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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 22-23, 2017
Atlanta, Georgia

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Final - February 8, 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
February 22-23, 2017

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, February 22			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Hepatitis B Vaccine**		
	Introduction		Dr. Arthur Reingold (ACIP, WG Chair)
	Revaccination for unprotected infants born to hepatitis B surface antigen (HBsAg)-positive mothers	Information & Discussion	Dr. Noele Nelson (CDC/NCHHSTP)
	Cost analysis of single-dose revaccination for infants born to hepatitis B surface antigen (HBsAg)-positive mothers		Mr. Eric Hall (Rollins School of Public Health, Emory University)
	Consideration of single dose re-vaccination for unprotected infants born to hepatitis B surface antigen (HBsAg)-positive mothers		Dr. Noele Nelson (CDC/NCHHSTP)
	Public comment		
	Recommendation vote	**Vote**	Dr. Noele Nelson (CDC/NCHHSTP)
	VFC resolution	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
9:30	***Break***		
10:00	**Influenza**		
	Introduction		Dr. Emmanuel (Chip) Walter (ACIP, WG Chair)
	Influenza surveillance update		Ms. Lynnette Brammer (CDC/NCIRD)
	Vaccine effectiveness update		Dr. Brendan Flannery (CDC/NCIRD)
	Flumist update	Information & Discussion	Dr. Helen Bright (MedImmune)
	Afluria update		Dr. Gregg Sylvester (Sequirus)
	Fluzone high-dose update		Dr. Stefan Gravenstein (Case Western Reserve University)
	Summary of session		Dr. Lisa Grohskopf (CDC/NCIRD)
12:00	***Lunch***		
1:15	**Herpes Zoster Vaccine**		
	Introduction		Dr. Ed Belongia (ACIP, WG Chair)
	Safety summary of candidate vaccine, herpes zoster subunit (HZ/su)		Dr. Romulo Colindres (GlaxoSmithKline)
	GRADE of HZ/su	Information & Discussion	Dr. Kathleen Dooling (CDC/NCIRD)
	Considerations for herpes zoster vaccine policy		Dr. Kathleen Dooling (CDC/NCIRD)
2:30	**Meningococcal Vaccines**		
	Introduction		Dr. David Stephens (ACIP, WG Chair)
	Considerations for MenB booster doses in groups at increased risk for serogroup B meningococcal disease		Ms. Jessica MacNeil (CDC/NCIRD)
	Update on the epidemiology of meningococcal disease and guidance for the control of meningococcal disease outbreaks in the U.S.	Information & Discussion	Dr. Sarah Meyer (CDC/NCIRD)
4:00	***Break***		
4:30	**Global Immunization Updates:**		
	Global Polio Eradication Initiative	Information	Dr. John Vertefeuille (CDC/CGH/GID)
	Global Measles/Rubella Elimination Initiative	Information	Dr. Gavin Grant (CDC/CGH/GID)
5:30	**Public Comment**		
5:40	**Adjourn**		

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	Thursday, February 23		
8:00	**Welcome**		Dr. Anne Schuchat (CDC, Acting Director)
8:30	**Agency Updates**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); CDC and Ex *Officio M* embers
8:45	**Vaccination Errors**		Dr. Tom Shimabukuro (CDC/NCEZID/ISO)
9:00	**Mumps Disease and Vaccine**		
	Introduction	Information & Discussion	Dr. Kelly Moore (ACIP, WG Chair)
	Mumps epidemiology and vaccination recommendations in the United States		Dr. Mona Marin (CDC/NCIRD)
9:40	**Dengue Virus Vaccines**		
	Introduction	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair)
	Dengue epidemiology and vaccine development		Dr. Steve Waterman (CDC/NCEZID)
10:20	**Zika Virus Vaccines**		
	Zika virus epidemiology update	Information	Dr. Marc Fischer (CDC/NCEZID)
	Zika vaccines in development		Dr. Gerald Kovacs (ASPR/BARDA)
11:00	***Break***		
11:20	**Adult Immunization**		
	Introduction	Information	Dr. Laura Riley (ACIP, WG Chair)
	Implementation of standards for adult immunization practice		Dr. David Kim (CDC/NCIRD)
11:50	**Yellow Fever Vaccine**		
	Introduction	Information	Dr. Chip Walter (ACIP, WG Chair)
	Update on yellow fever vaccine supply		Dr. David Greenberg (Sanofi Pasteur)
12:05	**Vaccine Supply**		Dr. Jeanne Santoli (CDC/NCIRD)
12:20	**Public Comment**		
12:30	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
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
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ADE	Antibody Dependent Enhancement
AE	Adverse Events
AFI	Acute Febrile Illness
AFIX	Assessment, Feedback, Incentives, and eXchange
AIM	Association of Immunization Managers
ANA	American Nurses Association
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Innovation Organization
BLA	Biologics License Application
BLS	Bureau of Labor Statistics
BPL	β-Propiolactone
CDC	Centers for Disease Control and Prevention
C. difficile	*Clostridium difficile*
cVDPV	Circulating Vaccine-Derived Polioviruses
CGMPs	Current Good Manufacturing Practice
CIRN	Canadian Immunization Research Network
CLD	Chronic Liver Disease
CMS	Center for Medicare and Medicaid
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
CRS	Congenital Rubella Syndrome
CWRU	Case Western Reserve University's
DCD	Department of Communicable Diseases Prevention, ERMO
DF	Dengue Fever
DFO	Designated Federal Official
DGMQ	Division of Global Migration and Quarantine
DHA	Defense Health Agency
DHF	Dengue Hemorrhagic Fever
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSS	Dengue Shock Syndrome
DtaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
DVBD	Division of Vector-Borne Diseases
DVH	Division of Viral Hepatitis
EAP	Expedited Access Pathway
ED	Emergency Department
EHDB	Enteric and Hepatic Diseases Branch
EHR	Electronic Health Record
EMA	European Medicines Agency

