understand both sides of this debate.

When I looked at peer reviewed articles and slides showing data from both sides of the vaccine debate, I realized the problem. I see people showing a snapshot of a problem that fits into their presentation. My hope is to mathematically show when we are looking at a snapshot or the whole picture. I think this will open minds and hearts on both sides of the argument and get us closer to resolution.

I do not believe that any data will calm a mother who lost their child soon after receiving his or her vaccinations. Nor will any data calm a mother who has lost a child to a vaccine preventable disease. You, as the ACIP, need to know true data in order to advise the CDC appropriately. I will be very clear about my philosophy. I believe that people have the right to be vaccinated and vaccinate their children. Additionally, from looking at this for the past 18 years from all perspectives and looking at the numbers, people have the right not to be vaccinated and not to vaccinate their children. We have entered the world of the insane by trying to push this further. You may be thinking about herd immunity. Prove it with model ready downloadable public data.

It is my hope that my initial models create discourse on the matter of vaccination. I am making the models public for both criticism and collaboration. People from other disciplines can suggest their own models, changes to the existing models, and provide more data points. I ask that you do the same with data in order to shift the debate and advance scientific inquiry. I ask that you link all models and data sources to the site on GitHub. https://github.com/vaccinemomma (I purposely chose this name and spelling for this site to remind me that this is personal. This is about me, my family, you, and your loved ones.)

I ask that the medical community and vaccine critics engage in healthy debate to gain common understandings and improve the welfare of our people. I do not know how these models will turn out with more granular data or the accuracy of the data. I do know that this data was collected with tax payer money and should be available to anyone wanting to do research.

However, I hope that we can find common ground, develop trust, and encourage trustworthy people to be the guardians of this information. Additionally, I hope that this is the beginning of discovery into infectious disease as there is much to be learned when looking at larger and larger data sets. I welcome any comments on flaws in logic of this report to further everyone's understanding of this issue. I purposely chose graphs that leaned more toward a vaccine choice stance because my audience for the report is you, the medical community and public health. I wanted to show you what your patients are seeing. I wanted to show how data can be manipulated for or against in the absence of statistically relevant boundaries in order to advance vaccine related scientific methodology.

Sincerely,
Andrea Woodruff

ADVANCING VACCINE RELATED SCIENTIFIC METHODOLOGY

Understanding Immunization and Infectious Diseases Modeling

Goal 1: Determine if an increase in immunization rates reduces preventable infectious disease in a statistically significant way.

Data components needed for determining if an increase in immunization rates reduces preventable infectious disease.

- Population: UN Data or Census.gov
- Immunization Rates by Age: WHO Data, CDC-NIS and NHIS Data, and State Data
- Vaccine Preventable Disease Incidence by Age: WHO Data, CDC MMWR Data, and State Data

What we found

WHO and UN data was downloadable, but not broken down by age and only going back to 1980 for some of the diseases on the US schedule. I would prefer to see before the vaccine was introduced and before the trials began.

Census, NIS-NHIS, and MMWR data were needed. I ran into problems when trying to access MMWR data in any format that can run through a model. MMWR data does not utilize a formal surveillance study design so this may not be the best source of data. Tycho may be the best source, but I have not received a note back from them that this is good data. Neither had statistically significant results in any of the models that I ran. (I have not finished running all the vaccines on the US schedule.) My guess is because it is not granular enough. Essentially, the MMWR data is virtually unusable because it only goes back to 2014. I am working with the department in charge, but this data should be easily publicly available back to the point where it actually proves the point that matches the policy decisions.

Some states keep records and others do not. For the states that do keep records, I would need to go through several approvals. I have not heard of a state equipped to run any models. If there are any, please let me know. I emailed all of them. Some said all their information was public, but it was not set up to run data through. If information is not downloadable, it is not helpful to someone running a model to check for statistical significance.

Considering the problems that have occurred with several CDC researchers regarding vaccine data. Usable public data would go a long way with re-establishing public trust. It seems from an outsider's prospective that in order to get good data that is not even identifiable that you have to be in agreement with the status quo. I paid for all of this with my tax dollars. Why do I not have access to it? Is it impossible to clean out the identifiable information and give make relevant information public? If there was one case of rubella in one state, how am I supposed to identify that person? I am told that the law there is to protect personal privacy, but is it? This is not one child with rubella in a school of 300 children. It is a person with rubella in a state. All the roadblocks simply instill a feeling of distrust.

What models have we run?

UN-WHO Data

1. Linear Regression
2. Linear Regression US Data Only
3. Autoregressive Using World Data
4. Autoregressive Using US Data Only
5. Hierarchical model using the world and countries as the hierarchies for the Intercepts and a Global Disease Reduction Factor Based on the Vaccination Rate.
6. Hierarchical model using the world, region, and country as the hierarchies for the intercepts and a global disease reduction factor based on the vaccination rate
7. AR1 Hierarchical Model
8. Others, depending on data availability and new hypothesis

Census, NIS, NHIS, MMWR or (non-public data)

- Similar to UN-WHO Data

Census, State Immunization Rates, State (non-public data)

- Similar to UN-WHO Data

How should the data be accessed?

In order to access all the data, CDC reports should be accessible either in a large file, like the WHO data, or should be available through an API, so that analytics toolkits like python and R can download them programmatically.
How is statistical significance determined when running data through models?

1. R-Squared: Goodness of model fit. How much of the variability in the data is explained in the model. Usually, the R-squared value should be at least 50%, which would be over .5.

2. T-Statistic on the parameters: The degree of confidence that we can have that each model parameter is not zero. Zero means no effect. Not zero means there is some effect either decreasing or increasing the rate of incidences.

3. F-Statistic on the model itself: How likely is it that any model parameter is not zero? Means that if it is not zero then at least something is affecting it.
4. These are in order of importance: R-squared and T are more important than F.

5. For a Bayesian Model: DIC-Deviance Information Criteria. This is more relative when comparing models. The more negative the better the fit.

Example of Lack of Fit for US Measles Data with WHO UN Data (1980-2015)

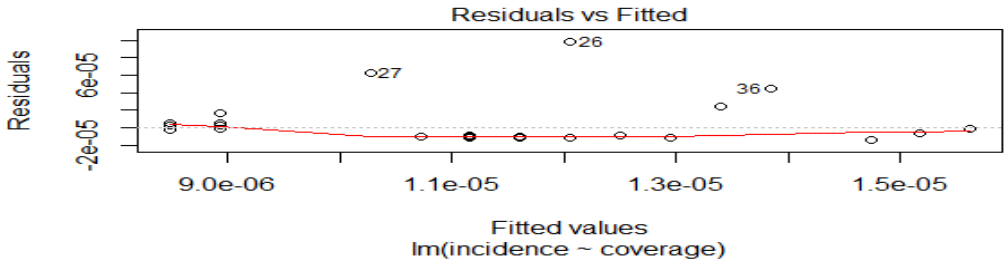
Residuals:

Min	1Q	Median	3Q	Max
-1.354e-05	-1.099e-05	-1.055e-05	4.200e-08	9.784e-05

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	5.218e-05	9.264e-05	0.563	0.577
coverage	-4.458e-05	1.010e-04	-0.441	0.662

Residual standard error: 2.378e-05 on 34 degrees of freedom
Multiple R-squared: 0.005698, Adjusted R-squared: -0.02355
F-statistic: 0.1949 on 1 and 34 DF, p-value: 0.6617
Graph of a Poor Fit



Please tell us what is wrong with the models? I see there are clearly other factors at play. We could not get any of the models to fit with the data publicly available when trying to see if the higher the vaccination rate the lower the disease rate. The example above is a standard linear model. What models are you doing that are fitting better? What assumptions are you making?

Who is checking those assumptions?

Data

Models are only as good as the data fed into them. This is why comparing multiple data sources is important at the state, federal, and global level. There should be a central repository for all public data internationally. The WHO has started this, but improvement is needed to truly reach a logical conclusion. The ACIP says that they only recommend vaccines and anyone is free to decline, but that is not what is happening. We are moving toward mandates with California being the most prominent example in the United States, but where are the budgets at the state level to actually verify that what is presented is accurate and significant? Some of the states do not even keep their own statistics much less have the ability to run models. Essentially, the recommendations from the ACIP are not questioned by the medical community and financially encouraged lawmakers.

Goal 2: Determining if There is a Better Way to Reduce Disease Rates

Look at anomalies in known vaccine data to see if any patterns exist that can improve policy.

Determine what data is lacking and what needs to be kept in order to find novel ways to tackle infectious disease.

Determine what assumptions are used in current modeling for lives saved, diseases prevented, healthcare costs, and indirect costs. Analyze the effects of changes in assumptions on the outcome.

Determine if the results from Healthy People 2010 are statistically significant regarding their ability to reduce disease.

Determine if the recommendations included in Interventions and Resources give statistically significant results and what is their magnitude.

Goal 3: Have publicly available downloadable data (CSV format), models, and conclusions in order to increase transparency and encourage debate, generating new ways to approach vaccine related problems. (GitHub)

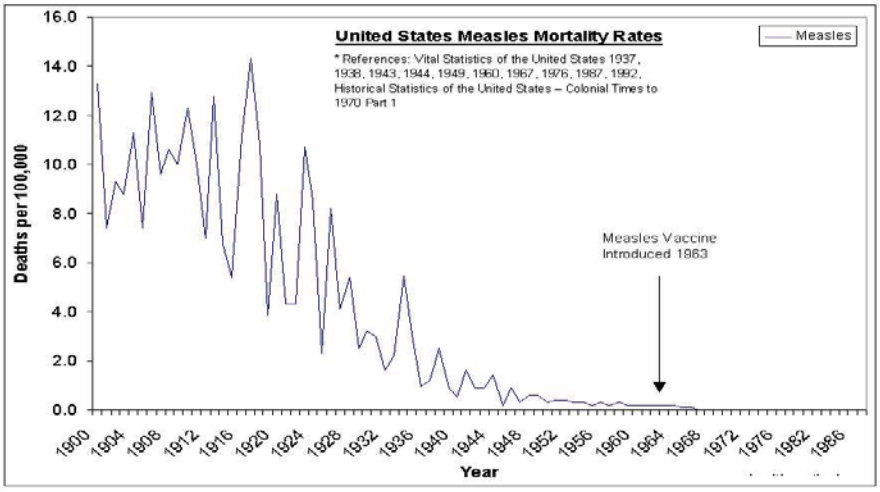
Emerging Issues in Immunization and Infectious Diseases

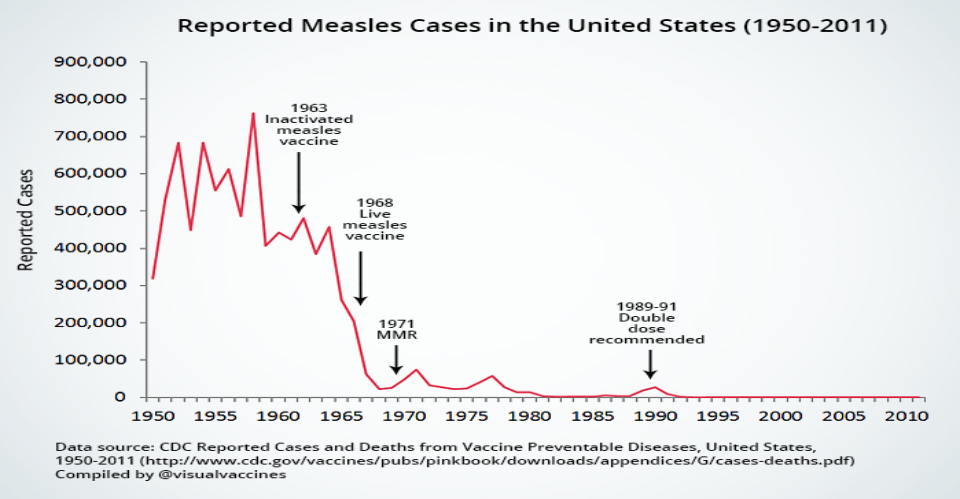
Determine if the Health People 2020 goals are likely the best way to look at the problem or if there are other outcomes in data that suggest a different path. Gather buy-in by various vaccine choice groups to the information presented by allowing all information to be transparent.

Examples of “Snapshot” Data

I cannot confirm all the data in the graphs is accurate because not all data is publicly available from government sources. This does not instill confidence in the vaccine choice groups or the next generation of medical professionals who know how to use some of the methodologies that I have suggested. However, these are the charts that vaccine recipients are seeing.

Measles





The measles vaccine was marketed in the US as a convenience vaccine. Mainly due to the data above. It looks like it worked for that purpose. How did we get to the point where children must get two doses before they are allowed to attend school in California? One thought is that, we developed a fear of Subacute Sclerosing Panencephalitis and maybe rightfully so. I do not know because I am not a virologist or a medical professional qualified to ensure the accuracy of these reports, but anyone thinking can see that the CDC report is shaky. How many doctors would really look at a patient and think that a patient seems to be presenting with SSPE especially with a seven-year lag in symptoms? I believe SSPE exists from the autopsy reports. I just would not start taking away parents' rights to make decisions for their children over an accumulation "evidence" no matter how much money is put into repeating the same reports or how pretty the power point slides are www.cdc.gov/mmwr/preview/mmwrhtml/00001185.htm

"The average interval between onset of measles and onset of SSPE is approximately 7 years." I have not seen complete numbers on this, but with the low numbers of measles and high number of vaccination rates I would ask what the risk of each is now. It seems that there is missing information when I read the proof behind certain policies. The information seems slanted very much toward the pro-vaccine side and anyone who questions any aspect of vaccine policy is discredited. I do not hear debate at the ACIP meetings. I hear one or two weakly worded mild questions or comments that are quickly dismissed because there is "data" showing evidence.

This is why we need diverse thought and statistically valid information when presenting graphs and referring to data. It may be relevant or it may not be. If it is, then it supports the idea of making all the data public in the interest of public health.
As far as SSPE showing up seven years later, does the Department of Health and Human Services have this in the vaccine injury table?

I am not as interested in compensation for individuals if there are cofactors or if a higher percentage would get the illness from the disease. The ability to choose a vaccine with publicly available data gives the patient some of the responsibility. Coercion, mandates, hidden information gives culpability to the people making the decisions for the public. I would like honest people looking at the data critically who have different viewpoints and then see them come together to debate. For the vaccine injured, I would like better diagnosis and treatment. We are caught up on compensation and liability. The liability has already been removed for the doctors and manufactures. This is a false concern keeping us from moving forward. Allow

known policy mistakes to continue should be the biggest financial concern of the vaccine injury court.

The further back the data goes the more complete picture we get. Modeling shows us when we have enough data points that we are actually looking at a full picture and when there are other factors than just the vaccine at work. It occurred to me that maybe the historical data presented online was “fake news” or propaganda.

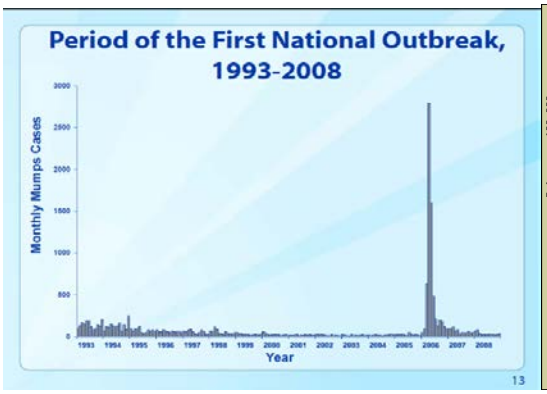
I spot checked the measles death information above with vital statistics on the CDC website.

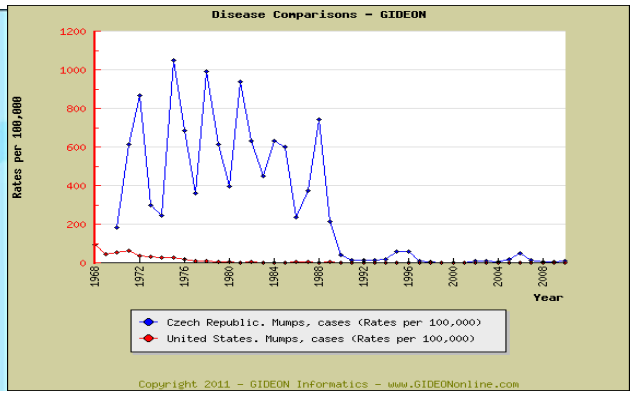
www.cdc.gov/nchs/products/vsus/vsus_1890_1938.htm
www.cdc.gov/nchs/data/vsushistorical/mortstatsh_1936.pdf (Measles 1934-1.0 and 1936-3.1)
www.cdc.gov/nchs/data/vsushistorical/mortstatsh_1917.pdf (Measles 1917-14.3 and 1915-5.4)

The screen shots turned out like this so please check yourself. The measles graph at least seemed accurate to me.

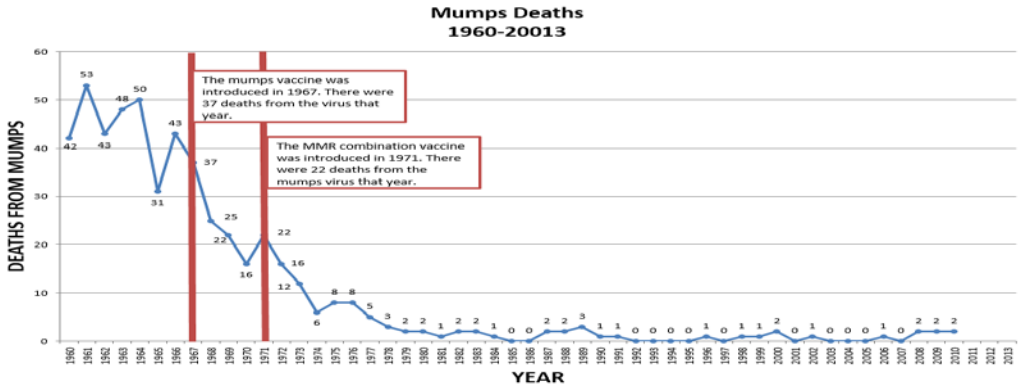
Mumps

Diseases do not recognize borders, but they still have statistically different transmission rates within borders. The first chart shows the US National Outbreak. The second chart compares the Czech Republic to the US.





The main concern with the mumps outbreak is that generally vaccines show to have waning immunity. We should be asking, “Are the real risks of complications statistically significant?” There were 37 deaths from mumps ages not specified when the mumps vaccine was first released. To put that in prospective, approximately 3500 infants die annually in the United States from sleep-related infant deaths, including sudden infant death syndrome (SIDS; International Classification of Diseases, 10th Revision [ICD-10], R95), ill-defined deaths (ICD-10 R99), and accidental suffocation and strangulation in bed (ICD-10 W75). One question to ask is how much of a danger is it to choose to have natural immunity? We are concerned about the immunocompromised and rightfully so. I am interested in knowing if there are higher rates of immunocompromised people and why? I am also interested in knowing if these viruses have mutated over the years? Are these viruses somehow deadlier now? If not, why the push for mandates now?