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EMR	Electronic Medical Record
EMRO	Regional Office for the Eastern Mediterranean
EPHBPP	Enhanced Perinatal B Prevention Hepatitis B Prevention Program
EMA	European Medicines Agency
EOCs	Emergency Operation Centers
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GID	Global Immunization Division
GMC	Geometric Mean Concentrations
GPEI	Global Polio Eradication Initiative
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HA	Hemagglutinin
HbeAg	Hepatitis B e Surface Antigen
HBIG	Hepatitis B Immunoglobulin
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Vaccine
HCP	Healthcare Personnel
HCV	Hepatitis C Virus
HD	High-Dose
HepB	Hepatitis B
HepB-BD	HepB Birth Dose
HHS	(Department of) Health and Human Services
HI	Hemagglutination Inhibition
Hib	*Haemophilus Influenzae* Type B
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Human Complement Serum Bactericidal Antibody
HZ	Herpes Zoster
HZ/su	HZ Subunit Vaccine
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IgA	Immunoglobulin A
IHB	Immunization Healthcare Branch
IHR	International Health Regulations
IHS	Indian Health Services
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IMS	Insurance Management Services
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
IRB	Institutional Review Board
ISD	Immunization Services Division
ITT	Intention-To-Treat
ISO	Immunization Safety Office
JAMA	*Journal of the American Medical Association*
JE	Japanese Encephalitis
JID	*Journal of Infectious Diseases*
LAIV	Live Attenuated Influenza Vaccine
LID	Laboratory of Infectious Diseases

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LPN	Licensed Practical Nurse
LTCF	Long-Term Care Facilities
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MI	Myocardial Infarction
MMR	Measles, Mumps and Rubella
MMRV	Measles, Mumps, Rubella, and Varicella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
mRNA	Messenger RNA
NA	Neuraminidase
NACCHO	National Association of County and City Health Officials
NAIIS	National Adult and Influenza Immunization Summit
NAIP	*National Adult Immunization Plan*
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
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHP	Non-Human Primates
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIP	*National Immunization Plan*
NMA	National Meningitis Association
NNDSS	National Notifiable Diseases Surveillance System
NNT	The Number-Needed-to-Treat
NHs	Nursing Homes
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NYC	New York City
OMB	Office of Management and Budget
OPHPR	Office of Public Health Preparedness and Response
OPV	Oral Polio Vaccine
PAHO	Pan American Health Organization
PHBPP	National Perinatal Hepatitis B Prevention Program
PhRMA	Pharmaceutical Research and Manufacturers of America
pIMDs	Potential Immune Mediated Diseases
PHN	Post Herpetic Neuralgia
Poly-A	Polyadenosine
PRN	Pertactin
PT	Pertussis Toxin
PVST	Post-Vaccination Serologic Testing
QIV	Quadrivalent Influenza Vaccine
qPCR	Real-Time Polymerase Chain Reaction
R&D	Research and Development
RCT	Randomized Controlled Trial
RN	Registered Nurse
RNA	Ribonucleic Acid

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RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
S. aureus	*Staphylococcus aureus*
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	Supplementary Immunization Activities
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SD	Standard-Dose
SES	Socioeconomic Status
SME	Subject Matter Experts
SRTI	Systemic Respiratory Tract Infection
TB	Tuberculosis
TBE	Tick Borne Encephalitis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TDOC	Sodium Tauro Deoxycholate
TIV	Trivalent Influenza Vaccine
UF	Undifferentiated Fever
UK	United Kingdom
UN	United Nations
URI	Urinary Tract Infection
US	United States
UTR	Untranslated Region
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VistA	Veterans Information Systems and Technology Architecture
VLP	Virus-Like Particle
VRBPAC	Vaccines and Related Biological Products Advisory Committee VRBPAC
VSD	Vaccine Safety Datalink
VZV	Varicella Zoster Virus
VTEU	Vaccine and Therapeutic Evaluation Units
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WNV	West Nile Virus
WPV	Wild Poliovirus
WRAIR	Walter Reed Army Institute of Research
YF	Yellow Fever
ZIP	Zika in Infants and Pregnancy Study

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

Call To Order / Welcome

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett called the February 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 February 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 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, June 21-22, 2017. Registration for all meeting attendees is required. The registration deadline for Non-US citizens is May 22, 2017 and for US citizens, registration closes June 7, 2017. Registration is not required for webcast viewing. As a reminder for non-United States (US) citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms are submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to help with any questions about the process.

Dr. Cohn reported the following member substitutions during this meeting:

Liaison Representatives

- ❑ Dr. Corey Robertson is representing Pharmaceutical Research and Manufacturers of America (PhRMA)
- ❑ Dr. Bonnie Maldonado is representing the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP)

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- ❑ Dr. Alexandra Woodward is representing Biotechnology Innovation Organization (BIO)
- ❑ Carol Hayes will be representing American Nurses Association (ANA) in addition to her own organization
- ❑ Dr. Bill Schaffner will be representing Infectious Disease Society of America (IDSA) in addition to his own organization

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. These may be submitted as e-mail attachments to Dr. Jean Clare Smith at jsmith2@cdc.gov

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 four ACIP publications since February 2016, which are reflected in the following table:

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ACIP Recommendations Published Since February 2016

Title	Publication Date	MMWR Reference
Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2017	February 10, 2017	MMWR. 2016;66(5);136-8
Advisory Committee on Immunization Practices Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger — United States, 2017	February 10, 2017	MMWR. 2016;66(5);134-5
Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices	December 16, 2016	MMWR. 2016;65(49);1405-8
Recommendations for Use of Meningococcal Conjugate Vaccines in HIV-Infected Persons — Advisory Committee on Immunization Practices, 2016	November 4, 2016	MMWR. 2016;65(43);1189-94

http://www.cdc.gov/vaccines/HCP/acip-recs/recs-by-date.html 11

Visitors / Farewells / Roll Call

Nancy Bennett, MD, MS
ACIP Chair

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

- Dr. Rana Hajjeh, Director, Department of Communicable Diseases Prevention & Control (DCD), Regional Office for the Eastern Mediterranean (EMRO)
- Dr. C. Irtaza Ahmad, Technical Officer, Vaccine Preventable Diseases & Immunization, DCD, EMRO

She then wished a fond farewell to three ACIP members:

Dr. Bruce Gellin

Dr. Gellin has been the *Ex-Officio* representative at the ACIP for the last 15 years in his role as Director of the National Vaccine Program Office (NVPO). He will be leaving NVPO at the end of the month to take on a new role as President of Global Immunizations at the Sabin Vaccine Institute. ACIP honored Dr. Bruce Gellin for his many years of service and thanked him for his constant support and insight for the ACIP over the years, and is thrilled that he will continue to work in immunization at a global level. Dr. Bennett emphasized that he would be sorely missed and thanked him for his service.

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Dr. Richard Gorman

Dr. Richard Gorman has been serving as the National Institutes of Health (NIH) *Ex-Officio* representative for the last 8 years. He has been a constant source of insight and support to ACIP. Dr. Bennett personally thanked him because he frequently answers the questions she forgets to ask.

Dr. Ian Gemmill

Dr. Ian Gemmill has been serving as the Liaison Member for the National Advisory Committee on Immunization (NACI) for Canada as he completes his term as Chair of that committee. He also has brought important insights to ACIP, often clarifying the limitation of the committee's vision. By having the opportunity to hear about another country's approach, ACIP learns a great deal.

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

- ❑ Robert Atmar receives research support from Takeda Vaccines
- ❑ Dr. Romero has a non-research related conflict with Merck and will not be voting on the Hepatitis B vaccine
- ❑ The remainder of the ACIP members declared no conflicts

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

ACIP February 23, 2017: Dr. Schuchat's Welcoming Remarks

Anne Schuchat, MD (RADM, USPHS)
Acting Director, Centers for Disease Control and Prevention
Acting Administrator, Agency for Toxic Substances and Disease Registry
Rear Admiral, US Public Health Service

Thanks so much. It is a special honor, special feeling, to come back to see you all today in this time when I am serving as Acting Director for the agency. It's an incredible privilege to be Acting Director, and you are such a special group of people doing such an incredibly difficult

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and incredibly important work for the nation. So, I was pleased when Amanda asked me to stop by.

My main message is to thank you. I want to thank the members of the committee and Dr. Bennett for her chairing of the committee in such a professional and efficient way. You take time out of incredibly busy schedules to do very complex and tedious work, and the nation really thanks you for it. I want to thank the liaisons. I know that we have quite a few here who are representing all kinds of professional expertise, and bringing that programmatic and professional input into our guidelines helping us avoid what Dr. Frieden used to call the "eye-rolling" that happens when CDC issues guidance. You are the no "eye-rolling" contingency here—you around the central group. I also want to thank the *ex officios* who are helping us be one extremely coordinated federal vaccine enterprise. I appreciate what each of you do and want to make special reference to Bruce Gellin, who is going to be retiring soon from 15 years of service at the National Vaccine Program Office (NVPO). A real treasure to have you there for those years, and a great partner to us at CDC. I also want to thank the public for the voices that you bring to ACIP, both in the room and between meetings—the letters that you send and the public comments that you make. You make sure that the meeting is serving the nation at all times.

Personally, as you know, I was the National Center for Immunization and Respiratory Diseases (NCIRD) Director for a decade and during that period and since then, the ACIP has made extraordinary improvements. The process was good and it has gotten even better with integration of GRADE (Grading of Recommendation Assessment, Development and Evaluation) to the deliberations, so we have a very transparent and systematic way that evidence is reviewed, including values being considered. The webcasting has opened these meetings up even wider. The public can see these meetings not just by traveling to Atlanta, but from anywhere in the world. The major changes that you all have made: the votes that you have taken that have added vaccines, that have increased doses when we needed a booster and taken doses away when they were not essential, such as the HPV for younger teens and I guess the hepatitis B deliberation that you had yesterday for infants; the review of the schedules every single year looking at new information on efficacy or effectiveness, on safety signals, on performance over time with waning immunity, and the attempt to harmonize with the professional groups so that clinicians have clear and consistent advice whenever possible; the meetings themselves, which regularly review the critical vaccine issues from each working group (WG), as well as key outbreaks that may have implications for future recommendations; and the regular review of safety for any kind of signals that may have occurred.

This process is not easy, and there is uncompensated time that each of you gives, and the staff who support you for the logistics of the meeting, as well as the technical and superb scientific program inputs to the working groups. So, this is a process that I think the nation can be very proud of and I am personally very proud of. I know how much experience is at this table, and on this committee, and around the world, and I just want to tell you how grateful I am for what you do every day and particularly in preparation for these meetings. You know, the nation depends on CDC and we depend on you and so thank you so much for all that you are doing for us and for letting me talk to you this morning. Thanks.

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Hepatitis Vaccines

Introduction

Art Reingold, M.D. Hepatitis Vaccines Work Group

Dr. Reingold reminded everyone that in October 2016, ACIP approved new hepatitis B (HepB) vaccination recommendations. Currently, the recommendations are in CDC clearance and will be published as a comprehensive summary of previously published recommendations from ACIP and CDC for the prevention of hepatitis B virus (HBV) infection in the US.

He indicated that this session would include a presentation on revaccination for unprotected infants born to hepatitis B surface antigen (HBsAg)-positive mothers who do not respond to the initial hepatitis B vaccination series, as well as a cost analysis presentation on single-dose revaccination for infants born to HBsAg-positive mothers. The presentations would be followed by a vote, including a VFC vote, for approval of permissive language for single-dose revaccination followed by post-vaccination serologic testing (and completion of the 2nd series followed by post-vaccination serologic testing, if necessary) for infants born to HBsAg-positive mothers.