Rubella

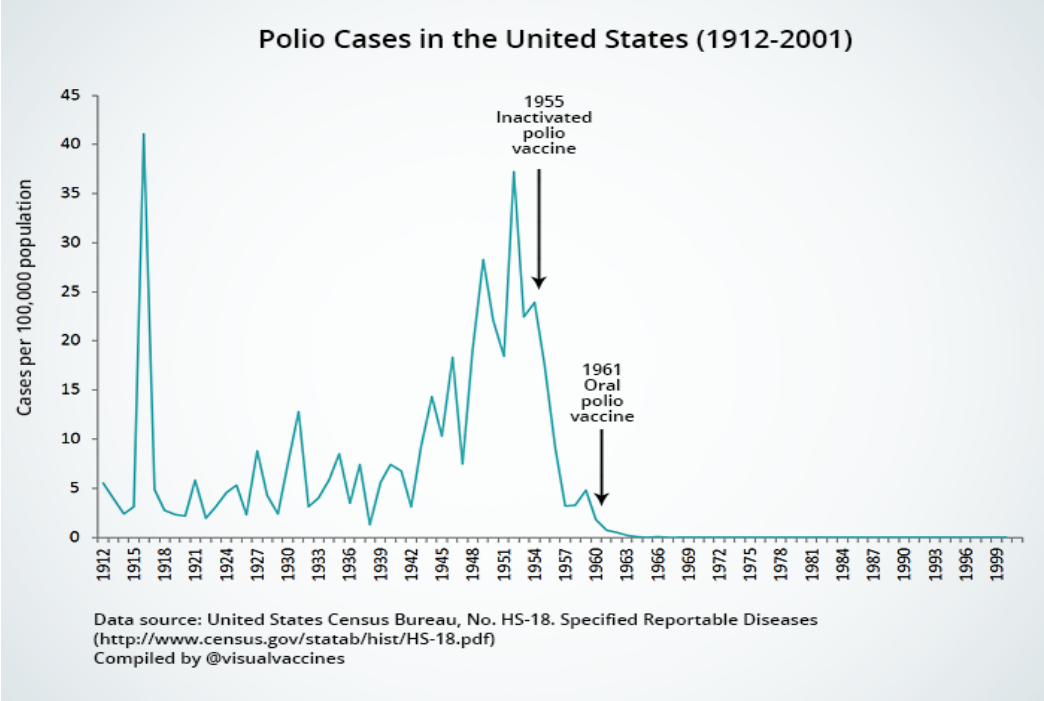
When presenting graphs, it is important to tell when the trials began and look at the disease incidence several years before.

1941: Gregg identifies rubella
1947: First known trials of serum or IGIM
1962: Pandemic strikes Europe, reaching US in 1963 to 1964.
1969: Three rubella vaccines licensed.

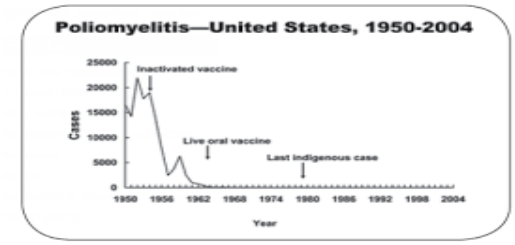
Are the trial dates and locations made public? Are we clear when vaccines are being licensed globally? This would help confirm that the vaccine was not causing the pandemic.

Polio

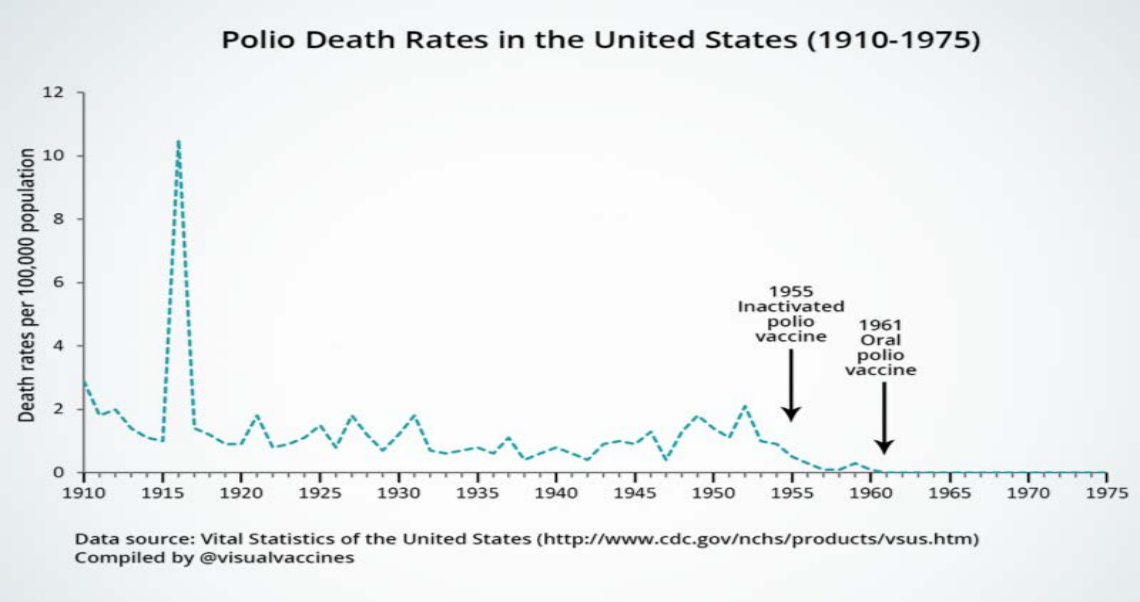
Viral etiology of poliomyelitis by 1909. Trials began in 1935. As stated before a public repository of all trials in order for the vaccine to be released is important in maintaining public trust.

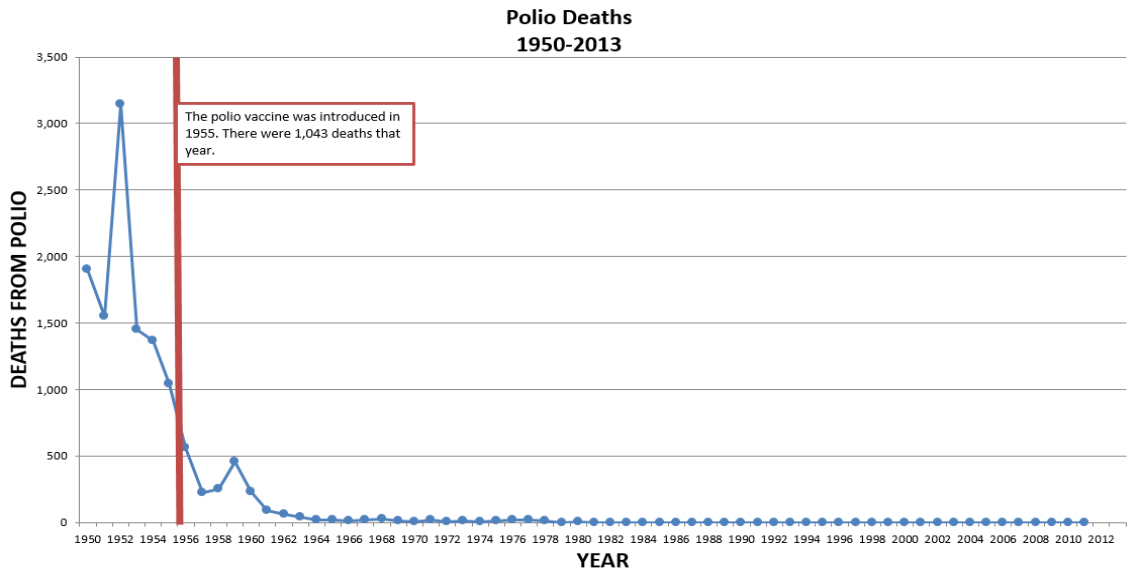


As presented in the CDC Pink Book:

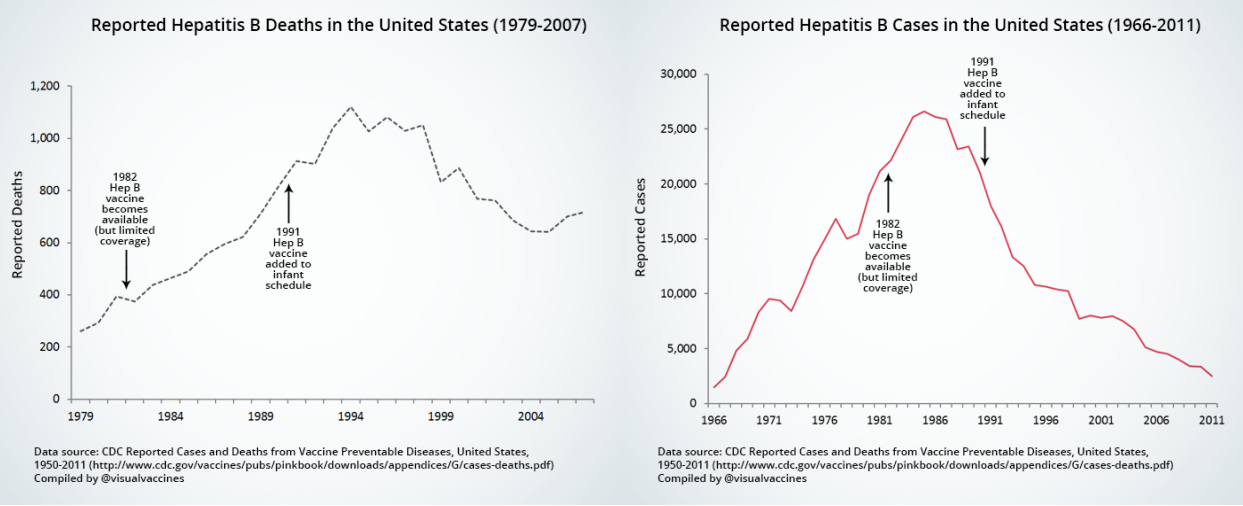


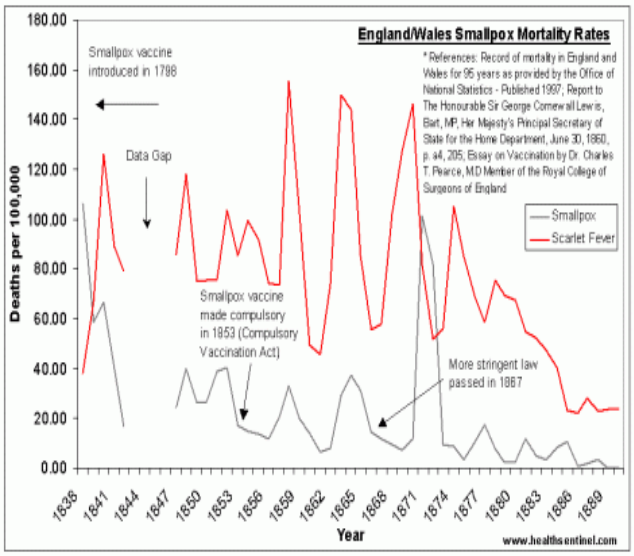
This is a perfect example of “snap shot” data:

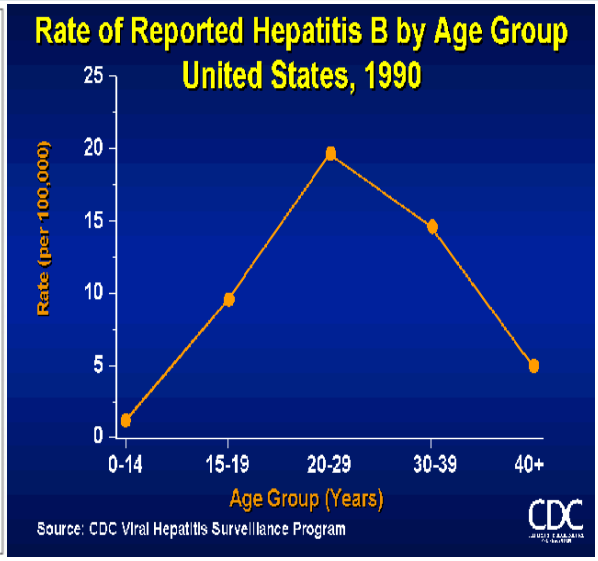


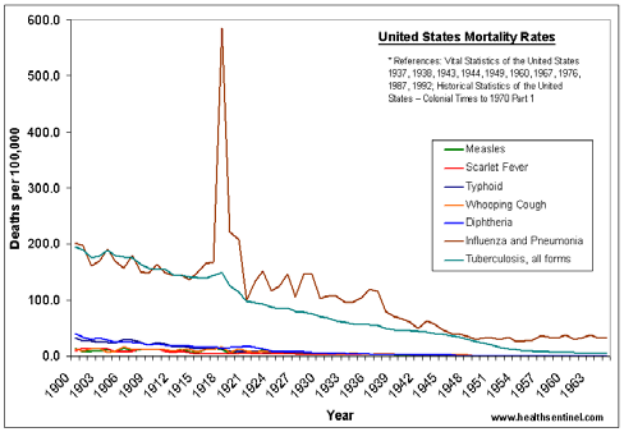


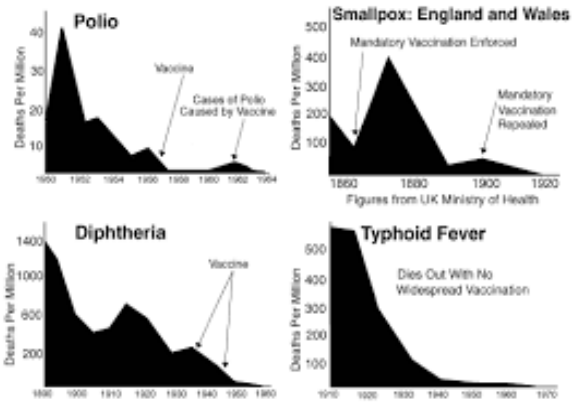
Other Examples of "Snapshot" Data:









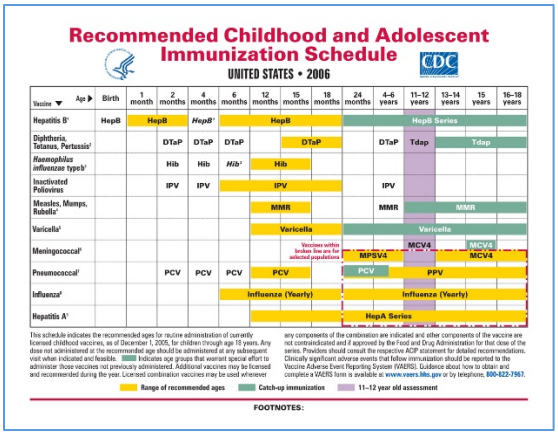


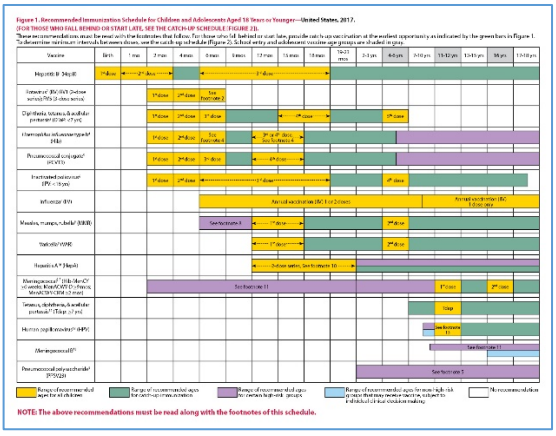
I hope you see the need for looking at the whole picture and this requires more data points. I will feel comfortable when I see something statistically significant in the models. After that, I would like to look at the analytics within that. There is so much to learn, but we need data sets in formats that are available for anyone not financially tied to the vaccine industry. No matter what the outcome, there will be those who want vaccines and there will be those who do not. The choice should be theirs because there are no certainties in science. It is my sincere hope that your committee benefits from this information and can advance vaccine related scientific methodology.

Tribute to CAPT Jean Clare Smith

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn indicated that they wanted to take the opportunity to acknowledge someone who has been the heart and soul of ACIP for many years, CAPT Jean Clare Smith. Given that Dr. Smith is moving into a new position at CDC, they wanted to take a moment to acknowledge her. Dr. Smith joined CDC 25 years ago as an Epidemic Intelligence Service (EIS) Officer. Dr. Smith started saving the world many years ago. In 1992, she was featured in an article regarding a foodborne outbreak that she worked on that broke out among bankers. She traced the foodborne illness back to the eggs of a caterer who was making homemade mayonnaise. After EIS, Dr. Smith's dedication to public health led her to live in India-Nepal, where she worked tirelessly for years on polio eradication during a time when enormous progress toward elimination was made in the region. In 2006, Dr. Smith became a Medical Officer for ACIP Secretariat. This is what the childhood immunization schedule looked like in that year compared to the current schedule 11 years later:





There is so much behind each of these recommendations. Dr. Smith has spearheaded the many critical improvements in terms of the way ACIP functions, including GRADE evidence-based recommendations and the way economic analyses are presented to ACIP. More than anything, Dr. Smith has been an advisor, mentor, and supporter for dozens of CDC staff and over 40 ACIP members over the years.

While Dr. Smith will always be part of the ACIP family, everyone is so grateful for her tireless efforts to bring ACIP to where it is today, all while raising her beautiful daughter pictured here:

Everyone is excited for Dr. Smith in her new role. She will not be far away as she continues to work on educating providers about ACIP recommendations.

Dr. Smith thanked everyone and quipped that as a 65-year-old mother of a 19-year-old daughter, there is no retirement for her anytime soon, and she has started receiving piles of Medicare mailings.

Dr. Bennett expressed her gratitude and emphasized that there is no way they could ever express how much Dr. Smith has meant to all of them. On a personal note, Dr. Bennett said she would never have taken this job if not for Dr. Smith.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that a number of important and great things are going on in NCIRD, which were described in a 2-page report provided to ACIP members. She conceded her time to Dr. Cohn for the tribute to CAPT Jean Smith.

Centers for Medicare and Medicaid Services (CMS)

Ms. Hahn indicated that there were no updates for CMS.

Department of Defense (DoD)

Dr. Yacovone reported that the Defense Health Agency (DHA) Immunization Healthcare Branch (IHB) continues to work with all branches of the service on mitigating strategies to conserve available doses of yellow fever (YF) vaccine due to the YF vaccine shortages. DoD has reduced utilization by more than 60%, maximized its stock with an aggressive redistribution

program, and worked in partnership with Sanofi Pasteur on strategies to help delay a national stock-out. The DoD routinely vaccinates recruits to protect against Adenovirus Types 4 and 7 early in initial entry training. Recently completed FDA-mandated post-licensure surveillance studies reported sustained reductions in acute respiratory disease and an excellent safety profile in this population following reinstatement of a universal vaccination of recruits. These publications include one in *Infectious Disease* and another in *Vaccine* on the incidence of respiratory illness and safety.

Future goals of the Adenovirus Vaccine Program include modernization of the Adenovirus vaccine production in partnership with industry, and consideration for expansion of vaccination to military service academies in addition to DoD's recruit population. For its Japanese Encephalitis Vaccine (JEV) Program, DoD has completed all of JEV IXIARO® FDA required post-licensure studies. A final manuscript of surveillance of AEs was submitted to the FDA this week for review and comments. In terms of metabolomics research, DoD completed a pilot study to assess metabolites as markers of AEs following smallpox vaccination. This study demonstrates the potential for metabolites to identify mechanisms associated with subjects who developed AEs following immunizations that was published in *Vaccine* in March 2017.

Food and Drug Administration (FDA)

Dr. Sun reported that the FDA held an advisory committee meeting on May 17, 2017 for which the topic of discussion regarded how to move forward with the development of vaccines for infant immunization with respiratory syncytial virus (RSV) vaccine, given the past history of the formalin-inactivated vaccine causing enhanced disease. FDA has the advisory committee's feedback and is working with several manufacturers on developing RSV vaccines for that population.

Regarding the 21st Century Cures Act 2016 and how it impacts vaccines, there are numerous provisions. The provision that is most relevant to ACIP is Title III Subtitle C: Modern Trial Design Evidence and Development Section 3022—Real World Evidence. The act requires FDA to establish a program to evaluate potential use of real world evidence for two purposes, which are to: 1) help to support the approval of a new indication for a drug approved under section 505(c); and 2) help to support or satisfy post-approval study requirements. "Real world evidence" is defined as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials." The act goes on to state that "The framework shall include sources of real world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities." The implication for this is that the impact of ACIP recommendations will be enhanced because the FDA believes that the nature of ACIP recommendations will dictate how real-world evidence will be able to be developed.