The next topic to be addressed by the HepB Work Group (WG) will be an update to the ACIP recommendations for hepatitis A (HepA) vaccine, proposed for presentation during the June 2017 ACIP meeting.

Revaccination for Unprotected Infants Born to HBsAg-Positive Mothers

Noele Nelson, MD, PhD, MPH
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Nelson reminded everyone of the current recommendation for revaccination of infants born to HBsAg-positive mothers:

Current Recommendation

- ❑ Providers should order post-vaccination serologic testing (PVST), consisting of hepatitis B surface antigen [HBsAg] and antibody to HBsAg [anti-HBs], for infants born to HBsAg-positive mothers at age 9–12 months (or 1–2 months after the final dose of the vaccine series, if the series is delayed)[1]
- ❑ HBsAg-negative infants with anti-HBs levels ≥10 mIU/ml* are protected and need no further medical management[2]
- ❑ HBsAg-negative infants with anti-HBs levels <10 mIU/mL* should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine[2]

[1]Schillie S, et. al. MMWR Morb Mortal Wkly Rep. 2015 Oct 9;64(39):1118-20.
[2] Mast EE, MMWR Recomm Rep. 2005 Dec 23;54(RR-16):1-31.
*Anti-HBs ≥10 mIU/mL, when following a complete Hepatitis B vaccine series, is serologic correlate of protection (Jack et al., J Infect Dis 1999)
Note: Available data do not suggest a benefit from administering additional hepatitis B vaccine doses to infants who have not attained anti-HBs ≥10 mIU/mL following receipt of two complete hepatitis B vaccine series.

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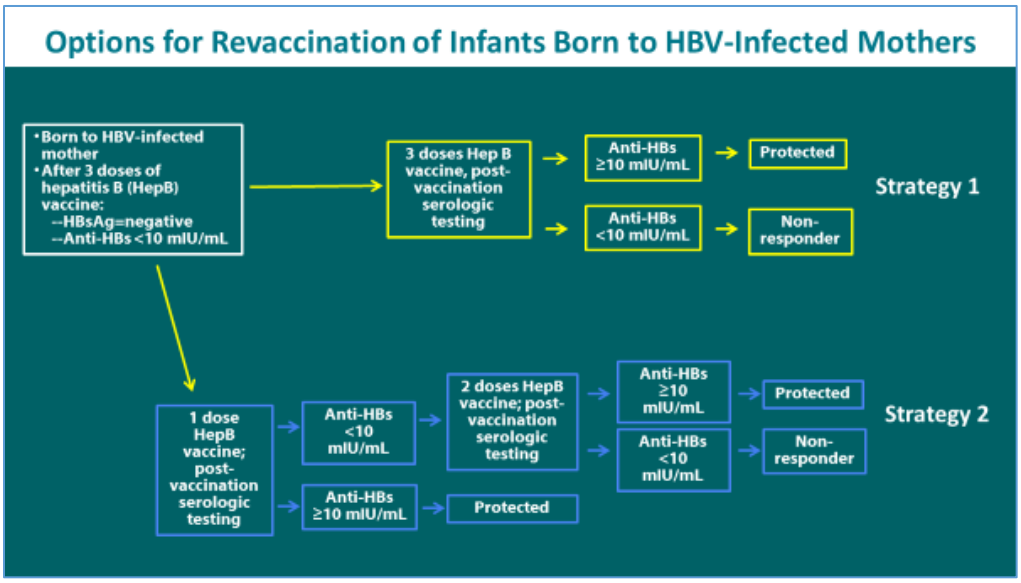
Considerations

- ❑ Some infants may need only a single revaccination dose to achieve protective anti-HBs levels
- ❑ Single dose revaccination may conserve public health resources by shortening the duration of case management
  - ➢ For some infants, providing case management services through completion of a 2nd hepatitis B (HepB) vaccine series is difficult (e.g., infant moves out of the country)

To set the stage for the remaining presentations regarding what the WG was proposing, Dr. Nelson showed the following comparison of the existing language to the proposed revised language:

Existing Language	**Revised Language (Proposed)**
❑ HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine.[1,2]	❑ HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose HepB series and **postvaccination serologic testing (PVST)** performed 1-2 months after the final dose of vaccine. ❑ **Alternatively, these infants may be re-vaccinated with a single dose of HepB vaccine and retested 1-2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine, followed by testing 1-2 months later.** ❑ Available data do not suggest a benefit from administering additional HepB vaccine doses to infants who have not attained anti-HBs ≥10 mIU/mL following receipt of two complete HepB vaccine series.
[1]Schillie S, et. al. MMWR Morb Mortal Wkly Rep. 2015 Oct 9;64(39):1118-20. [2] Mast EE, MMWR Recomm Rep. 2005 Dec 23;54(RR-16):1-31.	

Two strategies are depicted in the following algorithm:



In terms of background, the perinatal HepB prevention program was established in 1990 and was funded by CDC Immunization Cooperative Agreements (Section 317 funding). There are

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programs in 64 jurisdictions (50 states, 6 cities, 5 territories & 3 freely associated island nations) that work collaboratively with NCHHSTP's Division of Viral Hepatitis (DVH). Each year, all Perinatal Coordinators from this program are surveyed. In terms of the outcomes from 2014, the number of infants enrolled was 11,157. Based on modeling, this number was expected to be approximately 18,807 as a lower limit or a point estimate of 26,236. These estimates are being evaluated currently and are anticipated to be published in 2017. Therefore, the remaining data are reported as percentages and not actual numbers. The percent of all enrolled infants with PEP within 1 calendar day of birth was about 97%. The percent with HepB immunoglobulin (HBIG) and series complete by 8 months was about 74%. The percent of all enrolled infants with post-vaccination serologic testing (PVST) results was about 64%. The percent of all enrolled infants with HBsAg-positive results was about 0.4%. The percent of all enrolled infants with protective levels of anti-HBs, after three doses of vaccine, was about 95%. The percent of all enrolled infants that need revaccination was 2%, while those with indeterminant results was about 2%. Considering that potentially 4% of infants enrolled in the program require revaccination, that is about 450 infants pertaining to the recommendations under consideration.