FDA is also charged with developing a guidance on this topic, and there is likely to be additional collaboration with ACIP on doing this. On March 13, 2017, FDA approved the supplement for the 3-dose Trumenba® series and the confirmatory study for the accelerated approval. Pfizer presented data from their breadth of coverage using additional Serogroup B meningococcal (MenB) strains as measured by the serum bactericidal antibody (SBA) levels. That supplement also included data on concomitant administration of Menactra®, which also was approved. Drs. Walter Ornstein, Larry Pickering, Carol Baker, and Sun have submitted an article to *Vaccine* on the topic of ACIP and FDA collaborations on vaccines in the US, and how they have reviewed the approvals over the last 10 years and ACIP recommendations. This should be published in the next 3 months.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that HRSA has been very busy in the National Vaccine Injury Compensation Program (VICP). Thus far, 853 claims have been received in 2017. As of March 2017, $127 million in awards have been paid to petitioners and $13 million have been paid in attorney fees and costs. That includes costs for compensations, dismissed claims, and interim fees. HRSA's website includes current information about the program. The Final Rule that made revisions to the Vaccine Injury Table was published in January 2017 and is effective for claims that are filed after March 21, 2017. HRSA continues its outreach efforts to make people aware of this program.

Indian Health Services (IHS)

Ms. Groom reported that IHS had full implementation of their mandatory HCP influenza vaccination policy this influenza season. Their final data shows that the agency did achieve the Healthy People 2020 goal of 90% coverage for HCP across IHS. For FY2018, IHS is implementing a composite measure agency-wide to monitor compliance with adult immunizations for Tdap, Td-containing vaccine in the last 10 years, zoster, and pneumococcal vaccine.

National Institutes of Health (NIH)

Dr. Lambert reported that a Phase I clinical trial has been initiated of the new recombinant RSV vaccine. This effort is under the development of the Vaccine Research Center at the National Institution of Allergy and Infectious Diseases (NAIAD). NIH also initiated a Phase II clinical trial of a zika vaccination, which is a DNA-based vaccine that showed promise in Phase I clinical trials. The Phase II clinical trial has a 2-staged study design. Part A will enroll healthy adults that will show safety and immunogenicity, and will help determine the optimal dosage. Part B will enroll up to 2400 healthy adults 15 through 35 years of age. This part of the trial aims to determine if the vaccine can effectively protect against Zika-related disease when someone is naturally exposed to the virus. Sites will include the three locations from Part A (Houston, Miami, and San Juan) and six additional countries that have had zika (two additional sites in San Juan, two sites in Costa Rica, and one site each in Peru, Brazil, Panama and Mexico). Late last year, NIH supported a workshop on waning immunity associated with microbial vaccines. That was published in May 2017 in an American Society for Microbiology (ASM) Journal, and compared and contrasted 6 microbial vaccines (*Bordetella pertussis, Salmonella typhi, Neisseria meningitidis,* influenza, mumps, malaria) in terms of what is known about them and their duration of protection. The articles also included recommendations for opportunities for additional research support.

National Vaccine Program Office (NVPO) / National Vaccine Advisory Committee (NVAC)

Dr. Shen reported that since departing NVPO, Dr. Gellin has left federal service and is now serving as a leader at the Sabin Vaccine Institute. On May 9, 2017, NVPO along with CDC and the Immunization Action Coalition (IAC) co-chaired the IAC-hosted 6th annual National Adult Influenza and Immunization Summit (NAIIS). There were over 350 attendees who represented 150 organizations across the federal space, local and state health departments, professional associations, foundations, networks, academia, et cetera. This year's theme was "Prioritizing Prevention: Strategies to Improve Adult Vaccination within the Transforming Health System." This year, there also was a pre-meeting on leveraging and transforming health systems to

improve adult vaccination, which was co-sponsored by AMGA™ and NAIIS. NVPO will be producing a white paper from that pre-meeting, and the slides are on the NAIIS website.

Also related to adults, NVPO and IHS co-lead the NAIIS Quality and Performance Measures Workgroup. NVPO has a contract through the National Committee for Quality Assurance (NCQA) and has completed recruitment. Through the summer, NCQU will be testing NVPO's maternal immunization composite measure that includes Tdap and influenza. This measure will be included in the Healthcare Effectiveness Data and Information Set (HEDIS). Many who work in health systems appreciate the implications of being part of HEDIS.

Through the NAIIS, NVPO will have its End-Stage Renal Disease (ESRD) Measure Working Group and has engaged with CMS's ESRD program, including their Quality Incentives Program and Networks Program for Quality Improvement and Programs. NVPO will update ACIP in the fall on the adult composite. This composite is comprised of Tdap, pneumococcal, zoster, and potentially influenza.

Regarding the 21st Century Cures Act, NVPO is leading the HHS Inter-Agency Working Group, which is comprised of FDA, CDC, NIH, and Biomedical Advanced Research and Development Authority (BARDA) on delivering on Section 3093. This section requires the Secretary of HHS to deliver a report to Congress pertaining to vaccine innovation, which is due in December 2017 one year from the enactment of the law.

Earlier in June, NVPO announced the winners of its inaugural UpShot Awards celebrating the great work being done to enhance the vaccine immunization system. Excellence in Vaccine Safety went to Dr. Roger Baxter, Co-Director, Kaiser Permanente Vaccine Study Center; Excellence in Vaccine Communication went to Dr. William Schaffner, Medical Director, NFID; Excellence in Vaccine Supply, Access, and Use went to HLN Consulting; and Excellence in Global Prevention went to PATH.

NVAC held its meeting on June 6, 2017. The meeting was framed around the top 3 opportunity areas as identified by the NVAC Midcourse Review: Immunization Information Systems (IIS), Vaccine Confidence, Financial and Systems Barriers to Administration of Vaccine. Slides will be available on the NVPO website in about one week.

The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) is charged with developing recommendations on incentivizing development for therapeutics, diagnostics, and vaccines. The Vaccines Working Group draft report was presented during the May public meeting, but did not include their recommendations. Their full report will be presented this fall at the September 13-14, 2017 PACCARB meeting for a full vote of the PACCARB. The recommendations of PACCARB go to the Secretary of HHS, who then transmits them to the President. A number of NVAC members also sit on that working group.

Dengue Virus Vaccine

Introduction

Emmanuel (Chip) Walter, MD, MPH
Chair, Flavivirus Vaccines Work Group
Advisory Committee on Immunization Practices

Dr. Walter reminded everyone that during the February 2017 ACIP meeting, there was an update on general dengue epidemiology and vaccine development. Since that time, the WG has met about every two weeks and continued review of dengue epidemiology, immunology, and diagnostics to prepare for submission of the dengue vaccine Biologics License Application (BLA). They have learned that the dengue vaccine BLA submission has been delayed. Though initially the submission was anticipated to be in 2017, it will probably be sometime in 2018.

Future WG plans are to continue review DENGVAXIA® clinical trials, the cost-effectiveness of dengue vaccines, and GRADE; hear presentations by Sanofi Pasteur; and draft recommendations for use. In preparation for all of this, a presentation was delivered during this session on dengue epidemiology in the US, Puerto Rico (PR), and other US territories.

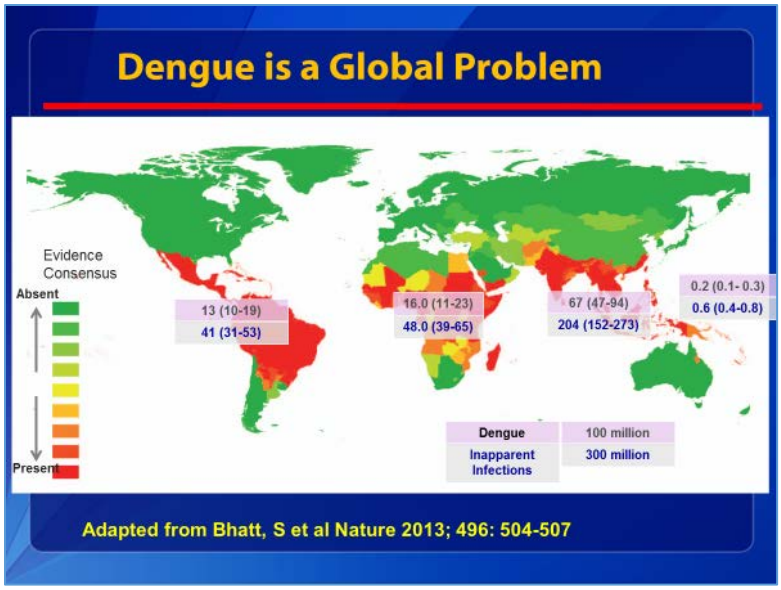
Dengue Virus Vaccines

Steve Waterman, MD, MPH
Chief, Dengue Branch
Centers for Disease Control and Prevention
San Juan, Puerto Rico

Dr. Waterman presented available data on dengue epidemiology in the US and its territories. It is important to note dengue was only made reportable by CSTE in 2010. After recapitulating the fundamentals of dengue epidemiology, he covered the jurisdictions and geographic areas in the US affected by dengue, roughly in order of transmission intensity and burden.

Dengue viruses (DENV) comprise four related serotypes. Zika is closely related to dengue. An infection with a given serotype provides long-term protection, and a short period of up to about 6 months of cross-protective immunity. Thus, theoretically, one can experience four dengue infections in a lifetime. Humans acquire dengue through the bite of dengue-infected *Aedes* mosquitoes, principally *Aedes aegypti*, in a man-mosquito-man transmission cycle without intermediate hosts. The incubation period in both man and mosquitoes before becoming infectious is about a week.

Dengue is arguably the most important arbovirus in terms of worldwide morbidity and mortality across the tropical and sub-tropical Western Hemisphere, Africa, the Middle East, Asia, and the Pacific, with an estimated 100 million dengue cases including 2 million severe illnesses and 20,000 deaths a year:



Dengue is an acute febrile illness (AFI) syndrome resembling many other infectious diseases such as measles, leptospirosis, and rickettsial disease. Epidemics typically have a cyclical pattern over years and with seasonal incidence correlated with higher rainfall months. In highly endemic areas, multiple serotypes may circulate simultaneously. The peak age of incidence varies by region, the more endemic, the younger the median age incidence in general. Severe dengue often manifests as a capillary leakage syndrome known as dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) which occurs precipitously several days into the illness and is potentially fatal, although with adequate fluid support, mortality should be reduced to less than 1% [Guidelines for Clinical Evaluation of Dengue Vaccine in Dengue Endemic Areas. Vaccine 2008;26:4113-4119].

Secondary infection, a second dengue infection with a different serotype with the associated immune response mediated in part by the prior infection, is a documented important risk factor but is not necessary a condition for severe disease. In addition to this likely immune system mediated risk factor, viral strain and host characteristics (co-morbidities, young age, female) are risk factors for disease severity.

The framework for thinking about dengue risk and possible vaccine recommendations centers on presence of the vector. Again, the principal vector is *Aedes aegypti*, but other *Aedes* species such as *albopictus* in Hawaii and *polynesiensis* in the Pacific are vectors as well. The history of and potential for virus transmission is also important. Puerto Rico is highly endemic for dengue. The Virgin Islands and Pacific territories also have high, if not endemic, levels of transmission. Southern US states, such as Texas and Florida, have experienced dengue outbreaks in recent years, as has Hawaii. A number of other Southern and Southern border states, such as Louisiana and Arizona respectively, are at risk for dengue because of an abundance of *Aedes aegypti*, imported infections, and proximity to endemic areas. Of course, imported cases can occur where the vector is not present.

Puerto Rico has a history of major epidemics. Puerto Rico's first major epidemics were reported in 1915 and 1945. The Commonwealth of Puerto Rico has had a population of over 3 million persons since the late 1970s. In 1963, DENV was first isolated in Puerto Rico during a DENV 3 outbreak. The first laboratory-confirmed case of DHF was reported in 1975. The first time

circulation of more than one DENV type was documented was in a 1977 outbreak. During that outbreak 12,733 cases were reported (3.75/1000 population) and 355,000 were estimated to have occurred. DENV-1, -2, and -3 were detected. Six large, island-wide outbreaks took place between 1969-1986.

The only documented dengue vector in Puerto Rico is *Aedes aegypti*. Dengue is endemic in Puerto Rico, with typically two to three epidemics each decade. Up to 27,000 cases have been reported through passive surveillance in an epidemic year, with several thousand cases even in some non-epidemic years. Three to four dengue viruses have circulated simultaneously in Puerto Rico since the mid-1980s. Seasonal peak dengue activity is in the late summer to fall months. Incidence is, as expected, highest in urban areas. Clinical disease report rates are highest in those 10 through 19 years of age, with no incidence difference by sex.

Again, dengue incidence cycles as serotype specific susceptibles are depleted and build back up over several years. There were two large outbreaks in the 1990s with multiple serotypes, which were predominantly DENV-2 in 1995 and DENV-4 in 1998. There were three large outbreaks in the 2000s, with the last occurring in 2012-2013. DENV-1 and DENV-3 predominated in those outbreaks. DENV-1, -2, and -4 dominated in Puerto Rico from 1986 through 1997. DENV-3 reappeared in the 1998 outbreak and remained in circulation until early 2010. By 2000, few cases of DENV-4 and DENV-1 were detected until reappearing during the 2007 outbreak. DENV-2 has been detected every year; however, the proportion of isolates typing as DENV-2 were low from 2000-2002 and recently in 2011-2012. All four viruses were circulating in 2015-2016 when DENV-2 seemed to be on the increase again, with DENV-4 being the most common subtype.

Typically, about half (49%) of all laboratory-positive cases reported through passive surveillance are among adults 20 years of age or older, as occurred in 2010-2012. The median age was 18 years and the range spanned from infancy to centenarians. The highest number of cases and rate of laboratory positive dengue was among children and adolescents 10 through 19 years of age. Laboratory-positive cases during 2010-2012 track with dengue deaths. The mortality rate per 100,000 was highest in 2010 with 39 deaths (1.05 deaths/100,000). There were 6 deaths in 2011 (0.16 deaths/100,000) and 13 deaths in 2012 (0.35 deaths/100,000). The case fatality in 2010 (39 deaths/10,970 laboratory-positive cases) and 2011 (6 deaths/1547 laboratory-positive cases) was 0.4 deaths/100 laboratory-positive cases and 0.2% in 2012 (13 deaths/6057 LP cases). In contrast to the higher rate of disease reports in adolescents, only 6 of the 58 laboratory-confirmed deaths were in children and only one was in those 10 through 19 years of age. Rather, deaths were most common in adults between 20 to 88 years of age. In Puerto Rico, 52 of 58 (90%) of laboratory-positive deaths occurred in adults from 2010 through 2012.

The seroprevalence of dengue infection and the proportion of primary and secondary infections is an important consideration in thinking about the DENGVAXIA® vaccine. In a 2006 Puerto Rico blood donor serosurvey among adults, 92% were seropositive for past dengue infection and most of the infections were secondary. The antibody pattern result indicated that 96% of those tested had had two or more dengue infections[1]. Among Puerto Rico laboratory-positive dengue cases in 2010, 80% of all infections had a secondary dengue antibody pattern. Primary infection was more common in those 1 through 4 years of age, and more than 80% of cases had secondary antibody responses[2] [[1]Mohammed et al., Transfusion, 2012; [2]Sharp et al., PLoS NTD, 2013].

Moving to the US Virgin Islands (USVI), about 60 miles east of Puerto Rico, based on their passive case reporting, USVI has experienced periodic outbreaks between 1986-2012. During the last outbreak in 2012, CDC DB assisted the USVI DOH in conducting a seroincidence study in schools in St. Croix. Of school-aged children/adolescents and teachers, 20% and 17% respectively were acutely or recently infected with dengue virus, and 80% of school aged children and adolescents and 98% of teachers had serologic evidence of prior flavivirus infection.

Multiple *Aedes* species are present in the US Pacific territories which include American Samoa, Guam, the Northern Mariana Islands, Palau, the Marshall Islands, and the Federated States of Micronesia. Periodic dengue outbreaks have been detected among the Pacific Islands since 1958, usually with only one dengue serotype at a time[1]. A 2010 serosurvey in American Samoa among adults found that 96% percent of the sampled population had dengue antibody[2]. CDC collaborated on an outbreak investigation in American Samoa in 2015 where 479 (1% of the population) suspected dengue cases were reported. Reverse transcriptase polymerase chain reaction (RT-PCR) testing detected DENV-3 only. Four persons died, for a case fatality rate of about 1%. The most common vectors were *Aedes aegypti* and *Aedes albopictus* [[1]Hammon et al., *Am J Trop Med Hyg*, 1958; [2]Lau, EID, 2013].

The region of the continental US most at risk for dengue is the Southeastern US-Mexico border in the so-called Lower Rio Grande Valley. Mexico has become increasingly endemic for dengue since the 1980s. US transmission stems from Northward movement of DENV across the border during large outbreaks in Northern Mexican border states such as Tamaulipas and Nuevo Leon. South Texas is the only US border region with documented local transmission. However, dengue outbreaks have occurred along the border of Arizona and California in recent years where *Aedes aegypti* has been recently introduced, so these areas are at risk in the future.

Texas has an impressive history of several large dengue outbreaks, including a 1885-1886 outbreak in Austin during which an estimated 70% of residents were affected and in 1922 in a statewide outbreak involving an estimated 500,000 cases throughout the state. The first dengue post World War II (WWII) outbreak occurred in the lower Rio Grande Valley of Texas in 1980 when a number of cases were identified that did not have a travel history across the border to Mexico [Ehrenkranz et al., *NEJM* 1971].

CDC worked with Texas and Mexico to investigate a 1999 dengue outbreak in the sister cities of Laredo, Texas and Nuevo Laredo, Tamaulipas. The following satellite image shows the Rio Grande river dividing these adjacent communities:

Using a modified WHO cluster sampling approach, a serosurvey on both sides of the border showed higher incidence of IgM positive recent infections on the Mexico side despite higher mosquito density indices on the US side. While most cases on the US side had a travel history to Mexico, a number did not. The IgG antibody prevalence indicating prior dengue infection among sampled US residents of Laredo was 22.5%. This often cited study by Reiter found suggested household environmental characteristics, such as lack of air conditioning, was an important risk factor for dengue infection in this setting [Reiter et al. *Emerging Infectious Diseases* 2003].

The CDC Border Infectious Disease Surveillance (BIDS) Program enhanced AFI surveillance collaboration with Texas detected the first locally-acquired case of DHF in the continental US in 2005 during a DENV-2 outbreak with the Southeast Asia strain associated with severe disease. Again, higher rates of recent infections were seen on the Matamoros, Mexico side, but 38% of surveyed Cameron County residents had IgG antibody of 38% and 25% of persons participating in the serosurvey who had not traveled out of the US were seropositive for dengue. This was the first time DHF was reported in the US. Of cases reported to the Cameron County Health Department, 25 (89%) were hospitalized, 16 of whom had DHF syndrome[1]. The most recent Texas outbreak, again in Cameron County, was in 2013 with 53 laboratory-confirmed cases, with 55% of whom were hospitalized. Almost half of the reported cases were locally acquired. Local transmission was also documented by a serosurvey among household members of dengue cases[2] [[1]Ramos et al *Am J Trop Med Hyg 78(3) 2008; MMWR 56 2007*; [2]Thomas et al. Emerg Inf Dis 2016].

Florida has had a number of outbreaks since 2009. In 2009, Florida had its first dengue outbreak in 64 years detected after a traveler from New York was diagnosed with dengue after returning home from Key West, the string of islands extending off the southern tip of Florida. The 2009 investigation revealed 27 laboratory-positive locally-acquired cases in Key West residents and 5% of residents surveyed at the end of the outbreak (n=240) had had a recent dengue infection. DENV-1 was the only type identified. In 2010, during March to November, 66 locally-acquired dengue cases were identified in Monroe County.