Dr. Nelson presented some studies that were used to inform the economic model to be presented during this session. With regard to the proportion of infants protected after the initial vaccination series, a study by Ko et al of HepB vaccine response using data from the Enhanced Perinatal B Prevention Hepatitis B Prevention Program (EPHBPP) found about a 95% response rate among infants who completed a 3- or 4-dose HepB vaccine series.[1] A cost-effective analysis of a perinatal HepB by Barbosa et al included results from a Cochrane Review; a clinical trial of infant outcomes among HBsAg-positive infants born to HBsAg-positive mothers found a 92% efficacy for infants who received HBIG + the birth dose of HepB vaccine and the remaining doses on time.[2] Another study by Schillie et al, also looking at EPHBPP data evaluated factors associated with infection status in infants born to HBsAg-positive mothers and found that 99% of infants were negative after receipt of ≥3 vaccine doses.[3] [[1]Ko et al., Hepatitis B vaccine response using data from the Enhanced Perinatal B Prevention Hepatitis B Prevention Program (EPHBPP); [2]Barbosa et al., Efficacy of vaccine and HBIG by time of administration and completion of vaccination series; [3]Schillie et al., EPHBPP data, factors associated with infection status among infants born to HBsAg-positive mothers].

No studies specifically considered the proportion of individuals who do not respond to the initial HepB vaccine series who are seroprotected after one additional dose which was a key question of the analysis. However, two studies from Thailand assessed infants who were vaccinated with four doses at a time point after each vaccine dose. In the Lolekha et al study, in Schedule A, infants who received vaccine at birth, 1, and 6 months had a 92% response at 9 months (3 months after the last dose) and about an 89% response at 13 months (about 7 months after the last dose). In Schedule B, infants who received vaccine at birth, 1, 2, 12 months had an 86.5% response at 9 months and a 94.4% response at 13 months. In Schedule A, the decline is not surprising since it is known that the antibody declines over time.[1] A similar study by Assateerawatt et al assessed two groups of infants born to positive mothers with a somewhat higher birth weight of ≥2500g. Group A received HBIG + vaccine at 0 and vaccine at 1, 2 and 12 months. Group B received no HBIG and vaccine at 0, 1, 2 and 12 months.[2] There was no significant difference among the groups. In Group A, there was a 96% seroconversion rate at 12 months and 100% at 13 months. In Group B, there was a 95.2% seroconversion rate at 12 months and 95.7% at 13 months after the fourth dose [[1]Lolekha S, et al., Vaccine 2002; 20(31-32): 3739-43; and [2]Assateerawatt A, et al., Asian Pacific journal of allergy and immunology 1993; 11(1): 85-91].

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Ko et al specifically assessed the question regarding what percent of infants who do not respond to the initial hepatitis B vaccine series are protected after a complete second vaccine series. The study found that of non-responder infants who completed a second vaccination series at the time of analysis in the study, 95% demonstrated a response after the second series [Ko et al., Vaccine 2014; 32(18): 2127-33].

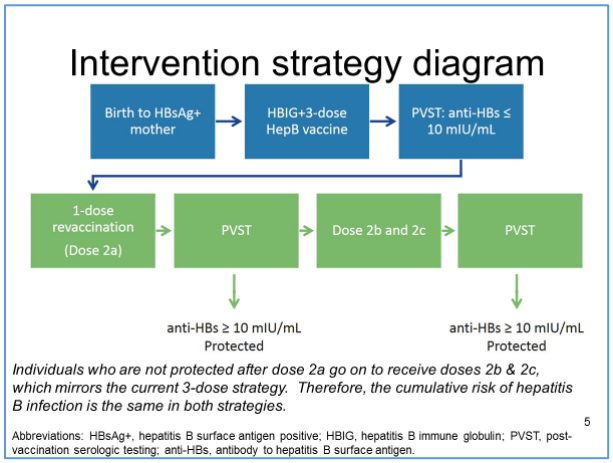
In terms of the limitations, these studies were not designed specifically to evaluate response to single dose revaccination in initial infant non-responders. There was variability among the studies with regard to maternal HBsAg status, HBIG administration, schedule, HBeAg status, and infant birth weight (<2000g vs. ≥2000g). In general, limited data are available on this topic.

Data also were considered from three sites that are part of the Perinatal HepB Prevention Program. The records were reviewed for infants born to HBsAg-positive mothers from 2012 through 2016 in Georgia, Michigan, and New York City (NYC) who received 3 doses of hepatitis B vaccine and PVST with anti-HBs <10 mIU/mL, followed by single dose revaccination with anti-HBs measurement. Of the 15 infants found, 14 (or 93%) had anti-HBs ≥10 mIU/mL after single dose revaccination. This provides further evidence that most infants who do not respond to the initial vaccine series do respond after a single dose revaccination.

Cost Analysis of Single Dose Revaccination for Infants Born to HBsAg-Positive Mothers

Eric Hall, MPH
Rollins School of Public Health
Emory University

Mr. Hall presented on assessing the cost-effectiveness of a single-dose of HepB revaccination among infants not responding to the initial vaccine series and born to HAV-infected mothers. The motivating study question for this analysis was, “Is a one-dose HepB revaccination strategy among infants born to HepB-infected mothers who do not respond to the initial vaccine series cost-effective compared to the current recommended three dose strategy?” The analysis used a societal perspective, considered direct and indirect costs, and considered a one-dose revaccination strategy. A one-year intervention timeframe and a one-year analytic horizon were used. Discounting was not included due to the one-year horizon. Any costs that differ between these two strategies occur during the revaccination process. Here is a diagram of the proposed intervention strategy:



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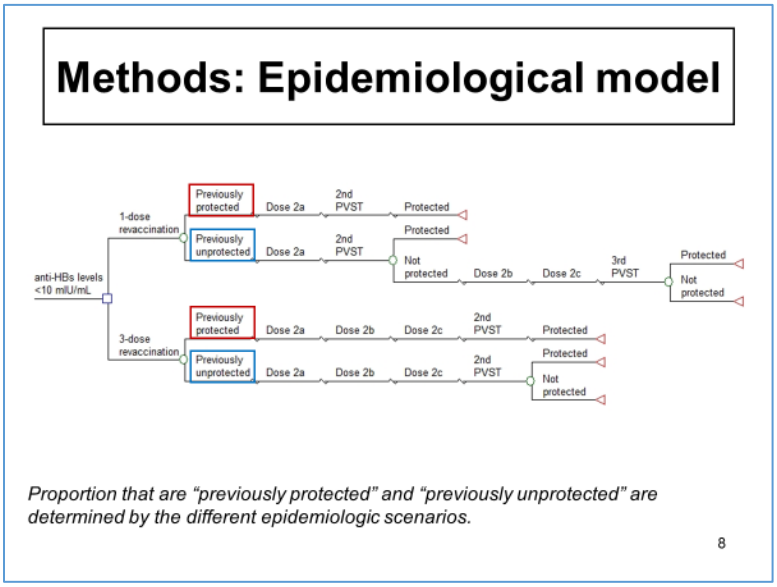
The top part in blue is the first vaccine series for an infant born to a mother who tested positive to HBsAg, who then goes on to receive HBIG and a three-dose HepB vaccine series. The infant goes on to receive PVST. If the antibody levels are ≥ 10 mIU/mL, the infant is considered to be protected. If the antibody levels are <10 mIU/mL, the infant is indicated for revaccination. Infants who are not protected after dose 2a go on to receive doses 2b and 2c, which mirrors the current 3-dose revaccination strategy. Therefore, the cumulative risk of hepatitis B infection is the same in both strategies and health outcomes were assumed to not differ between the current strategy and the proposed strategy.

The two strategies were assessed through a decision tree model utilized to assess the cost per person in the 1-dose and 3-dose revaccination strategies. The costs per person equaled the sum of direct and indirect costs associated with each vaccine dose and each PVST. These comparisons were made under a variety of epidemiologic scenarios identified as A, B, and C. In terms of health outcomes, the model estimated the number of protected and unprotected individuals under each epidemiological scenario. The number of protected individuals and cumulative risk of infection are assumed to be the same for each strategy. There is not a difference in health outcomes between the two strategies. The decision tree diagram used for this analysis is shown below:



On the far left is a cohort of infants who were born to mothers who tested positive with HBsAg and received the initial dose of the 3-vaccine series, received the first PVST, and had antibody <10 mIU/mL. The blue square is the decision node. The top portion of this diagram represents the proposed 1-dose revaccination strategy and the bottom portion represents the current 3-dose strategy. The green circles are chance nodes. Associated probabilities are attached with each chance node that determine which series of branches an individual will follow. Key variables are boxed in red and blue and represent infants that were previously protected and previously unprotected. This composite variable was used to set the different epidemiologic scenarios mentioned earlier. The motivation for creating these different scenarios came from the work Dr. Nelson mentioned that was done by their colleagues at DVH. That work indicated that if a vaccinated infant had a PVST that was delayed beyond the recommended time frame, antibody levels could wane below 10 mIU/mL even though they are actually protected.

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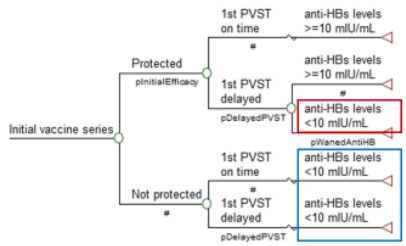
This diagram depicts the various scenarios:

Methods: Scenarios



Scenario	P protected after initial series	Timing of PVST	P of anti-HBs <10 among seroprotected	1st PVST: P <10mIU/mL	N indicated for revaccination	P of indicated w/protection
A	0.980	All PVSTs on time	0.000	0.020	496	0.000
B	0.973	20.4% >6 months	0.107[d]	0.048	1,190	0.438
C	0.668	21.3% >6 months	0.121[d]	0.349	8,650	0.049

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A portion of the infants with delayed PVSTs can be indicated for revaccination even though they actually have previous protection. The investigators created different scenarios that represent a different proportion of the cohort in which that is the case. At the bottom of the diagram are the different variables and inputs that create scenarios A, B, and C. In these, the efficacy of the initial vaccine series is varied, as are the proportion of the infants who received a delayed PVST, the proportion of infants whose antibody levels waned below 10 mIU/mL and were indicated for revaccination, and the resulting proportion of the total cohort indicated for revaccination who actually did have previous protection. The red and blue boxes are the infants indicated for revaccination. They go into the corresponding red and blue boxes from the previous diagram.

Here are the table of probabilities and parameters and costs associated with each PVST that were input into this model:

Methods: Inputs – Probabilities

Parameter	Base case	Lower	Upper	Definition/assumptions	Source
Population and risk					
N infants born to HBsAg+ mother	24,784				1
P of infants protected after initial vaccination series	0.973	0.668	0.980	Base case is weighted average based on birth weight[2,5]. Upper efficacy limit[4]. Lower value is weighted average from previous analysis[3].	1,2,3,4
P of 1st PVSTs >6 months after final dose	0.204	0	0.213	Upper value is the 95% confidence interval upper limit	2,5
P of anti-HBs <10 among seroprotected with a PVST >6months	0.107	0	0.121	Weighted average of 7-8 months, 9-10 months, 11-12 months, 13-14 months and 15-16 months after final vaccine dose. Upper value is the 95% confidence interval upper limit	Calculated[2,5]
Decision tree analysis					
P of infants indicated for revaccination who are previously protected	0.438	0	0.500	Scenarios calculated from population and risk parameters.	Calculated
P protected from single revaccination dose (dose 2a)	0.778	0.000	0.900	Base case is calculated from two studies with a 4-dose schedule of 0, 1, 2, 12 months.	Calculated[4,6,7]
P protected from 2nd full series	0.948	0.918	0.978	Among infants in PBHPP	2