Two sporadic locally-acquired dengue cases occurred in Florida in 2010. One DENV-1 case was detected in Miami-Dade County, and one DENV-3 case was detected in Broward county. In 2011, the Florida Department of Health reported 7 dengue cases with no travel history in the 2 weeks prior to illness onset. The cases resided in Hillsborough (1), Martin (1), Miami-Dade (3), and Palm Beach (2) counties. In 2012, Florida had 4 sporadic locally-acquired dengue cases, with two in Miami-Dade and one each in Seminole and Osceola Counties. A locally-acquired dengue outbreak took place in Martin and Saint Lucie Counties beginning in June 2013 and continuing through September 2013. There was one sporadic case that year in Miami-Dade County. Of the ill cases initially identified, 21 had DENV-1 and no travel history. The median age was 48 years, with a range of 4 through 63 years. More than 85% were white non-Hispanic. A seroincidence study suggested that 7% of the residents were infected. Sequencing studies in Martin County in 2013 compared to the 2009 virus in Key West, the viruses were different, so this was reintroduction not ongoing endemic transmission in Florida [CDC Dengue Branch and Florida Department of Health].

Hawaii also has a history of dengue outbreaks, but was quiescent after WWII for a period of time. *Aedes aegypti* was the vector implicated in these early outbreaks. However, sometime early in the 20th Century, *Aedes albopictus* was introduced into Hawaii and has become the dominant mosquito in Hawaii. Hawaii experienced a dengue outbreak in 2001 that affected three islands. From May 2011 to February of the following year, 1644 suspected dengue cases with no recent travel history were tested for dengue, of which 122 were laboratory positive. Laboratory-positive cases were detected on 3 of the 6 islands, Kauai, Oahu, and Maui, with 2/3 of the cases on Maui. A serosurvey in the small Maui rural community of Nahiku showed a 39% attack rate with evidence of prior undetected transmission. DENV-1 was the only serotype identified and was thought to be most closely related to a strain from Tahiti, which is important. The median age of laboratory-positive cases was 41 years. Three of the 122 cases were hospitalized, there were no DHF/DSS cases, and there were no deaths. A small cluster of 5 non-severe dengue cases, two confirmed with DENV-1, was identified in early 2011 in the neighborhood of Pearl City, Oahu. The index case was a traveler and subsequently 4 local residents without travel history became ill and had confirmed dengue. A dengue outbreak occurred recently in 2015 on the Big Island of Hawaii, with 264 laboratory-confirmed infections. Cases had a median age of 29 years, and early data indicated a 14% hospitalization rate. The outbreak strain was a DENV-1 strain different from the 2001 Hawaii outbreak strain. Dengue was the isolated virus from *Aedes albopictus*. Possible focal areas with *Aedes aegpyti* contributed to outbreak transmission.

In summary, dengue is highly endemic in Puerto Rico with simultaneous circulation of multiple serotypes. Limited seroprevalence data strongly suggest that most of the population has had at least one dengue infection by the second decade of life. During large outbreaks, hundreds of hospitalizations and tens of deaths occur. Dengue is common and may be endemic in the Virgin Islands and American Samoa and other US Pacific territories. Seroprevalence data are limited. South Texas has had repeated small dengue outbreaks with local transmission since the 1980s. Seroprevalence data over 10 years old suggests that there is a border crossing sub-population with significant past exposure to dengue. Other US-Mexico border states are at risk for dengue, but there is no evidence of local transmission to date. South Florida has had repeated small dengue outbreaks since 2009. Hawaii has had two outbreaks and a small cluster of cases since 2001, that was transmitted primarily by *Aedes albopictus*.

Yellow Fever Vaccine

Introduction

Emmanuel (Chip) Walter, MD, MPH
Chair, Flavivirus Vaccines Work Group
Advisory Committee on Immunization Practices

Dr. Walter reminded everyone that intermittent production issues have periodically resulted in temporary supply shortages of yellow fever (YF) vaccine, YF-VAX®, in the US. Since November 2015, ordering restrictions have been in place for YF-VAX® due to supply shortages. In October 2016 and February 2017, the WG briefed ACIP about YF-VAX® production and contingency plans to address any supply shortages. Presentations during the June 2017 ACIP Meeting included: 1) an update on implementation of an Investigational New Drug (IND) and YF vaccine distribution; and 2) a review of protocol inclusion criteria and the current ACIP

recommendations.

Update on YF Vaccine Supply

David Greenberg, MD
Associate Vice President and Regional Medical Head, North America
Sanofi Pasteur

Dr. David Greenberg reported that to improve supply of yellow fever vaccine in the US, Sanofi Pasteur is transitioning manufacturing of YF-VAX® to a new state-of-the-art facility that is expected to be operational by mid-2018. Manufacturing issues resulted in a gap in YF-VAX® vaccine supply from the time of the shutdown of the old facility to operation of the new facility. Ordering restrictions have stretched the remaining supply of YF-VAX® vaccine. Sanofi Pasteur expects to stock-out of YF-VAX® in early July 2017.

Sanofi Pasteur's focus has been to provide a continuous supply of YF vaccine in the US for travelers, government employees, military, and other response groups who need to be immunized. To this end, they have held stakeholder discussions for over a year with CDC, FDA, DoD, and others to manage the remaining supply of YF-VAX® vaccine and to import an alternative YF vaccine.

An essential component of the stakeholder discussions has been to work closely with the FDA to import Stamaril®, the YF vaccine Sanofi Pasteur manufactures in France that is not licensed in the US, under an IND and distribute it in the US via an Expanded Access Program (EAP). The EAP protocol allows for Stamaril® vaccine to be used by authorized healthcare providers who undergo training. As a result of these efforts, and to maintain supply of YF vaccine in the US, Sanofi Pasteur started shipping Stamaril® vaccine to EAP-certified sites on May 23, 2017.

As noted previously, Stamaril® vaccine is the YF vaccine manufactured by Sanofi Pasteur in France. It is a live attenuated vaccine that contains the YF virus 17D-204 strain. This is the same strain contained in YF-VAX®. Stamaril® vaccine is used globally in more than 70 countries, and has been licensed for more than 30 years. More than 430 million doses have been distributed globally. Stamaril® vaccine is supplied as a vial of lyophilized powder and a syringe prefilled with diluent.

CDC staff collaborated with Sanofi Pasteur to publish this report on the YF fever vaccine shortage in the *MMWR*, appeared online on April 28, 2017. It reviews the events leading up to the shortage, the collective efforts to provide a continuous supply of YF vaccine in the US despite the shortage, and the process of selecting and certifying Stamaril® sites.

Sanofi Pasteur is in the process of enrolling approximately 250 clinical sites to administer Stamaril® vaccine to patients under the EAP. Sanofi Pasteur sought to have Stamaril® vaccine available at the highest volume clinical sites in the country because they would likely be the best equipped and staffed to handle many patients seeking vaccination. Therefore, sites where more than 250 doses were ordered in 2016 were asked to participate in the EAP. In addition, multi-site organizations that collectively ordered at least 250 doses in 2016 were offered a single site. Lower volume sites were added, especially in states and territories that otherwise would have been without a site based on the high-volume requirement. All 50 states; Washington, DC; and territories are covered. Site personnel are required to follow the EAP protocol, undergo training, obtain informed consent from vaccinees or parents if the recipient is aged <18 years,

track use of the vaccine, and report AEs. HCPs in clinics not participating have been notified to direct their patients to Stamaril® sites listed on the CDC website as shown:

wwwnc.cdc.gov/travel/page/search-for-stamaril-clinics

As of June 15th, 250 sites have confirmed their interest in participation. Of these, 207 sites have signed the protocol agreement. The remaining 43 sites are waiting for their internal management approval or IRB approval. Training has been completed by 199 sites, 175 sites have IRB approval, and 128 sites have ordered about 13,000 doses so far. Of the originally invited sites, 17 have declined participation. They are mutually exclusive of the 250 sites who have confirmed their participation.

In summary, Sanofi Pasteur expects to stock-out of YF-VAX® in early July 2017. Stamaril® vaccine is now being distributed in the US under an expanded access IND that was approved by the FDA. Sanofi Pasteur is in the process of enrolling 250 sites and many are up and running. As of June 15th, 250 sites have confirmed their interest in participating, 199 sites are trained, and 128 have Stamaril® in their refrigerators for their incoming patients. The CDC YF website with the URL shown earlier is updated regularly with Stamaril® sites as they are approved and trained. Sanofi Pasteur will supply Stamaril® vaccine to the EAP-certified sites until the new production of YF-VAX® becomes available in mid-2018.

Review of Current ACIP Recommendations for YF Vaccine and EAP Program Protocol Criteria for Stamaril®

J. Erin Staples, MD, PhD
Arboviral Diseases Branch
Division of Vector-borne Diseases

Dr. Staples indicated that the objective of this session was to highlight the differences between current ACIP recommendations and the EAP IND protocol for Stamaril® for ACIP's awareness. The current ACIP recommendations were published in 2010 and recommend the use of YF vaccine for persons aged ≥9 months who are traveling to or living in areas at risk for YF virus transmission. Because of rare but serious AEs, healthcare providers should vaccinate only persons at risk for exposure to YF virus or who require proof of vaccination for entry. To minimize risk for SAE, healthcare providers should observe contraindications and consider precautions to vaccination before administering this live-attenuated viral vaccine.

During the period while YF-VAX® is unavailable in the US, Stamaril® will be available only at selected clinics through an IRB-approved protocol. Persons needing vaccination will be screened for inclusion and exclusion criteria. Consent and, when applicable, assent will be obtained prior to administering Stamaril®. Since Stamaril® has been available for decades outside of the US and has a safety profile similar to YF-VAX®, AE possibly related to vaccination and SAE will be passively collected rather than solicited. Persons who receive vaccines in clinics that are administering Stamaril® are recommended to report AE to Sanofi Pasteur rather than VAERS.

Overall, ACIP recommendations and the protocol criteria are very similar. Contraindications or exclusionary criteria under the ACIP recommendations and the EAP protocol criteria for receiving Stamaril® under the EAP protocol are very similar and include:

- ❑ Allergy to vaccine components
- ❑ Age <6 months
- ❑ Symptomatic HIV or asymptomatic HIV with severe immune suppression
- ❑ Thymus disorder
- ❑ Primary immunodeficiencies
- ❑ Malignant neoplasms
- ❑ Transplantation
- ❑ Immunosuppressive and immunomodulatory therapies

Three precautions are also common to the ACIP recommendations and the EAP protocol, which include:

- ❑ Pregnancy
- ❑ Age ≥60 years
- ❑ Asymptomatic HIV with moderate immune suppression

With these groups in particular, there will be counseling about the risk of the disease versus the risk of vaccination. The decision to vaccinate will be based on that.

There are three differences between the current ACIP recommendations and the EAP protocol criteria. The first is persons with asymptomatic HIV infection with no evidence of immune suppression. Under the current ACIP recommendations, these individuals should receive the vaccine if they are at risk for coming in contact with YF virus or need it for proof for country entry. Under the current EAP protocol, however, they are listed as a precaution to vaccination. However, this should not necessarily impact the ability of persons with these conditions to receive the vaccine if they are truly at risk for acquiring the disease. Being 6 through 8 months of age is currently listed as a precaution under the ACIP recommendations, but this is an exclusionary criterion in the EAP protocol, meaning infants 6 through 8 months of age will not be able to receive Stamaril® while YF-VAX® is unavailable in the US. This is also true for breastfeeding, which is listed as a precaution in the ACIP recommendations for vaccination, but is an exclusionary criterion for EAP protocol unless breastfeeding can be discontinued for 14 days following vaccination. Since infants 6 through 8 months of age and breastfeeding women could previously receive YF vaccine but will be excluded under the EAP protocol, these groups are advised to defer travel to risk areas if possible. If that is not possible, strict mosquito prevention measures should be used to lower their risk of disease.

Discussion Points

Dr. Schaffner (NFID) said he was under the impression that one dose of YF vaccine would be sufficient for lifetime protection, and wondered whether that should be a deferral criterion if someone did not really need it.

Dr. Staples replied that in the current ACIP recommendation that was approved in 2015, the booster dose of YF vaccine previously recommended every 10 years has been removed for most individuals. The EAP protocol specifically addresses people who have not received the vaccine previously and are seeking the vaccine to protect themselves against the disease.

Dr. Reingold requested clarity regarding whether if travel could not be avoided, those 6 through 8 months of age and breastfeeding mothers would go unvaccinated and would rely strictly on

mosquito prevention measures. In many countries, they would not be allowed to enter without the yellow card showing that they had received YF vaccine.

Dr. Staples clarified that they will not be able to receive the vaccine, so the alternative prevention measure is to use mosquito precaution. The preference is for them to defer travel if possible, but not everybody can.

Regarding the selection of the Stamaril® sites, Dr. Hunter asked what percentage of travelers receive the recommended vaccine and whether non-adherent travelers are geographically concentrated. If so, it seems that the site selection process that emphasizes previous high-utilization clinics potentially increases non-adherence by decreasing access.

Dr. Greenberg responded that, indeed, it made sense for Sanofi Pasteur to seek out the highest volume centers because they traditionally and historically have ordered the greatest number of doses and were thought to be the most apt to handle individuals who might otherwise not have gone to that clinic from the surrounding area. The high-volume sites are spread across the country and an effort has been made to fill gaps with lower volume sites.

Dr. Stapes added that some surveys have been conducted of travelers who present to travel clinics and are seeking advice about receiving vaccines, so that is already a selective population. The group that tends not to be aware of or potentially even will not want to accept the YF vaccine tends to be people who are originally from or are visiting friends and family in endemic areas. Understanding that the actual proportion of travelers who choose not to get the vaccine or never get the vaccine is challenging, CDC tried to conduct a pilot survey previously among airports that would get at the population who will be traveling to an at-risk area, but do not have good information about the overall acceptance among just anybody getting on an airplane. Geographic concentration is a challenging question, but many of the people potentially at-risk will be in high-population centers where there are several Stamaril® clinics. CDC is working very closely with Sanofi Pasteur as they phase into running out of YF-VAX® to understand if there are going to be critical gaps that need to be filled.

Dr. Fryhofer (ACP) pointed out that while ACIP recommends a single lifetime dose of YF vaccine, some of the countries to which people may travel have not shifted to a single dose even though WHO has approved a single lifetime vaccination. She inquired as to whether any steps are being taken to help those countries understand that a single lifetime dose is sufficient so that patients who have had YF vaccine can travel. Given that a booster previously was required every 10 years, some patients may have received a YF vaccine years ago and may not have the documentation. She wondered whether there is anything their physician can do to renew that documentation and certification.

Dr. Staples replied that WHO is working with countries that are still requiring booster doses. CDC tries to keep the most current information available on the travel website so that travelers can find out what countries are requiring. This is an ongoing discussion with certain countries about that regulation and the need to show proof of vaccination. People historically have lost their yellow cards and there is specific information under the International Heath Regulations (IHR) that a physician can reissue it, but it should be done with validation that the person received the vaccine. Preferably, the clinic that initially administered the card should replace the card.

Dr. Greenberg clarified that the EAP protocol is agnostic to prior doses. If the HCP at the Stamaril® site believes it is appropriate to immunize a person, they will follow the EAP protocol based on the inclusion/exclusion criteria. There is no exclusion for someone who previously received vaccine many years ago. They are to follow the ACIP recommendations, but ultimately, it is the HCP's decision regarding whether to administer the vaccine and they will administer the vaccine under the EAP protocol.

Dr. Moore indicated that in her state, two of the clinics that will be providing Stamaril® are public health departments. They have discussed the fact that this is a public service, and that because they are high-volume travel centers, it is important to make sure that vaccine is available in their area. Otherwise, people would be traveling hours to reach a clinic if they did not participate. Their hesitation had to do with the extra amount of time it would take to administer Stamaril® to a patient compared to a routine YF vaccination. Because they are high-volume, that extra time is amplified because they will be dealing with so many more patients. She wondered about how much extra time it takes to administer Stamaril® in terms of going through the EAP process.

Dr. Greenberg responded that it really is a matter of the informed consent. It may take an extra 20 minutes for the first patient, but by the time a clinic gets to patient 10 or 100, it should not take that long. The informed consent process is, of course, important but is the same counseling that the HCP should have provided when administering YF-VAX®. He does not believe it will be a burden.

Dr. Thompson (NVAC) commented that according to the current WHO-UNICEF vaccine schedule, the countries that have YF vaccine in their schedules generally deliver one dose at 9 months of age and after. Children 6 through 8 months of age would not be eligible even in-country. There would be an interesting discussion about whether those children could be excluded from country entry because they do not have proof of vaccine. She also wondered what the evidence was behind the exclusion of breastfeeding women in terms of whether there was a study showing that there is risk of transmitting the virus from the vaccine to the infant, or if it has not been studied and is precautionary.

Dr. Staples responded that most countries do not require proof of vaccination for those under 9 months of age, and some do not require it for those less than 12 months of age. Regarding the evidence related to breastfeeding, the first case of an infant who acquired vaccine-induced encephalitis occurred in 2010. The mother had been vaccinated, but the child had not been and was approximately 4 weeks old when they were exposed through breastfeeding. Subsequent to that, there were two additional case reports published out of Brazil of infants with encephalitis. They were less than 6 weeks of age when exposed. Because the vaccine is known to be neurotropic in very young infants, that is why it is contraindicated for children less than 6 months of age. That has led to the precautions and, in this case, the EAP protocol contraindication.

Dr. Grogg (AOA) asked what vaccine someone would receive if they arrived at the border of Uganda and had not had YF vaccine. Where he is in the "Bible Belt," there are mission teams leaving the country who need YF vaccine, so public education is necessary. One of the sites nationwide is the most expensive for travel site consultation and travel vaccines. A lot of patients cannot afford that particular site that was chosen throughout the US.

Regarding some of the sites being the most expensive, Dr. Greenberg said they are sensitive to that but had to make decisions months ago about how to set up this program of 250 sites. There is no way for them to know what a site charges for travel counseling or administration. Those decisions had to be made independent of that sort of information. However, Sanofi Pasteur is receptive and does want to collect that information. The imperative was to get the sites up and running, but he welcomes comments pertaining cost.

In terms of receiving vaccines outside of the US, Dr. Staples indicated that short of YF-VAX® and a vaccine produced in China, the rest of the vaccines available in all other locations are WHO pre-qualified vaccines. Stamaril® is one of those. The other WHO pre-qualified manufactures include: 1) Bio-Manguinhos in Brazil, which makes a 17DD vaccine; 2) Institute Pasteur of Dakar in Senegal that produces vaccine, but is currently offline; and 3) Chumakov Institute in Russia. These vaccines are widely available throughout the rest of the world. In terms of public education, CDC has been engaged in a lot of outreach with various partners to keep information updated. Another *MMWR* will be published soon on the shortages and the implications of that. Additional outreach will be done with specific travel medicine clinics and state health departments to ensure that they are aware of the need to switch over to the Stamaril® protocol, which is allowing the US to continue to provide YF vaccine to at-risk travelers.

Dr. Sun (FDA) acknowledged Sanofi Pasteur, CDC, and DoD for working to address the shortage issue. Unfortunately, this is a situation in which a vaccine has only one supplier and illustrates what can occur when there is disruption.

Introduction

Kelly L. Moore MD, MPH
Director, Tennessee Immunization Program
Chair, Mumps ACIP Work Group

Dr. Moore reminded everyone that the objective for the Mumps WG is to evaluate and propose policy options to prevent or control mumps outbreaks in the US. The activities related to that are focused on: 1) Review the epidemiology of mumps in the 2-dose vaccine era, including the international experience; 2) Review available evidence on duration of immunity for mumps after 2 doses of MMR and other risk factors for vaccine failure; 3) Review the available evidence on the benefit provided by a third dose of MMR for mumps outbreak control; and 4) Evaluate programmatic implications and the cost of various policy options for a third dose of MMR to prevent or control mumps outbreaks.