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Methods: Inputs – Costs

Costs	Base case	Lower	Upper	Definition/assumptions	Source
P of vaccines purchased publicly	0.530	0.000	1.000	n/a	8
Cost of 1 vaccine dose, private	$22.40			Engerix B, private sector cost	9
Cost of 1 vaccine dose, public	$11.60			Engerix B, private sector cost	9
Cost of 1 vaccine dose, average	$16.68	$11.60	$22.40	Base case is weighted average	Calculated
P of vaccines administered publicly	0.200	0.000	1.000	n/a	8,10
Cost of vaccine administration, private	$29.63			Converted to 2016 USD with medical care CPI	8,11
Cost of vaccine administration, public	$8.31			Converted to 2016 USD with medical care CPI	8,11
Cost of administering 1 vaccine dose, weighted average	$25.37	$8.31	$29.63	Base case is a weighted average	Calculated
Cost of HBsAg testing to identify infection	$14.07	$11.26	$16.88	Hepatitis B surface antigen eia (CPT code 87340). National limitation amount with range of ±20%	12
Cost of HBsAG confirmatory test	$14.07	$11.26	$16.88	Hepatitis B surface antigen eia (CPT code 87341), only used if test 87340 is positive. National limitation amount with range of ±20%.	12
Cost of anti-HBs to identify immunity	$20.42	$16.34	$24.50	Hepatitis B surface antibody (CPT code 86317). National limitation amount with range of ±20%	12
Cost of blood draw	$3.00	$2.40	$3.60	Routine venipuncture (CPT code 36415). National limitation amount with range of ±20%	12
Cost of outpatient consultation for testing and results interpretation	$70.74	$56.59	$84.89	Included in all PVSTs. Converted to 2016 USD with medical care CPI and calculated range of ±20%	1,11
Cost of caregiver missing work (2 hours for each PVST/vaccine visit)	$17.40	$7.25	$44.29	Per hour. Base case is median national average from May 2015.	13
Cost of travel to receive vaccine	$24.04	$5.00	$35.00	Converted to 2016 USD with overall CPI	8,11

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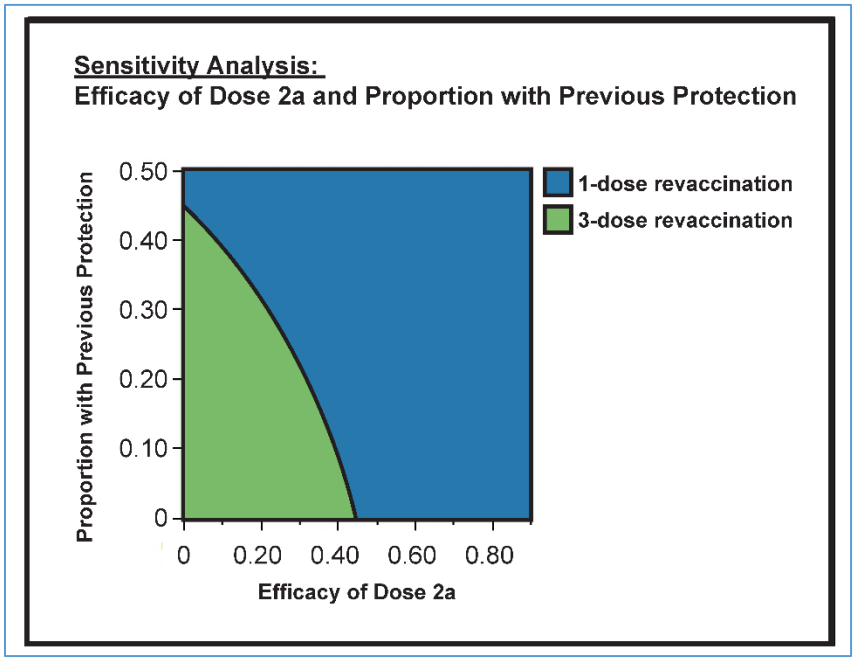
A few sensitivity analyses were conducted on some of these variables. The first one, and perhaps one of the most important, was a univariate threshold analysis of the proportion protected by a single dose of revaccination (Dose 2a). While there is an estimate of what that parameter might be, it is based on very limited data. The researchers opened up the range in this sensitivity analysis from 0.0 to 0.9 to determine what level would be needed to favor one strategy over the other. Secondly, a tornado diagram was constructed in which all probability and cost parameters were considered. Finally, a two-way sensitivity analysis looked at the efficacy of dose 2a and the composite variable that represents the proportion of infants indicated for revaccination who actually previously were protected.

Across all three scenarios, the 1-dose revaccination strategy was a lower cost option. The results assume that every single vaccination visit occurred as a previously unscheduled visit, so each one included an additional trip to the clinic. The researchers also considered scenarios in which 1, 2, or 3 of those revaccination visits occurred during a previously scheduled well-child visit. Those visits did not include the added cost of the caregiver taking time off work to travel to the clinic, because they were assumed to be previously scheduled visits. The 1-dose revaccination strategy remained the lower cost option across the board. Here is a figure of the two-way sensitivity analyses:



The added protection from the single revaccination dose ranges from 0.0 to 0.9, with the proportion indicated for revaccination who were previously protected ranging from 0.0 to 0.5. The blue area in this figure represents the combinations where the 1-dose revaccination strategy is the lower cost option. The key point to notice from this is where the curve intersects the X axis at 0.45. Basically, for any scenario under any value for the proportion of infants with previous protection, the 1-dose revaccination strategy will be the lower cost option as long as the efficacy for Dose 2a is 0.45 or higher.