The Mumps WG has been quite busy over the last few months, engaging in biweekly conference calls and a brief on-line survey to obtain feedback from members of the WG. The focus in the past few months has been on reviewing the literature and unpublished data on the following:

- Mumps epidemiology in the US in the 2-dose era
- Immune response to mumps virus and mumps vaccination
- Persistence of immune response after 2-dose vaccination
- 2-dose VE and risk factors for vaccine failure
- Molecular epidemiology and antigenic differences between vaccine and circulating mumps strains
- Immune response to a 3rd dose of MMR vaccine
- Clinical studies after administration of a 3rd dose of MMR vaccine
  - 3rd dose for mumps outbreak control
  - Safety of the 3rd dose
- US military experience with mumps disease and vaccination

Regarding the timeline, the goal for the June 2017 meeting was to update ACIP on mumps epidemiology in the US in 2017, and discuss the evidence reviewed by the WG concerning laboratory and clinical studies of the 3rd dose of MMR vaccine. During the October 2017 meeting, the WG plans to summarize the evidence reviewed by the WG and present the WG's interpretation of the evidence. During the February 2018 meeting, the WG will present additional evidence from ongoing studies (e.g., cost of various policy options), and will present the WG's considerations and options in preparation for an ACIP vote.

This session included two presentations: 1) an update on mumps epidemiology and review of studies of a 3rd dose of MMR vaccine; and 2) the effectiveness of the 3rd dose of MMR vaccine in a mumps outbreak in a highly vaccinated university population in Iowa in 2015-2016.

Update on Mumps Epidemiology in the US for 2017 and Review of Published Studies of 3rd Dose MMR for Mumps Outbreak Control

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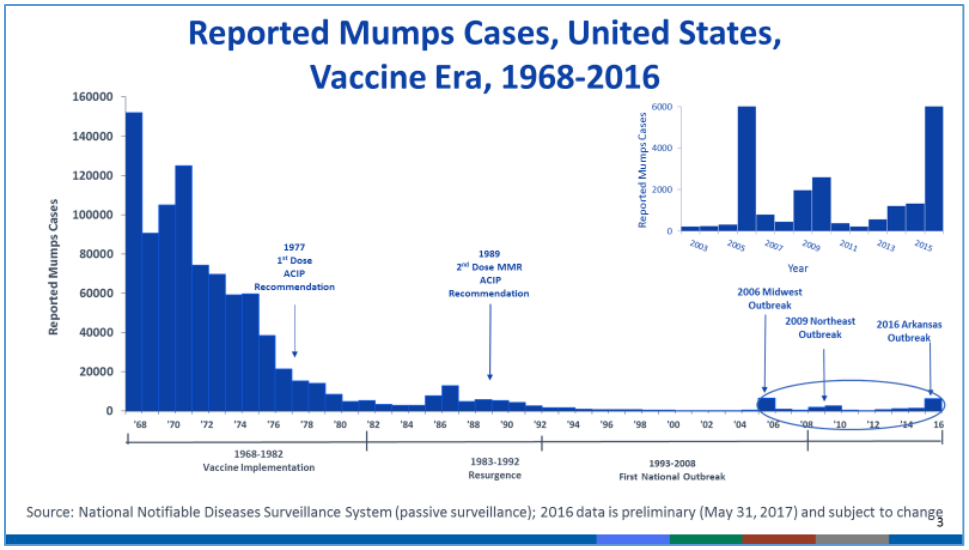
In this presentation, Dr. Marin provided an update on mumps epidemiology in the US in 2017 and presented the evidence reviewed by the WG concerning immune response to the 3rd dose of MMR vaccine, referred to hereafter as MMR3; published studies on use of MMR3 for mumps outbreak control; and safety of MMR3. Along with the next presentation, the information presented covers the evidence currently available on the use of MMR3. The WG deliberations and interpretation of the evidence on use of MMR3 are ongoing and will be presented during the October 2017 ACIP meeting.

This figure, presented during the February 2017 ACIP meeting, shows the reported mumps cases in the US during the vaccine era:



Overall, since vaccine program introduction, reported mumps cases declined by approximately 99%. However, several large mumps outbreaks have been reported from 2006 through 2016 resulting in an increased number of cases in certain years, as shown in the inset.

Examining more closely the most recent 6 years, since 2011 there has been an increasing trend in cases and outbreaks as reflected by a number of epidemiologic characteristics (case count, incidence, number of outbreak cases, proportion of outbreak-related cases among all reported cases, and number of jurisdictions reporting outbreak cases), with 2016 having the highest number of cases and jurisdictions with outbreak cases reported, not only within the past 6 years, but also within the past decade.

Comparing 2017 with 2016, preliminary data through the end of May suggest that 2017 appears on track with the trend seen in 2016 for the same characteristics. In 2017, the case count is already at 3300, half the number of cases reported in 2016, incidence is lower than in 2016 but higher than in any other year before 2016, outbreak cases represent two-thirds of all cases, and the number of jurisdictions with outbreak cases is the same as in 2016. It is important to note that a large mumps outbreak with more than 3500 cases in Arkansas, primarily among the Marshallese population, a close-knit community in Northwest Arkansas, accounted for about 2400 of the cases reported in 2016 and approximately 500 of the cases reported in 2017. However, even if the cases from this large outbreak were excluded, 2016 still continues to have the highest incidence and number of cases compared to previous years and 2017 has a similar trend.

In 2017, the highest incidence continues to be in the 18 to 22 age group, similar to previous years. The median age of patients with mumps is 23 years and 73% of those with known number of doses have 2 or more doses of MMR vaccine. To date in 2017, CDC is aware of at least 40 outbreaks, with about half (19) occurring in university settings and one third (14) community-wide, of which 8 have been in Marshallese communities which spread from the Arkansas outbreak. Other close contact settings also experienced outbreaks in 2017, including a military facility.

Several factors have been hypothesized to contribute to the increasing number of mumps outbreaks. As discussed during the last ACIP meeting, the vaccine effectiveness for 2 doses is estimated to be 88%, and therefore cases can still occur among vaccinated persons. Second, waning of vaccine-induced immunity, especially in the era of low disease incidence and absence of boosting from wild disease, has been demonstrated. Serologic evidence has shown that neutralizing antibody titers do decline over time; however, there are no established correlates of protection. Therefore, the implications of declining titers remain uncertain. Epidemiologic evidence also suggests waning of immunity with decreased VE and increased odds of contracting disease with time since vaccination, but evidence is still limited. Waning of immunity, however, does not explain the typically focal nature of outbreaks. Increased force of infection from intense exposure settings, such as college campuses or close-knit communities, where there is high population density and contact rates that facilitate transmission is frequently postulated as a risk factor for current mumps outbreaks. Concern also was raised that antigenic differences between the circulating and vaccine strains may lead to mumps vaccine-induced immunity being less effective against other strains. To date, studies showed that all sera from vaccinated children neutralized diverse mumps virus strains. However, the antibody levels against non-vaccine strains are lower than the levels against the vaccine strain and these differences may become more important over time. Lastly, the WG acknowledges the uncertainty and that there may be other factors not identified or measured.

Because waning of immunity after 2 doses of MMR vaccine is one of the hypotheses considered to explain the current mumps epidemiology, there is increased interest regarding the effect of the 3rd dose of MMR vaccine. Dr. Marin summarized the evidence related to the MMR3 reviewed by the WG, beginning with the laboratory evidence which describes the antibody response to MMR3.

Most of the available evidence on antibody response after MMR3 comes from the study by Parker Fiebelkorn et al that included a cohort of 656 young adults who received care at the Marshfield Clinic, a large HMO in rural Wisconsin. The median age at MMR3 was 21 years and the mean years since the second dose of MMR (or MMR2) was 15. This study examined GMTs for neutralizing antibody against the Jeryl Lynn vaccine virus and the proportion of participants seronegative or with low titers pre-MMR3 (defined as baseline), at 1 month and 1 year after MMR3. Compared with baseline, GMTs were significantly higher, albeit modestly, at 1 month and 1 year after MMR3. However, only 6% of subjects had a 4-fold rise or more from baseline to 1 month after MMR3 and 2% had a 4-fold rise or more from baseline to 1 year. At baseline, very few subjects had low or negative titers (7%). One year after MMR3 this proportion declined to 3%.

One other observation from this study was that post-vaccination titers were highly correlated with baseline titers, meaning that subjects with lower baseline titers were more likely to have lower titers at 1 month and 1 year after MMR3; whereas, subjects with higher baseline titers were more likely to have higher titers at 1 month and 1 year. These results were obtained when testing for whole virus neutralizing antibodies, but nearly identical findings were observed when antibodies to mumps-specific proteins were studied. Altogether, these findings may indicate an inherent trajectory for mumps titers or a set point for individual antibody levels that is minimally affected by MMR3 [Parker Fiebelkorn et al. *Open Forum Infect Dis*, 2014; unpublished data; Don Latner, PhD, [CDC] presentation to the Work Group, May 11, 2017].

In a much smaller study of 17 subjects aged 19 through 30 years of age who were seronegative for mumps despite 2 documented doses of MMR and received MMR3, all but one subject developed an IgG response when tested 2 to 3 months after MMR3. The response was rapid, observed at 7 to 10 days, with peak antibody activity present sometime between 7 to 10 days and 2 to 3 months. Antibody kinetics 2 to 3 months after MMR3 was not evaluated in this study [Date et al. *J Infect Dis*, 2008].

To date, the laboratory evidence on MMR3 use remains limited. In addition to the lack of a correlate of protection against which to assess the changes in antibody titers, in the studies conducted until now, the qualitative aspects of the immune response (antibody avidity, B-cell memory) or the strain-specific immune responses were not assessed.

In terms of the epidemiologic evidence related to the impact of MMR3 for mumps outbreak control, the WG is aware there have been outbreaks in which MMR3 was not administered as part of outbreak control and only standard outbreak control measures were implemented. All of these data will be considered as part of the WG's deliberations for use of MMR3 and will be presented in October. This session focused on the evidence related to impact of MMR3 use. Although several states have implemented MMR3 vaccination campaigns to control mumps outbreaks, there are only three studies that formally assessed the impact of MMR3 for outbreak control. Two were school-based, which Dr. Marin described. The other was conducted in a university setting and is described in the next presentation by Dr. Cardemil.

Third dose intervention campaigns were conducted in Orange County, New York where 81% of eligible students aged 11 through 17 years were vaccinated with MMR3[1] and in Guam where 33% of eligible students aged 9 through 14 yeas received MMR3[2]. In both studies, the attack rates were lower among MMR3 recipients than among MMR2 recipients. However, the results were not statistically significantly different. The small number of cases post-MMR3 intervention limited the power of the studies to detect a difference if one truly existed. In the Orange County study, the incremental VE of MMR3 was calculated as 88% although there was a large confidence interval that included zero. Additionally, in Orange County, the attack rates declined post-intervention among all age groups in the community, with the highest and significant decline among the age group targeted by vaccination in the schools, 11- through 17-year-olds followed by the 5- through 10-year-olds. While the attack rates declined after MMR3 administration, the MMR3 intervention occurred after the peak of each outbreak and the possibility of the declines being unrelated to the intervention could not be excluded [[1]Ogbuanu IU et al. *Pediatrics* 2012; [2] Nelson GE et al. *Pediatr Infect Dis J* 2013].

The safety data on MMR3 vaccine were collected as part of the same study that was conducted at the Marshfield Clinic to assess immune response to MMR3. A total of 662 young adults, with a median age of 21 years, received MMR3 and completed safety diaries. Data on 14 solicited symptoms were collected 2 weeks before and 4 weeks after MMR3. Significantly higher rates of AEs after MMR3 were demonstrated for 4 symptoms: headache, joint pain, diarrhea, and swollen glands. Overall, the proportion of subjects who reported these symptoms was low and the duration of symptoms was short. No SAEs requiring medical attention occurred. MMR3 appears safe and is well-tolerated in a young adult population [Unpublished data, Janell Routh, MD (CDC) presentation to the Work Group, May 11, 2017].

In terms of knowledge gaps, planned and ongoing studies to inform third dose deliberations include the following:

- ❑ Cost of public health response to contain a mumps outbreak in a university setting, including the MMR3 intervention at the University of Iowa in 2015-2016 and active pursuit of other settings
- ❑ Cost effectiveness analyses of various policy options for MMR3 to prevent or control mumps outbreaks
- ❑ Modeling of the impact of MMR3 on burden of mumps during a mumps outbreak
- ❑ Genotyping G-strain specific immune response to MMR3 and MMR2 >10 years
- ❑ More complete national data on epidemiology of and response to mumps outbreaks

In closing, Dr. Marin asked ACIP what additional 3rd dose data would be helpful to inform their deliberations.

Effectiveness of a 3rd MMR Dose During a Mumps Outbreak In a Highly Vaccinated University Population, 2015-2016

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Dr. Cardemil presented the investigation into the effectiveness of a 3rd dose of MMR used during a mumps outbreak in a highly vaccinated student population in Iowa. In 2015, a mumps outbreak was reported from Johnson County, Iowa. Most cases were in the University of Iowa, a setting with over 22,000 undergraduates and a 2-dose MMR requirement since 2012, with provider-verified doses uploaded to their electronic database. Health officials decided to implement a widespread 3rd dose campaign in the university, making this outbreak a good opportunity to evaluate the effectiveness of the 3rd dose.

There were 453 mumps cases reported during the outbreak, with 300 of these confirmed. The vaccination campaign was held in 8 clinics over six days from November 10-19, 2015 and was university-wide. Vaccine was offered free of charge for students under 25 years of age, during the daytime and evening hours, and at centralized locations (student union, large dormitories, large classroom buildings, sports medicine center). Most cases in the county, about 2/3, were in University of Iowa students.

The primary objective of this study was to estimate the VE of 3 versus 2 doses of MMR against mumps. Secondary objectives included assessing for waning immunity, as well as estimating the VE of 2 versus 0 doses. Case status was determined from the outbreak investigation, which was conducted as a separate investigation in parallel to this analysis, based on the CSTE case definition that included probable and confirmed mumps cases. The outbreak period was defined as starting on the first day of the academic fall semester and ending on the last day of the spring semester. University vaccination records were merged with student registration records, which included student demographic information, and vaccine records were verified as mentioned previously by a medically-trained provider who uploaded valid doses to the electronic database. A subset of vaccine dates was verified manually, including for students who did not have 2 MMR doses on file, for closely spaced vaccines and for implausible dates. Exemption status also was reviewed, if applicable. Students were included in the analysis if they were age-eligible for the MMR vaccination campaign, meaning they were 18 through 24 years of age by

the date of the first campaign, and enrolled full time in the 2015-2016 academic year. Students with positive titers in lieu of vaccination records or records that were not required by the university (prior military, part-time) were excluded from analysis.

Fisher's exact test was used to compare unadjusted attack rates, and multivariable Cox proportional hazards models were developed to determine risk-adjusted VE. The variables examined by case and vaccine status included: age, gender, race, undergraduate status, study program, receipt of campaign vaccination, years since MMR administration, age at vaccination. For the primary analysis of 3 versus 2 doses, the dataset was limited to students who had received 2 doses by the start of the outbreak period. A subset of these students received a 3rd dose during the outbreak. Incremental VE was defined as the additional reduction in mumps disease experienced by 3-dose recipients compared to 2-dose recipients. The 3rd dose receipt was treated as a time-varying covariate, and 4 models were utilized, each with a different post-vaccination timeframe based on the expected immune response at 7, 14, 21 and 28 days post-vaccination. To evaluate the VE of 2 versus 0 doses, a separate model was created with a shorter timeframe for analysis from the start of the outbreak period to just prior to the date of the first campaign, to avoid the influence of any change in exposure and risk during and after the campaign. Relative risk was estimated using the hazard ratio, and VE was calculated as 1 minus the relative risk times 100.

Regarding the time-varying covariate in this analysis, students analyzed entered the outbreak period with 2 doses. During the analysis period, 4 distinct possibilities existed. In the first scenario, a student enters the outbreak period with 2 doses, did not develop mumps or receive a 3rd dose and their person-time continued until the end of the outbreak period. In the second scenario, a student enters the outbreak period with 2 doses, develops mumps symptoms, and their person-time ends at the date of symptom onset. In the third scenario, a student enters with 2 doses, receives a 3rd dose, and after the specified time-period post-vaccination, continues their person-time in the analysis as a 3rd dose recipient. The final scenario is similar to the previous, but a 3-dose recipient develops mumps symptoms, so their person-time ends before the end of the outbreak period. Four models were developed to specify the start of immunological protection beginning at 7, 14, 21, or 28 days post-vaccination. Previous studies used 21 days to cover the average mumps incubation period of 16 to 18 days. However, the range for the incubation period is up to 25 days, and it may take a few weeks to develop an immune response post-vaccination. They also wanted to examine a slightly shorter period to allow for a more rapid anamnestic response.

Regarding the results, of those who received a first dose of MMR, 83% were administered at 12 through 23 months of age. Of those who received a 2nd dose of MMR, 82% were administered at 4 through 6 years of age, aligning with ACIP recommendations at the time of administration. A second wave of administrations for the 1st and 2nd doses were seen in the university age group, close to when the majority of 3rd doses were administered. In terms of the years since the 2nd dose of MMR by age at time of administration, the distribution of the variable years since receipt of MMR2 was clustered in 2 periods (administration at 4 through 6 years of age as per CDC recommendations, and just prior to and during university enrollment at 17 through 24 years of age), with a few students falling outside of the bimodal distribution. Years since receipt of MMR2 was examined as a continuous variable, a dichotomous variable (<13 years and ≥13 years since receipt of MMR2), and categorical variable (0-2 years, 3-12 years, 13-15 years, and 16-24 years since receipt of MMR2). Regardless of the variable type used in the model, the result was statistically significant for the primary analysis. Because the data are not linear, yet there is an increase in risk of disease with years since MMR2 administration, the results are reported using the categorical variable in order to demonstrate this stepwise increase in risk.

For the 2 versus 0 doses analysis, because of the smaller sample size of the 0-dose group, this 4-level stratification was not possible and the results are reported using the dichotomous variable.

Prior to the outbreak, 98.1% of students had 2 or more MMR doses, and 2.0% had 3 or more doses. At the end of the outbreak, 99.5% of students had 2 or more doses and 25.3% had 3 or more doses. The attack rate is inversely proportional to the number of MMR doses received, with the highest attack rate in the unvaccinated. The overall attack rate was 12.6 per 1,000 population. More distant receipt of MMR2 was associated with a higher attack rate. Both of these trends in attack rates were statistically significant. At the start of the outbreak, 19,705 students had 2 doses. Of these, 4778 (24%) students received a 3rd dose. Of the 4778 3rd doses that were administered during the outbreak period, 94% were administered during the fall campaign.

In the model which includes an immune response window of 28 days, students who received the 3rd MMR dose had a hazard ratio of 0.22. In other words, receipt of the 3rd dose was associated with lower risk of mumps disease as compared to 2-dose recipients. More distant receipt of MMR2 of 13 to 24 years prior to the outbreak was associated with higher risk of being a case. That is, students who received the 2nd dose 13 or more years prior to the outbreak had 9- to 14-fold increased risk of being a case as compared to students who received the 2nd dose more recently. The other 3 models with time period post-vaccinations of 7, 14 and 21 had very similar results. The main difference was in the risk of being a case by receipt of 3rd dose. The hazard ratios ranged from 0.22-0.40, indicating a reduction in risk of being a case with receipt of a 3rd dose.

The incremental VE of the 3rd versus 2nd MMR dose ranged from 60.2% at 7 days post-vaccination up to 78.2% at 28 days post-vaccination. The finding of an incremental VE of 60.2% at 7 days post-vaccination suggests there is benefit shortly after the campaign due to the anamnestic immune response. However, given the long incubation period for mumps of up to 25 days and the time needed to develop the immune response, an incremental VE of 78% at 28 days post-vaccination might be a better representation of the full effect of the 3rd dose. The one prior published study, which was mentioned by Dr. Marin, reported an incremental VE of the 3rd dose with a comparable point estimate of 88% using a 21-day post-vaccination window, but had wide confidence intervals that crossed zero. The probability of remaining mumps-free was higher with receipt of the 3rd MMR dose for all 4 post-vaccination timeframes examined. All models controlled for years since 2nd MMR dose.

VE of 2 versus 0 MMR doses differed by years since the second dose. VE was 89.4% (95% CI -2, 99) for students who received the second dose more recently (defined as less than 13 years prior to the outbreak), and 31.8% (95% CI -389, 91) for students who received the second dose 13 years or greater prior to the outbreak (past). These estimates had wide confidence intervals, particularly the past estimate, but when compared head-to-head, the difference between these 2 estimates was statistically significant.

There are limitations to this investigation. Perhaps most importantly, this was an observational study with possible unmeasured factors that could have led to over- or underestimation of VE. For example, it is possible that there was differential receipt of the 3rd dose based on risk. There were anecdotal reports that some students sought receipt of the MMR vaccine after a friend or roommate was diagnosed with mumps, or were urged by a parent to obtain the vaccine. If 3rd dose recipients were more frequently exposed to mumps than students who did not receive a 3rd dose, the estimates of the incremental VE of the 3rd dose would be

underestimated. To address the possibility of other unmeasured factors affecting VE, such as differential intensity among different ages, sensitivity analyses were conducted with time since MMR2 examined as a continuous and dichotomous variable and in a narrower age group. The effect of time since the second dose was maintained in these analyses. Second, because immunization status during the outbreak period was dynamic, and the student population was highly vaccinated with a small number of 0-dose students, the 2 vs 0 doses VE estimates had wide confidence intervals. The authors chose not to exclude any 0-dosers from the 2 versus 0 VE estimates, even though a large proportion of them received 1 or 2 doses during the outbreak period, and were unable to control for the receipt of any outbreak dose in this group, because the standard error for the covariate was very large, making the regression model unstable. However, even without this covariate, the estimates were very similar, giving the authors confidence that if anything, these estimates are more conservative, meaning that VE could be underestimated.

In conclusion, there are three main take home points from this investigation. First, in this highly vaccinated university setting, the vast majority of students had 2 or more MMR doses. However, this was not sufficient to prevent an outbreak in this close contact setting. Second, the 3rd dose of MMR that was administered as part of the university-wide campaign free of charge to all age eligible students was associated with a significantly decreased risk of mumps. The magnitude of that reduction is shown in the incremental VE estimate, which ranged from 60% to 78%. Third, waning immunity likely played a role in outbreak propagation, and the investigation revealed 3 pieces of evidence to support this. Cases were more likely to have received the second dose 13 or more years prior to the outbreak. Attack rates correlated significantly with time since the second dose, and the VE of 2 versus 0 doses was lower with more distant receipt of the second dose.

There are some considerations worth mentioning in the interpretation of the findings from this investigation. First, approximately 1 in 4 targeted students received the 3rd dose, and while that at first might appear to be a small proportion, it is within the range of previous additional dose interventions in similar settings in which anywhere from 16% to 81% of the target population was reached. Second, a campaign of this magnitude is no small achievement. It is no secret that it can be very time- and resource-intensive. While feasible in some settings, this might not be possible in others. Third, it is likely that other factors contributed to outbreak control, other than the use of the 3rd dose. Iowa is no stranger to mumps, having lived through the 2006 resurgence. This was a highly organized outbreak response with very strong participation and frequent communication between the public health officials at the state, local, and university levels. The student health center, fairly early in the outbreak, determined the need for standardized protocols for case identification, testing, and isolation recommendations. The student body was made aware of the outbreak by university officials through various modalities, and results from the outbreak investigation indicated very high self-reported adherence to isolation recommendations. Finally, and perhaps most importantly, the pre-existing 2-dose MMR requirement for the next semester's registration, without which this outbreak would have undoubtedly been much larger.

Discussion Points

Ms. Pellegrini inquired as to where the authors would have considered the peak of the Johnson County, Iowa outbreak to have occurred. It appeared that the vaccination campaign took place only among university students and about a month afterward there was a significant decline in the cases, which then dwindled over the next semester.

Dr. Cardemil replied that there were several peaks throughout this outbreak, but she was referring to the peak that had the highest number of cases for university students and the outbreak as a whole.

Dr. Patel (SME) added that the data in the study suggest that vaccination controlled the outbreak. CDC, the university, and the health department feel that in terms of control measures, vaccination response did help control this outbreak.

Dr. Stephens asked Dr. Cardemil to comment on genotype and whether there was any evidence of genotype drift, and whether antibody was assessed in the Iowa study.

Dr. Cardemil replied that they did not have the opportunity to examine serologic data in this investigation.

Dr. Rota (SME) added that CDC has been monitoring the sequences of most strains that have been circulating in the US since 2006, and there has been remarkably little sequence variation in the small region CDC is sequencing. The genotype has been consistently detected through the last several years. CDC is beginning to introduce next-generation sequencing (NGS) methods in order to develop WGS. He expects that there probably will be a large number of WGS available very soon. But at this time, based on what they are looking at in a small window, there are only 1 or 2 nucleotide changes in the region used to determine the genotype.

Dr. Patel (SME) clarified that no serologic studies were conducted with this outbreak.

Dr. Walter inquired as to the timing of the cases amongst those who had three doses relative to vaccination.

Dr. Cardemil replied that there were a number of 3-dose vaccine failures spread throughout the outbreak period. Most of the 3rd doses in this outbreak investigation were given during the vaccination campaign, so the majority of the 3rd dose failures followed that.

Dr. Lee inquired about secular trend as a potential confounder and whether another sensitivity analysis was or could be done to compare the 2-dose versus 3-dose recipients starting from the time of the initiation of the MMR 3rd dose vaccination campaign to determine whether the results were similar.

Dr. Cardemil responded that they did consider several potential other methods for analysis, taking into consideration how data such as these had been analyzed in previous outbreak settings with a 3rd dose campaign and ultimately decided on the use of a time-varying covariate because it allowed for underlying change in the hazard over time. What was challenging in this type of analysis, and in many of these similar analyses, is that the vaccination campaign does not occur all on one date. This campaign started on November 10th and through a series of different clinics, there was administration to a number of students through November 19th. If everyone was vaccinated on the same day, they could have chosen a 3-week period post-intervention and then looked before and after. That has been used previously, but in this scenario, due to the fluid nature of how the outbreak progressed as well as the vaccination campaign, the authors thought this method allowed for a much more granular look at the data. It also allowed the authors to look at the immune response post-vaccination, not just following the campaign which occurred over a number of days, but also for those students who received 3rd doses before and after the campaign.

Dr. Reingold asked whether there were enough outbreaks to look ecologically in terms of duration of outbreaks or attack rates in outbreaks where there has been response with vaccination versus those in which there has not. That might be more interesting to assess than what occurred in the context of one outbreak.

Dr. Patel (SME) replied that CDC plans to model this particular outbreak to assess what the impact would have been if there was not an implementation of a 3rd dose, as well as varying coverage rates of the 3rd dose. As Dr. Marin mentioned earlier, the WG is deliberating a number of outbreaks, such as the New York City outbreak which did not implement a 3rd dose and looking at that ecologically. Also as Dr. Marin mentioned, a data call will be going out to the states to understand a couple of epidemiologic factors (settings in which outbreaks occurred, age groups, interventions implemented), because not all states are doing the same thing. Hopefully, the WG will have more information for ACIP during the October 2017 meeting.

Dr. Atmar pointed out that the vaccine intervention occurred at the peak or back end of the outbreak. One issue he was struggling with was that those persons who received a 3rd dose and were included may have had a lower risk of infection. The type of analysis Dr. Lee proposed could address that. Even though it might be difficult, it would be reassuring if the 2-dose people after the end of the campaign plus some period for an immune response to have occurred still had higher risk than the 3-dose recipients. It may not be the primary analysis, but it would be a reassuring secondary analysis.

Dr. Cardemil responded that the authors did a number of sensitivity analyses with those specific questions in mind. One thing that is important to consider in this type of analysis is that the underlying risk is allowed to change over time when using the Cox regression. However, a number of other analyses were done. One thing they did was exclude cases prior to the campaign and analyze the data starting on the first date of the campaign and going forward. That basically reduces the sample size of the number of cases being kept in the analysis, keeping all of the students in the analysis who had 2 doses at the start of the outbreak. In that analysis, all of the incremental VE estimates for all 4 models continued to be statistically significant.

Dr. Plotkin (Vaccine Consultant) said he did not doubt that the trouble with the Jeryl Lynn strain is the poor B-cell memory that has been demonstrated. That is pretty clear as far as why there is waning. However, he pointed out that there were a lot of specific data that were important about strains. The Rubini strain was promoted as a vaccine, but had zero efficacy. The point is that in contrast to measles and rubella, little is known about the protective factors that generate protection from an attenuated mumps strain. They do differ quite a lot and are not like measles and rubella. He suggested asking countries that use other strains, such as Hoshino and Urabe, what their experience is with persistence of protection and epidemics in those who have received the vaccine. That might suggest a way of dealing with this situation. Of course, the advantage of Jeryl Lynn is its safety. Mumps is a *Paramyxovirus* and has many differences from other viruses. Dr. Plotkin's counsel is that a third dose may be useful to deal with an emergency, but they need to delve deeper into this problem.

Dr. Messonnier responded that CDC has thought about countries other than the US. Unfortunately, few of them have as high coverage as the US. CDC plans to contact other countries, and will be presenting some of those data during a future ACIP meeting.

Dr. Schaffner (NFID) noted that in the pre-vaccine era, it was known that mumps often infected individuals asymptomatically. In fact, only about a third of people developed symptoms. He wondered whether anyone had conducted a study of asymptomatic transmission in the setting of an immunized population. Regarding re-immunization, he wondered whether anyone had studied the dynamics of what happens to the inoculated virus dose in terms of whether it has a chance to replicate, and how much, in the recipient who has already been previously immunized. He also suggested that perhaps one of the interventions might be to encourage countries such as those in Europe and perhaps the Philippines where these viruses may come from, to immunize their children so that there is less mumps in the US as well.

Dr. Patel (SME) replied that CDC worked with Washington to conduct an asymptomatic shedding study during an outbreak they experienced earlier in 2017, and found zero shedding among the individuals who were in a fraternity/sorority type of setting. They only looked at shedding and did not assess serologic response in this particular study.

Regarding re-immunization, Dr. Marin said she was not aware of other studies. One of the questions that arose in the WG discussion regarded whether there is replication following the 3rd dose or if it just boosts the two. Other than the data she presented, there are no other data. The fold rise was low. Very few people had a 4-fold rise, but it is not clear what that means.

Dr. Hunter said he was struggling with the VE of 60% at 1 week after the 3rd dose, which seemed high to him and made him wonder whether the VE in the 25% of students who received the 3rd dose had to do with other behaviors, such as not sharing saliva, that would lead to a limitation in the study being an overestimate because of those reasons.

Dr. Cardemil noted that one thing that would be useful in future investigations whenever possible, which was considered at length when designing this particular study, would be to survey the members of the student body who were and were not vaccinated to determine exposures and behaviors for each of the students to examine whether there were differences in the 2- versus 3-dose recipients. When the authors came into this investigation, it was several months post the peak of the outbreak as well as post the vaccination campaign. In speaking with the university officials and looking back at their experiences in surveys of the study body, the authors anticipated that a very low response rate would be achieved. By the time the survey would have been done, it essentially would have been conducted a year post-outbreak. This raised issues such as recall bias. Going forward, it would be informative and instructive to be able to conduct that type of survey from the outset. In terms of interpreting the finding of a response post-vaccination, there are limited data from prior studies. The one Dr. Marin presented showed evidence of seroconversion at 7 to 10 days post-MMR3. It would be very instructive to have more to support that.

Dr. Zahn (NACCHO) recognized that having a vaccine campaign at that point helped, but the question from the local public health perspective will regard what to do thereafter. If there are only 10 cases, a large campaign may not be sensible. However, if a local small university has only 10 cases, it will still be in the newspaper and the decision will have to be made about whether to wait until there are a much larger number of cases before moving forward.

Dr. Decker (Sanofi Pasteur) said he shared the authors' conviction that the vaccination campaign and 3rd dose must have helped. Looking at the epi-curve, it seems that the ability to trust the analysis is shaken by an event over which they had no control and which is almost impossible to model. There is a full generation of cases after the vaccination campaign, most of whom went home for a month. When they returned, the outbreak was over. It is not clear how to model that. In addition, there are some numerators during Christmas break, so someone stayed. He did not know what the denominator was or if the attack rate was actually higher during the Christmas break when 90% of the students went home and 10% stayed behind and they all got mumps or not.

Dr. Messonnier responded that they could speak for an entire hour about this paper, and CDC staff would certainly be happy to stay around after the break for questions. However, she redirected everyone to the initial presentation and what the WG was really looking for during this session from ACIP members, which pertained to what else ACIP members would like to see that would help them make a decision.

Dr. Lee said she thought this was a very answerable question and that they have the data in hand. She suggested a matched cohort design matching on the date of vaccination to those who only received 2 doses. The 3rd dose campaign appears to have been effective, but this would provide an additional level of certainty around the information. She recognized that they would lose power, but that is why this would be helpful as a secondary analysis.

Understanding that a vote is anticipated in February 2018, Dr. Kimberlin (AAP) inquired as to what additional data are anticipated in October 2017 that would delay making a recommendation as hundreds of thousands of college students are preparing to go off to college, or if this could be done sooner.

Dr. Moore responded that the WG is working as quickly as they can. Through the last few months, they have heard the bulk of the data available now. In the coming months, they plan to further deliberate what they feel about those data and what else might be available to them in the near-term that could help make a clear decision. What has been presented to ACIP are a few pieces of the puzzle, but some pieces are still missing. She personally would like to understand the quality of the antibodies that are produced by a 3rd dose rather than just a quantitative minor bump that is shifting the curve. It is not clear whether that shift represents higher quality antibodies that might have greater avidity for the G strain as opposed to the A strain. Those are questions for which there are no answers yet. The WG is interested in making a decision as quickly as possible, but it has to be based on evidence not on speculation. Some of the information the WG hopes for will be done over the summer, such as the cost modeling. She also wants to understand what is occurring in the natural experiments that are occurring, and the data requests to the states that was mentioned. Every state is operating somewhat differently. Tennessee has some experience as do others from which they may be able to glean some additional information beyond the results presented that could help support a decision one way or the other. However, the WG generally likes to be able to present information to ACIP a session before a vote without having a lot of new critical information presented at the time of the vote. If there is a way to parse out some piece in October that the WG feels is relevant, they will push to do that. At this point, they are awaiting more information to support their decision.

Dr. Kimberlin (AAP) said with ongoing epidemic outbreaks, this could be the type of circumstance that would support the idea of moving more quickly in terms of not having a 4-month delay between the presentations, deliberations, and vote. He also pointed out that in 2012, these same discussions and presentations, though of prior outbreaks, occurred and over the course of a year ACIP deliberated on it. Ultimately, ACIP voted on a permissive use of a 3rd dose that health departments seemed to want to receive. He presumed the WG is utilizing that historic memory as well.

Dr. Moore replied that the WG is very keen to get to evidence-based recommendations as quickly as possible, and hopefully the ongoing outbreaks will give them the opportunity to gather more data to support a decision.

Meningococcal Vaccines

Introduction

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

Dr. Stephens reminded everyone that during the February 2017 ACIP meeting, the WG discussed considerations for MenB booster doses for groups at increased risk for MenB disease. There is concern about the rapid decline in the immune correlate of protection by 12 months after completion of the initial vaccination series. However, cases of MenB after vaccination have not been reported in persons at increased risk, except for patients receiving eculizumab. Additional data on antibody persistence and booster responses were felt to be needed.

In contacting the manufacturers, additional data will be forthcoming within the next few months for MenB-4C (Bexsero®), including: 1) persistence 4 years after the 2-dose series and immune response 3, 7, and 30 days after booster from Canadian and Australian adolescents, anticipated July 2017; and 2) persistence up to 7 years after a 2-dose series and immune responses 3, 7, and 30 days after booster from Chilean adolescents, anticipated September 2017. Additional information anticipated for MenB-FHbp (Trumenba®) regards persistence 1 year after a booster dose, with full data anticipated March 2018.

In terms of future activities, the WG will continue to review new data as it becomes available. In addition, the WG will review the complete GRADE evaluation for MenB boosters and will present their considerations to ACIP once additional data are evaluated and GRADE is complete.

A Policy Note regarding the updated recommendations for the use of MenB-FHbp (Trumenba®) was published in the *MMWR* on May 19, 2017.

The agenda for this session focused on meningococcal disease and vaccine response in patients receiving eculizumab (Soliris®). This was an informational session only.

Considerations for Serogroup B Meningococcal (MenB) Vaccine Booster Doses in Persons at Increased Risk for Serogroup B Meningococcal Disease

Lucy McNamara, PhD, MS
Epidemiologist, Meningitis and Vaccine Preventable Diseases Branch
Division of Bacterial Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. McNamara shared information about some work CDC has been doing to understand meningococcal disease cases in patients receiving the medication eculizumab, with the hope of having some discussion afterward about the best way to protect these patients moving forward. As a reminder, meningococcal disease is caused by the bacterium *Neisseria meningitidis*. It presents as meningitis, bloodstream infection (BSI), or both. The disease 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 rash. Meningococcal disease has a rapid onset and progression even in previously healthy people, and in some cases death can occur less than a day after onset. About 10% to 20% of meningococcal disease patients die even with appropriate antibiotic treatment, and 11% to 19% of survivors have serious long-term health issues such as cognitive deficits, hearing loss, or amputations due to necrosis of the extremities.

Eculizumab, or Soliris®, is a complement component inhibitor, specifically a monoclonal antibody against complement component C5, which is licensed in the US for the treatment of two rare, life-threatening illnesses. The first is paroxysmal nocturnal hemoglobinuria (PNH), for which eculizumab was licensed in 2007. For this illness, once a patient becomes ill enough to need eculizumab therapy, a lifelong course of eculizumab treatment is typically expected. The second illness is atypical hemolytic uremic syndrome (aHUS), for which eculizumab was approved in 2011. The optimal course of eculizumab therapy for aHUS is not clear. For some patients, lifelong treatment may be necessary, but for other patients a shorter course of treatment may be viable[1]. Both PNH and aHUS have an annual incidence of about 0.1-0.2 cases per 100,000 population[2,3]. As a late complement component inhibitor, eculizumab is known to be associated with an increased risk of meningococcal disease, and the FDA-approved prescribing information includes a black box warning for increased risk of meningococcal disease in recipients [[1]Zuber et al. 2012, Nat Rev Nephrol 8(11):643-57. [2]UK: Hill et al. 2006: http://www.bloodjournal.org/content/108/11/985 [3]Region not specified: Noris and Remuzzi: http://www.nejm.org/doi/full/10.1056/NEJMra0902814].

The manufacturer shared data on post-licensure cases of meningococcal disease among eculizumab recipients with FDA in 2014, and these data are publicly available online. The manufacturer reported 16 meningococcal disease cases, including 1 death, out of 5207 person-years of eculizumab exposure between 2007 and the first quarter of 2014. The age range of these patients was 17 to 45 years. All of these patients had reportedly received meningococcal vaccination. This report was prior to licensure of serogroup B meningococcal vaccines, so presumably the patients received serogroup ACWY conjugate or polysaccharide vaccines. Of the 16 cases, 1 was caused by serogroup B, 2 by serogroup C, 2 by serogroup Y, and 11 were reported to be due to an unknown serogroup. Overall, this is a meningococcal disease incidence in eculizumab recipients of 307 per 100,000 person-years, which is 1 to 2000 times greater than the baseline risk of meningococcal disease for healthy individuals in the US [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf].

Due to this increased risk of meningococcal disease with eculizumab, there is a Risk Evaluation and Mitigation Strategy (REMS) program in place for eculizumab. A REMS program is a program required by FDA to manage known or potential serious risks associated with a drug product. For Soliris®, the purpose of the REMS program is to mitigate the occurrence and morbidity associated with meningococcal infections by informing healthcare providers and patients about the increased risk for meningococcal infections with Soliris®, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

The Soliris® REMS program includes a patient medication guide, which is FDA-approved patient-focused labeling to help the patient understand the risk of meningococcal disease associated with Soliris®, as well as a patient safety information card that patients can carry in their wallet for their own reference and to alert providers to their increased risk of meningococcal disease. The program also includes prescriber certification in which providers must agree to counsel patients and provide the patients with educational materials, provide the medication guide to patients prior to each infusion, and review the educational materials and product labeling themselves and comply with directions for safe use, including ensuring that patients receive a meningococcal vaccine. However, the program materials do not include specific information about the different serogroup ACWY versus serogroup B meningococcal vaccines now available. In addition, providers must promptly report meningococcal disease cases to FDA or Alexion®, the manufacturer. Monitoring of the REMS program is ongoing, and REMS assessments are submitted to FDA by the manufacturer every two years.

Current ACIP guidelines indicate that eculizumab recipients should receive both serogroup ACWY(MenACWY)[1] and MenB[2] vaccines. The eculizumab product insert indicates that meningococcal vaccination should be administered at least 2 weeks prior to initiating eculizumab treatment.[3] If eculizumab treatment is initiated within 2 weeks of vaccination, the eculizumab product insert indicates that in clinical trials, antibiotic prophylaxis was usually provided until at least 2 weeks after vaccination. The insert further states that the "benefits and risks of antibiotic prophylaxis have not been established" [[1]Cohn et al. 2013 www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm [2]Folaranmi et al. 2015 www.cdc.gov/mmwr/preview/mmwrhtml/mm6422a3.htm [3]Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2007/125166lbl.pdf].

Turning to a case report that CDC became aware of late last year, Dr. McNamara explained that this report was of a tragic fatal meningococcal disease case in a 16-year-old girl with PNH who had just begun receiving eculizumab for PNH treatment. The case was initially reported to CDC as serogroup B. The patient had received both MenACWY and MenB vaccines about 6 months prior to beginning treatment with eculizumab. Just 1 week after starting eculizumab therapy, the patient developed meningococcal disease. Initially she presented with headache, one episode of vomiting, and generalized body pain and she quickly went to the ER; however, she had no fever and her symptoms resolved completely after treatment with a non-steroidal anti-inflammatory drug (NSAID) and anti-nausea medication. She was therefore discharged. Later that night, however, she developed purpura and became unresponsive. She was transported to an ED, but unfortunately died from Waterhouse-Friderichsen's syndrome (WFS).

The infecting meningococcal strain was sent to CDC, where additional testing showed that this strain was actually non-groupable (NG), not serogroup B. Meningococcal bacteria are classified into serogroups based on their polysaccharide capsule, which is a key virulence factor that helps the bacterium evade the host immune response. There are 12 serogroups, but 6 of these (A, B, C, W, X, and Y) are the primary causes of meningococcal disease worldwide. NG meningococcal bacteria are those that do not express the polysaccharide capsule at all. There are two reasons that a *Neisseria meningitidis* isolate might be classified as NG. First, the bacteria might have a functional capsule gene and just not be expressing it, but they may have the capacity to turn the capsule gene back on at a later point. Alternatively, the bacteria might lack the capsule gene altogether or have another major defect in the capsule expression machinery, and therefore be incapable of turning on capsule expression. NG meningococci very rarely cause invasive disease; however, asymptomatic carriage of NG meningococci is very common[1,2]. CDC recently performed several carriage evaluations among US college students and found that 10% to 24% of students have asymptomatic carriage of *Neisseria meningitidis* at any given time. The vast majority of these carried meningococci were NG [[1]Soeters et al. 2017 Clin Infect Dis 64(8):1115-22. [2]CDC unpublished data].

Returning to the case report, in this instance the strain was determined to be NG by slide agglutination (SASG), which looks for expression of the capsule; as well as by PCR, which looks for the capsule gene; and by whole genome sequencing (WGS). WGS, in fact, demonstrated a complete absence of the capsule gene, showing that this strain really had no capacity to turn capsule expression back on. WGS also showed that the sequence type, or strain, of the isolate was ST-2578, which is more commonly associated with asymptomatic carriage rather than invasive disease.

The meningococcal serogroup ACWY vaccines are based on the polysaccharide capsule antigen, so of course they do not provide any protection against NG meningococci. The MenB vaccines, though, are based on proteins that are not unique to serogroup B meningococci and that are potentially found in NG meningococci as well. However, the extent of MenB vaccine potential cross-protection for NG meningococcal strains has not been assessed. CDC's laboratory looked at the MenB-4C antigen sequences in the strain isolated from this case and determined that, in fact, the sequences of two of the antigens (FHbp and NhbA) were extremely similar or identical to the antigens contained in MenB-4C. NadA was not present and the PorA sequence in the strain did not match the PorA antigen in the vaccine. Dr. Dan Granoff's laboratory performed additional testing and showed that there was high expression of both FHbp and NhbA on the isolate based on flow cytometry[1] [[1]Data from Dan Granoff's laboratory, UCSF Benioff Children's Hospital Oakland].

To better understand the capacity of MenB-4C to protect against this strain, CDC sent the strain to Dr. Granoff for serum bactericidal activity (SBA) testing. He assessed serum bactericidal activity (SBA) in serum collected from 6 healthy adults before, 1 month after, and 4 to 6 months after receipt of either 2 or 3 doses of MenB-4C vaccine. A titer of 1:4 is usually considered protective. All 6 adults had pre-immunization titers of greater than 1:16, showing that even without immunization, the serum from all 6 of these adults was easily able to kill this bacterial strain. Titers further increased following MenB-4C immunization, although in most subjects they decreased to near baseline by 4 to 6 months after vaccination. Like the WGS data, these data suggest that this is not a meningococcal strain that would typically be able to cause disease [Data courtesy of Dr. Granoff].

Finally, CDC also was interested in looking at the patient's antibody levels to the antigens in the MenB-4C vaccine. The patient had a serum sample collected 3 days post-mortem, and CDC sent the serum sample to Dr. Granoff's laboratory for characterization. He compared the level of antibodies observed in the patient's serum specimen to the levels observed in specimens from other healthy adolescents who either had not received MenB-4C vaccine or who were 7 months out from receiving the second MenB-4C vaccine dose, much like this patient. His data show that the patient's anti-FHbp and anti-NhbA levels were much higher than levels observed in vaccinated healthy individuals; whereas, the patient's anti-NadA levels were comparable to those in unvaccinated individuals. These data show that at the time the patient died, she had very high antibody levels to the FHbp and NhbA present in the infecting strain, suggestive of a memory antibody response to these antigens [Data courtesy of Dr. Granoff].

To summarize the data from this case report, this was a fatal meningococcal disease case in an adolescent who had been treated with eculizumab and who had been vaccinated with both MenACWY and MenB vaccines about 6 months prior to disease onset. The strain was found to be NG both phenotypically by slide agglutination and genotypically by PCR and WGS. MenB-4C vaccine was expected to provide protection against this strain based on antigen typing, but in fact serum from normal healthy adults, both pre- and post-immunization with MenB-4C, easily killed this strain. The patient furthermore died despite what appeared to be a strong memory antibody response to this strain. Together, these data demonstrate that this case was caused by a meningococcal strain that would normally be expected to be nonpathogenic, but that in this patient caused fatal illness in spite of appropriate meningococcal vaccination.

After hearing about this case report, CDC put out an Epidemic Information Exchange (Epi-X) call for cases to try to learn about additional meningococcal disease cases in eculizumab recipients in the US. For those who are not familiar with Epi-X, this is CDC's web-based communications platform to share and request preliminary health surveillance information, and it includes users from CDC and state health departments. In this call for cases, CDC requested that state and large local health departments review existing case investigation records to identify meningococcal disease cases in eculizumab recipients from 2007 to the present. CDC posted the Epi-X on February 3, 2017 and has been following up directly with sites via email. Please note that CDC did not ask sites to obtain new information on cases or review medical records, although some sites chose to do so. This was just an initial attempt to find out what information the sites already had on cases in eculizumab recipients.

So far, CDC has received responses from 46 jurisdictions[1] and has identified a total of 16 cases, including the one just described in detail. Please note that these are not the same 16 cases mentioned in the introduction, which were reported by the manufacturer back in 2014, although the cases do likely overlap. For the 16 cases identified through the Epi-X, median patient age was 30 years, with a range of 16 through 83. Of the patients, 10 were taking eculizumab for treatment of PNH, 5 for aHUS, and one for Devic's disease through a clinical trial. All 16 of the cases presented with a BSI while only 6 had evidence of meningitis. All of the patients were hospitalized for an average of 6.6 days, with a range of 1 to 14 days. The only fatality was the case report just reviewed [[1]Information pending from: ID, MD, MS, NE, NM, WV].

CDC wanted to know the serogroup causing each of these cases. This table shows the serogroup of each case by SASG, which again is looking at capsule expression, and by PCR, which looks at whether the capsule gene is present:

Serogroup (SASG)	Serogroup (PCR)	N cases
NG	NG	4
Unknown	NG	1
NG	B	2
NG	C	1
NG	Y	3
Y	Y	4
Unknown	Unknown	1

Five of these cases were NG by PCR, showing that they do not have the gene to produce a capsule, and 6 more were NG by SASG, but did have a capsule gene detected by PCR. CDC is currently working on WGS of these strains to better understand whether these are strains that can readily turn capsule on and off or if there are other genetic defects preventing capsule expression. This work is still in progress, but CDC has completed sequencing for a few of these strains already, so it is possible to report that at least 3 of these 6 strains do have clear, non-reversible defects in the capsule operon that are expected to prevent capsule expression. That is a total of at least 8 of 16 cases (50%) caused by strains CDC considers to be truly NG.

CDC also collected information on case vaccination status, and found that of the 15 patients with known vaccination status, only 9 (60%) had documented receipt of MenACWY[1] vaccine prior to meningococcal disease onset. [Post meeting note 8/24/17: We have since gained more information and updated this to 14/16 with documented receipt of MenACWY vaccine. Please see recently published MMWR: www.cdc.gov/mmwr/volumes/66/wr/mm6627e1.htm?s_cid=mm6627e1_w]. Of the cases with disease onset in 2015-2016, after licensure of the MenB vaccines, only 3 of 7 (43%) had received one or more doses of MenB vaccine. Complete vaccination data are always challenging to obtain, particularly for adults, and thus these data may not be complete. However, they suggest that not all eculizumab recipients are receiving the ACIP-recommended meningococcal vaccines [[1]Vaccine type not specified for one patient, but received prior to MenB vaccine licensure].

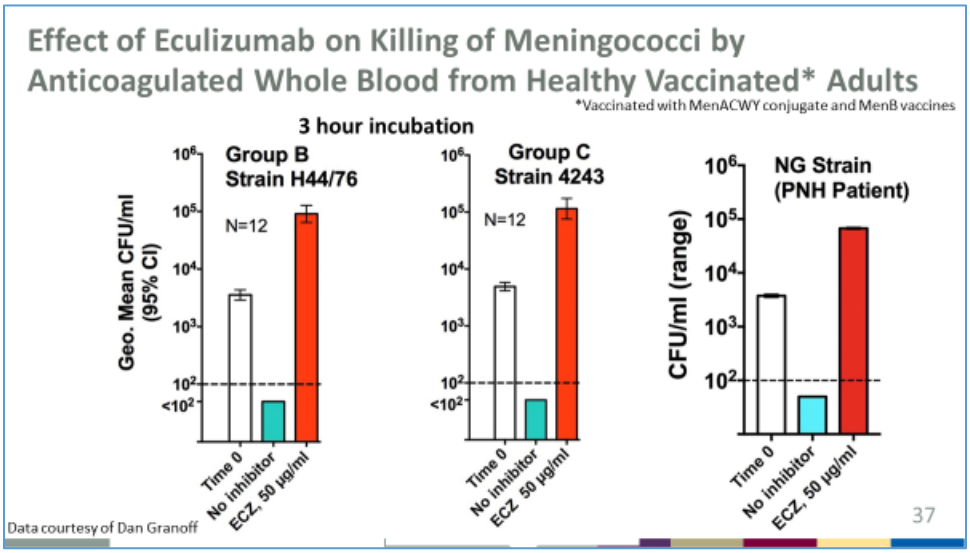
Of the 4 patients with disease caused by meningococci that were both phenotypically and genotypically serogroup Y, and so theoretically preventable with MenACWY vaccine, 2 (50%) had documented prior MenACWY vaccination. This is consistent with the data the manufacturer[1] shared with FDA and prior reports[2] showing that serogroup C, W, and Y disease could all occur in eculizumab recipients in spite of prior MenACWY vaccination. Finally, one patient was noted to be receiving prophylactic penicillin at the time of disease onset; however, this patient reported poor compliance [[1]http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf [2]Cullinan et al. 2015; Pediatrics 135(6):e1506-9].

To summarize the Epi-X data, among these reports CDC is seeing a high frequency of cases due to NG meningococci, with at least 8 of 16 total cases (50%) due to NG strains. Of the cases, 5 were due to meningococci that are NG by PCR and 3 more were phenotypically NG by SASG; had a gene for serogroup B, C, or Y capsule detected by PCR; but had a capsule operon

defect that would prevent capsule expression that was identified by whole genome sequencing. Further characterization of additional isolates is ongoing. Of the cases, 40% with known MenACWY vaccination status and 57% of cases with known MenB vaccination status and with disease onset in 2015-2016 had not been vaccinated with the respective vaccine prior to disease onset, although again routine case investigations may not always capture a patient's full vaccination history. Finally, 2 of 4 (50%) of the cases caused by meningococci that were phenotypically serogroup Y occurred in people who did have prior MenACWY vaccination documented. Together, these data suggest that vaccination provides incomplete protection to eculizumab recipients, both because of breakthrough cases of the serogroups that should be covered by the vaccines and because of the fairly high incidence of cases due to NG meningococcal bacteria, for which MenACWY vaccine provides no protection and for which the potential for cross-protection with MenB vaccines has not been assessed.

Dr. McNamara briefly shared some in vitro data that may shed some light on why patients on eculizumab therapy are so susceptible to meningococcal disease. As mentioned earlier, eculizumab binds to complement component C5 and blocks cleavage of this component into C5a and C5b. C5b is needed for the membrane attack complex, which underlies serum bactericidal activity, so based on this SBA would be expected to be heavily impaired in eculizumab recipients. In the absence of SBA, meningococcal killing hopefully would be accomplished through opsonophagocytosis (OPA). However, C5a, the other product of C5, promotes inflammation and phagocytosis. Therefore, an open question is whether eculizumab might inhibit OPA as well as SBA.

To answer this question, Dr. Granoff's laboratory has been performing some studies looking at the effects of eculizumab on whole blood killing of meningococci, which should encompass both SBA and OPA. These graphs summarize the results:



These graphs show geometric mean colony forming units (CFU) per ml of two different meningococcal strains, a serogroup B strain on the left and a serogroup C strain in the middle, following a 3-hour incubation with whole blood from 12 subjects who all received both MenACWY conjugate and MenB vaccines. In each graph, the first bar shows the CFU detected at time 0. In the second, blue, bar, it can be seen that after a 3-hour incubation with no inhibitor,

both strains of bacteria are consistently killed. The orange bars show what happens when a physiologically relevant concentration of eculizumab is added. Instead of being killed, the bacteria are able to rapidly replicate. Dr. Granoff performed a similar assay using the NG strain from the fatal case described earlier in this presentation, shown on the right. In this case, the assay was performed with whole blood from just one donor, a healthy adult who had received 2 doses of MenB-4C. Even this unencapsulated strain, which is easily killed by serum from most healthy unvaccinated adults, cannot be killed by whole blood from a vaccinated donor in the presence of eculizumab. Together, these data suggest that either eculizumab does inhibit opsonophagocytic activity, or that OPA in the absence of SBA is not able to inhibit growth of these strains even in whole blood from vaccinated subjects.

To summarize, eculizumab is associated with a 1- to 2000-fold increased incidence of meningococcal disease, and the case report and Epi-X data CDC collected suggest that a high proportion of the meningococcal disease cases in eculizumab recipients in the US are due to NG *Neisseria meningitidis*. These meningococci do not normally cause disease and since they lack a capsule, no protection against them is offered by MenACWY vaccine. The MenB vaccines may theoretically provide protection against these strains, but the proportion of NG strains for which MenB vaccines might offer cross-protection has not been assessed. Furthermore, both in the data CDC collected through the Epi-X and in prior reports from the manufacturer and literature, they have seen that breakthrough serogroup C, W, and Y cases can occur in eculizumab recipients in spite of MenACWY vaccination. CDC also heard of a few case reports from other countries of serogroup B meningococcal disease in eculizumab recipients who have received a MenB vaccine. Finally, in vitro data from Dr. Granoff's laboratory show that eculizumab not only blocks SBA, but also impairs whole blood killing of meningococci, showing that OPA is either inhibited by eculizumab or is inadequate for meningococcal killing in the absence of SBA.

Together, these points lead to two key concerns. First, patients on eculizumab are at risk of meningococcal disease due to both typical disease-causing strains and strains that do not normally cause disease, but that are frequently carried asymptomatically in the nasopharynx. Second, vaccination offers limited or possibly no protection against meningococcal disease for patients on eculizumab. In reviewing these data, CDC has been discussing whether there should be a role for antibiotic chemoprophylaxis for patients taking eculizumab. Some countries recommend antibiotic prophylaxis for the duration of eculizumab treatment. UK guidance states that patients are advised to take daily prophylactic antibiotics, either penicillin or erythromycin for those with penicillin allergies[1]. Similarly, guidance in France is to take continuous antibiotic chemoprophylaxis until 60 days after stopping eculizumab treatment[2]. In the US, CDC is aware that some individual providers also choose to recommend antibiotic prophylaxis for the duration of eculizumab treatment for some or all of their patients; however, there is no official guidance on this topic in the US [[1]http://www.pnhleeds.co.uk/professionals/meningococcal-infection-and-eculizumab/; [2]Zuber et al. 2012 Nat Rev Nephrol 8(11):643-57, http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=447].

Based on the literature and recommendations in other countries, penicillin appears to be the most commonly used antibiotic for long-term prophylaxis for eculizumab recipients. However, there are limited data available on the efficacy of this prophylaxis. Meningococcal strains with both intermediate susceptibility to penicillin and penicillin-resistance have been identified, and there are a few published reports of breakthrough cases in eculizumab recipients on penicillin that are due to meningococcal strains with intermediate penicillin susceptibility or resistance[1,2]. Recent studies of invasive meningococcal isolates from the US showed that between 10% and 37% had intermediate susceptibility to penicillin[3,4]. However, penicillin resistance remains rare

and has been identified in only about 1% of US strains. Several studies in Europe have found similar or greater prevalence of intermediate susceptibility and resistance to penicillin among invasive isolates, but again, the majority of these isolates have intermediate susceptibility rather than full resistance[5-7]. The clinical implications of intermediate penicillin susceptibility are unclear [[1]Cullinan et al. 2015; Pediatrics 135(6):e1506-9; [2]Parikh et al. IPNC 2016 abstract, available at: http://www.ipnc2016.org/;[3]Harcourt et al. 2015, OFID 2(3):ofv117, [4]Blain et al. 2016, OFID 3(3):ofw152 [5]Canica et al. 2004 EID 10(3):526-9 [6]Bijlsma et al. 2014 Lancet ID 14(9):805-12 [7]Bertrand et al. 2012 Antimicrob Agents Chemother 56(5):2268-72].

Although there are also limited data specifically assessing the safety of long-term penicillin therapy[1], it is generally considered to be safe and is routinely used for prophylaxis for rheumatic fever, as well as prevention of *Streptococcus pneumoniae (S. pneumoniae)* infection in asplenic children[2] [[1]https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm072755.htm [2]Enzler et al. 2011, Mayo Clin Proc86(7):686-701].

This raises a key discussion question, which regards whether antibiotic chemoprophylaxis for meningococcal disease should be recommended for eculizumab recipients in the US in addition to vaccination. If so, should this be penicillin or are there other good options for long-term antibiotic prophylaxis? Should antibiotics be recommended for all eculizumab recipients or for a subset, for instance, those expected to have a shorter course of treatment? Some aHUS patients may have a shorter course of treatment than PNH patients, for example, for whom treatment is typically expected to be life-long. Or should prophylaxis be limited to those in higher risk age groups? CDC does not really have data on which age groups of eculizumab recipients are at highest risk, but in the general population it is known that infants, adolescents, and older adults are at higher risk for meningococcal disease. If the concern is about disease due to strains more commonly associated with asymptomatic carriage, it is also known that asymptomatic carriage typically peaks among young adults. CDC does not anticipate an ACIP vote on this topic, but wanted to open it up for discussion with ACIP to acquire insight and ideas. CDC also hopes that ACIP can help identify additional stakeholders to engage on this issue.

Discussion Points

Dr. Romero emphasized that biologics are very important, but as they are being used, more is being learned about their unintended side-effects. His opinion is that antibiotics and chemoprophylaxis should be considered for these patients. However, it is not clear that there is enough information in these populations using this drug to break it out into saying it is infants, adolescents, or young adults who require this. Without looking at the data closer, he would probably recommend that all persons receiving eculizumab, short- or long-term, receive antimicrobial prophylaxis. They probably would need to discuss further whether that prophylaxis should be penicillin or some other drug. Certainly, one of the patients reported poor compliance to the regimen, which brings to mind whether other options are necessary. It is also important to consider whether these patients need a salvage protocol. Many patients have cell-mediated effects or congenital neutropenia, so their parents are given a dose of X and are told to give it if the child becomes sick and proceed immediately to the ED.

Dr. Walter concurred with Dr. Romero with regard to recommending the use of prophylaxis in this case.

Dr. Bennett inquired as to whether there were any comparable data on the 16 cases reported to the manufacturers that differ from the other 16 cases.

Dr. McNamara replied that the 16 cases reported from the manufacturer occurred from 2007 to the first quarter of 2014; whereas, the 16 she reported on occurred from 2008 and 2016. They know that there are different cases, but some are likely to be the same. CDC does not have access to very much information on the cases that have been reported to the manufacturer apart from what she presented, but is working to obtain that information.

Dr. Romero asked where they were observing higher incidences of other bacterial infections in these patients.

Dr. McNamara replied that there was some documentation of other infections that have occurred in eculizumab recipients. There is nothing else that looks like it has as dramatic an increase in incidence as meningococcal disease. The REMS program and black box warning are specifically focused on meningococcal disease.

Dr. Hunter inquired about the denominator of prevalence of the disease for which eculizumab is used. In his role as the sexually transmitted disease (STD) consultant for the City of Milwaukee Health Department, he argued against using benzathine penicillin as a prophylaxis so that it is available for syphilis.

Dr. McNamara replied that they do not have information specifically on the denominator aside from the information shared with the manufacturer and FDA of the 5207 person years of exposure in the US from 2007 to 2014. It is important to note that not all people with PNH or aHUS would be on eculizumab therapy at any given time.

Ms. Pellegrini was very troubled by the reports of under-vaccination in this population and whether that is due to providers not being diligent or patients not complying. There seems to be a role for CDC and FDA to work together to address compliance with the REMS requirements. If the REMS requirements are not being abided by appropriately, that is a tremendous problem. If the vaccines are not being administered, perhaps the education is also not occurring and parents, caregivers, and patients are not being appropriately sensitized to what they need to look for and how to care for themselves.

Dr. Sun (FDA) indicated that the REMS requirements are detailed and comprehensive. The data are reviewed periodically, including compliance data. He understood the point being made about the need for vaccination, but stressed the importance of also recognizing that in this particular case, vaccination may provide a false sense of security that it is actually doing something that it may not be.

Before weighing in on antimicrobial prophylaxis, Dr. Atmar would like to understand more about the minimal inhibitory concentration (MIC) for meningococci compared to group A strep or *Streptococcus pneumoniae* where it has been used effectively. If the MICs are similar, there is a chance it will be beneficial, but if they are a log higher on average, this may lead to a false sense of security in relying on antimicrobial prophylaxis. Failures have been observed.

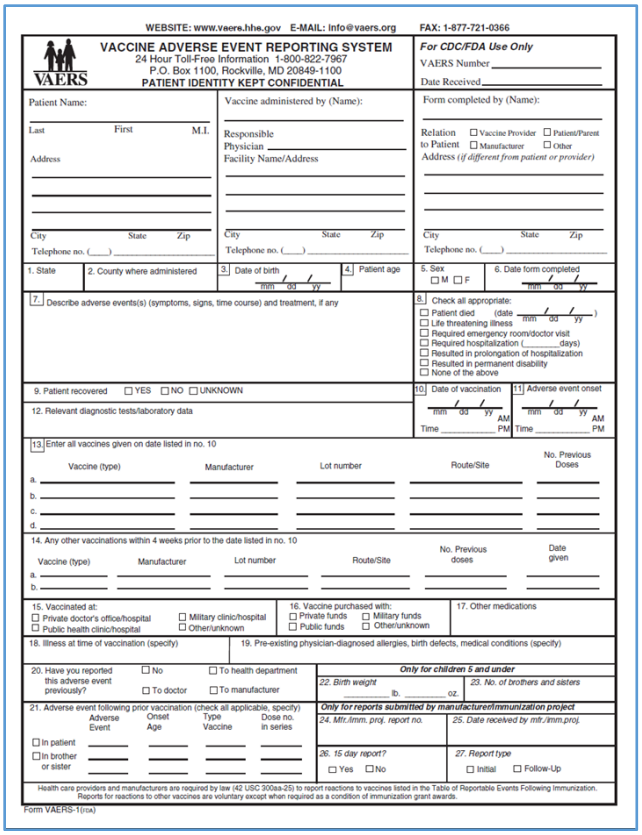
Dr. Stephens noted that most strains in this country remain susceptible to penicillin at reasonable MICs. There are intermediate strains on the order of 20% or so. One option for Dr. Romero's suggestion to consider a salvage protocol could be ceftriaxone. It is used in other countries in settings where meningococcal disease is suspected, and that point could be made about providing families with ceftriaxone as an IM injection in cases like this. Ceftriaxone potentially could be used as a longer-term prevention methodology.

Dr. Friedand (GSK) acknowledged that is a very challenging area. He brought to the attention of ACIP that an international workshop will be convened in September 2017 in Prague on meningococcal disease and complement deficiency to continue to understand the knowledge in this very important area. The data remain limited and are technically challenging. He reminded everyone that during the last ACIP meeting in February 2017, GSK presented the results of a clinical study of response to MenB-4C among individuals with immunodeficiencies, including 7 patients who were treated with eculizumab. In that study, those patients receiving eculizumab did have the lowest response to the vaccines compared to people with other complement deficiencies, although there was evidence of SBA? activity in some individuals taking eculizumab. In addition, during the September 2016 International Pathogenic *Neisseria* Conference in Manchester, there was a presentation from Public Health England on the results of 23 individuals who have received eculizumab. There they found that while eculizumab blocks SBA, it was not blocked in all subjects. Interestingly, they found that OPA activity was maintained and was not blocked in their subjects. These results suggest that completing vaccination can still be beneficial for these patients.

Vaccine Adverse Event Reporting (VAERS) 2.0 Form

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro indicated that this presentation would serve as the announcement of the new VAERS 2.0 form. As a reminder, VAERS is the national spontaneous reporting system for monitoring the safety of US-licensed vaccines that is co-managed by CDC and FDA. The current VAERS form, which is called the VAERS-1 form, has been in use since 1990. The paper version of this form must be filled out by hand and mailed or faxed in. An online reporting tool allows for web-based reporting of the VAERS-1 data. The following is the VAERS-1 form:



WEBSITE: www.vaers.hhs.gov E-MAIL: info@vaers.org FAX: 1-877-721-0366

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number
Date Received

Patient Name: Last First M.I.
Address
City State Zip
Telephone no. (___)

Vaccine administered by (Name):
Responsible Physician
Facility Name/Address
City State Zip
Telephone no. (___)

Form completed by (Name):
Relation ☐ Vaccine Provider ☐ Patient/Parent to Patient ☐ Manufacturer ☐ Other
Address (if different from patient or provider)
City State Zip
Telephone no. (___)

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm dd yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy Time ____ AM PM

11. Adverse event onset mm dd yy Time ____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight lb. ____ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

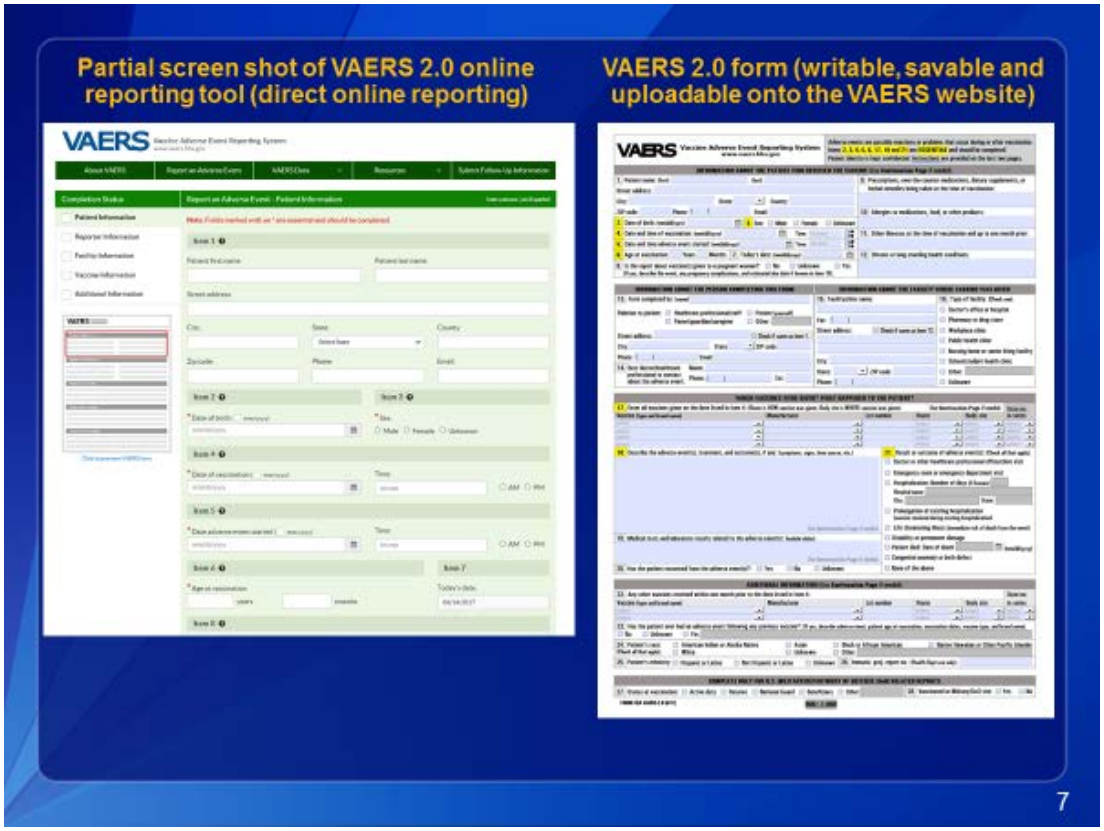
Form VAERS-1(n/a)

VAERS 2.0 consists of two major initiatives. One is a new VAERS form with revised data elements, which is called the VAERS 2.0 reporting form. The other is an updated process for submitting VAERS reports that includes two options: 1) updated online reporting tool; and 2) writable PDF form combined with electronic document upload capability.

Proposed changes to the current VAERS form were first presented to ACIP, NVAC, and the Advisory Commission on Childhood Vaccines (ACCV) in September and October 2014. Proposed changes also were posted in the *Federal Register* for public comment in November 2014 (https://www.federalregister.gov/documents/2014/11/24/2014-27678/request-for-comment-on-draft-vaccines-adverse-event-reporting-system-vaers-20-form). CDC conducted extensive user testing during the development and revision process. Changes to the VAERS form were finalized in 2016. The new VAERS 2.0 form has updated data elements, such as pregnancy status, race, and ethnicity. New features include writable and savable options, and some smart features like logic checks to prevent users from entering non-logical answers. Information technology (IT) upgrades to the VAERS website were completed in 2017 to incorporate new data elements into a reconfigured online reporting tool, and to accommodate a new electronic document upload process.

Starting on June 30, 2017 and extending through the end of December 2017, CDC and FDA will implement the VAERS 2.0 form and phase out the VAERS-1 form. VAERS 2.0 is for reporting by HCP, patients, parents, guardians, caregivers, and other non-manufacturer reporters. Reporters will be able to use the VAERS 2.0 online reporting tool to submit reports through direct online reporting, or download and complete the writable and savable VAERS 2.0 form and submit using an electronic document upload feature. Vaccine manufacturers report through a different process using the FDA Electronic Submissions Gateway (ESG).

Here are the online and writable/uploadable samples of the new VAERS 2.0 form:



"Essential" items, or high value data elements, are highlighted with asterisks in the online reporting tool and with yellow boxes in the writable PDF form.

Instructions for reporting to VAERS will be available at https://vaers.hhs.gov/reportevent.html. The URL will be activated June 30, 2017. Additional assistance is available via email at info@vaers.org or by phone at 1-800-822-7967. Transition to the VAERS 2.0 form is expected to be completed by the end of December 2017. Accommodations will be made for individuals unable to submit reports electronically.

Day 2: Public Comment

Ms. Patsy Stinchfield
Director, Infection Prevention and Control at Children's Minnesota
ACIP Liaison Member for the National Association of Pediatric Nurse Practitioners

Given that many people had asked about the Minnesota measles outbreak, she provided a brief update. She reported that Minnesota is still in the midst of this outbreak that began April 11, 2017. At the time of this report, there were 78 cases. Children's Minnesota has taken care of 53 of those 78, with 21 admissions mostly for dehydration. There have been no cases requiring intensive care, and there have been no deaths. Of the 78 cases, 71 were completely

unvaccinated. The age group is primarily pre-school children between 1 and 4 years of age. Of the cases, 83% were Somali Minnesotans. There has been a lot of activity from anti-vaccine groups talking with Somali families about MMR and autism. A lot of work is underway in the community, including efforts by Lynn Bahta from the Minnesota Department of Health (MDH) who was in attendance at this ACIP meeting, to work with Somali religious leaders to try to break that link. The last positive rash onset occurred on the 13th. If there are no more cases by the end of July, the outbreak will be over. Notably, there have been over 8880 exposures. Given that many exposures in 6 schools, 12 child care centers, and many clinics and EDs and a high immunization rate, there have been only the 78 cases. This surpassed all 70 US 2016 cases within 7 weeks. The MMR vaccine rates, particularly in the Somali community and typically in Hennepin County, would be about 500 Somali individuals getting vaccinated per week. After the outbreak began, there were 3 straight weeks of over 3000 MMR vaccines delivered. Outbreaks do change minds and Minnesota has seen this happen. The hope is that this will come to an end, and she will be happy to present more data during the October 2017 ACIP meeting.

Dr. Amy Middleman
ACIP Liaison Member
Society for Adolescent Health and Medicine

Dr. Middleman announced that the Society for Adolescent Health and Medicine (SAHM) published a position statement in the April 2017 issue of the *Journal of Adolescent Health* (*JAH*) supporting the establishment of a 16-year-old immunization platform. The platform would create an expectation among providers, parents, and patients to address immunizations that are due or overdue by 16 years of age and also would provide the opportunity to address other comprehensive and preventive healthcare needs. SAHM also recognizes with great appreciation the gray shading emphasizing this age group on the 2017 Immunization Schedule published by CDC, American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and American Congress of Obstetricians and Gynecologists (ACOG).

Certification

Upon reviewing the foregoing version of the June 21-22, 2017 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

CHAIR

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

EXECUTIVE SECRETARY

COHN, Amanda, MD
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National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS

ATMAR, Robert L., MD
John S. Dunn Clinical Research Professor in Infectious Diseases
Interim Chief, Section of Infectious Diseases
Departments of Medicine and Molecular Virology & Microbiology
Baylor College of Medicine
Chief, Infectious Diseases Service
Ben Taub General Hospital, Harris Health System
Houston, TX
Term: 7/1/2016 – 6/30/2020

BELONGIA, Edward, MD
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Term: 07/01/2014-06/30/2018

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

HUNTER, Paul, MD
Associate Professor of Family Medicine and Community Health
University of Wisconsin School of Medicine and Public Health
Associate Medical Director
City of Milwaukee Health Department
Milwaukee, WI
Term: 7/1/2016 – 6/30/2020

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

LEE, Grace M., MD, MPH
Associate Professor of Population Medicine & Pediatrics
Director, Center for Healthcare Research in Pediatrics (CHeRP)
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Associate Medical Director of Infection Control, Boston Children's Hospital
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Term: 7/1/2016 – 6/30/2020

MOORE, Kelly, MD, MPH,
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Tennessee Department of Health
Assistant Clinical Professor, Department of Health Policy
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PELLEGRINI, Cynthia
Senior Vice President
Public Policy and Government Affairs
March of Dimes
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Term: 07/01/2013-06/30/2017

REINGOLD, Arthur L., MD
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ROMERO, José R., MD, FAAP
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Horace C. Cabe Endowed Chair in Infectious Diseases
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Term: 07/01/2014-06/30/2018

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

SZILAGYI, Peter MD, MPH
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Executive Vice-Chair and Vice-Chair for Research
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Term: 7/1/2016 – 6/30-2020

WALTER, Emmanuel (Chip), Jr., MD, MPH
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Term: 07/01/2015-06/30/2019

***EX OFFICIO* MEMBERS**

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Indian Health Service
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Red Book Editor
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Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

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Association of Immunization Managers (AIM)
FINLEY, Christine, RN, MPH
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Association for Prevention Teaching and Research (APTR)
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Association of State and Territorial Health Officials (ASTHO)
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State Health Officer
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Biotechnology Industry Organization (BIO)
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Idaho Department of Health and Welfare
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Canadian National Advisory Committee on Immunization (NACI)
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ZAHN, Matthew, MD
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National Immunization Council and Child Health Program, Mexico
VILLASEÑOR RUIZ, Ignacio, MD
Directora del Programa de Atencion da la Salud de la Infancia y la Adolescencia / Director General, Child and Adolescent Health
Centro Nacional Para la Salud de la Infancia Y La Adolescencia / National Center for Child and Adolescent Health
Ministry of Health / Secretaría de Salud
Mexico

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WHITLEY-WILLIAMS, Patricia, MD
Professor and Chair
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Robert Wood Johnson Medical School
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Pediatric Infectious Diseases Society (PIDS)
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