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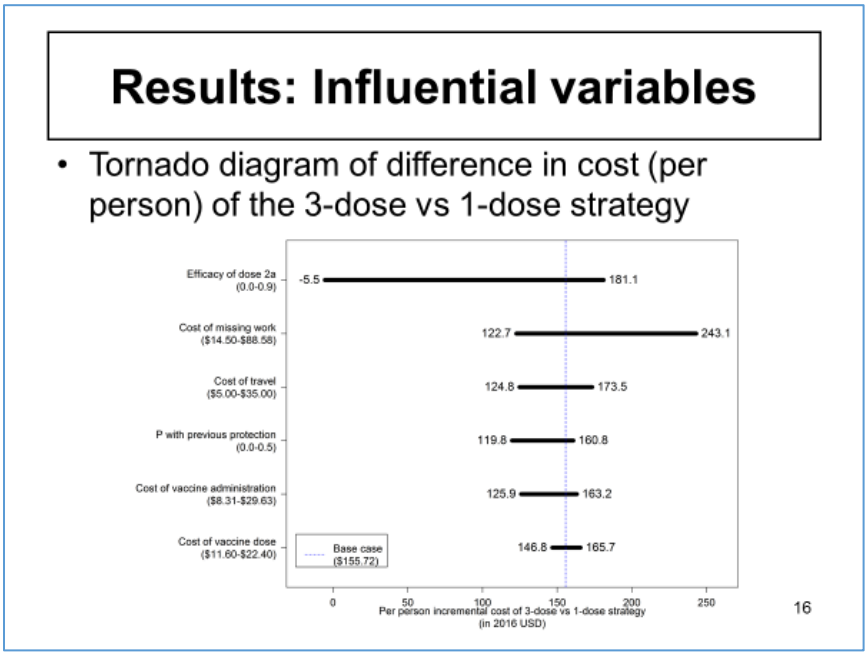
Here is a tornado diagram that displays the difference in cost per person between the 3-dose and 1-dose strategy:



The X axis is the difference in cost per person between the two strategies. The blue vertical line represents that differences under the base case scenario that was presented in the earlier table of results. If the variables on the Y axis individually took on the most extreme values in their possible ranges, the diagram shows how they would affect the individual results in difference in cost per person between the 3-dose and 1-dose revaccination strategies.

To summarize the findings, a 1-dose revaccination strategy reduces costs compared to the current 3-dose strategy across a wide array of scenarios. The 1-dose revaccination strategy is a lower cost option under the assumption that 1, 2, or 3 of the vaccinations occur during a previously scheduled well-child visit.

There are a few assumptions and limitations to this analysis. The assumption was made that the risk of infection was the same in 1-dose and 3-dose revaccination strategies. This assumption was dependent on the proposed structure of the 1-dose revaccination strategy in which individuals who were not protected after Dose 2a went on to receive Doses 2b and 2c, thus having the same experience as everybody in the current 3-dose revaccination strategy. Dropout was assumed to be the same in both strategies. Also assumed was that infants born to mothers infected with HepB were correctly identified and that they received the initial vaccine series and PVST.

In terms of how this work relates to other studies, a recent study assessed the cost-effectiveness of the National Perinatal Hepatitis B Prevention Program (PHBPP) and concluded that the program is a cost-effective use of resources.[1] The authors advocate for an expansion of the program to ensure that it reaches all children born to HepB-infected mothers. In 2015, it was recommended that initial PVSTs occur 1 to 2 months after completion of the initial vaccine series (9 through 12 months of age) for infants born to hepatitis B-infected mothers to ensure PVST test results are representative of protection.[5] Implementing this 1-dose revaccination

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strategy also will help correctly identify protected individuals without them having to undergo a full 3-dose revaccination series [[1]Barbosa, C., Smith, E. A., Hoerger, T. J., Fenlon, N., Schillie, S. F., Bradley, C., & Murphy, T. V. (2014). Cost-effectiveness analysis of the national Perinatal Hepatitis B Prevention Program. *Pediatrics, 133*(2), 243-253. doi:10.1542/peds.2013-0718; [5]Schillie, S., Murphy, T. V., Fenlon, N., Ko, S., & Ward, J. W. (2015). Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. *MMWR Morb Mortal Wkly Rep, 64*(39), 1118-1120. doi:10.15585/mmwr.mm6439a6].

Both this report and this presentation underwent a peer review in accordance with the ACIP Guidance for Health Economic Studies.[14] One question from that review was, "Why weren't revaccination using 2-doses and no-revaccination considered as strategies?" After giving two additional doses, it is more practical to continue with a third dose rather than include another PVST after Dose 2b and possible continued non-response. Single-dose revaccination is most consistent with other recommendations (e.g., for health-care personnel). A non-intervention (no revaccination) strategy was not included because it would be unethical to leave infants who do not respond to the initial vaccine series unprotected [[14]Centers for Disease Control and Prevention (CDC). (2017). Advisory Committee on Immunization Practices: Guidance for Health Economics Studies. Retrieved from https://www.cdc.gov/vaccines/acip/committee/guidance/economic-studies.html].

Discussion Points

Dr. Walter applauded the group for looking at ways to simplify the revaccination regimen. Noting the recommendation to perform a blood draw after receiving two series of vaccines, he wondered whether there were any actionable items if the test is negative and the infant is not seroprotected.

Dr. Nelson responded that the evidence suggests that it does not make sense to then proceed with a third revaccination series. At that point, the parent or family would have to be counseled that their infant is at high risk for infection and should be followed accordingly.

Dr. Schillie (SME) added that there is language to that effect in the draft recommendations. There also is a separate table for management following discreet exposures for unprotected persons, so that would also be applicable to infants who do not develop protective anti-HBs following appropriate vaccination.

Ms. Pellegrini asked to what extent the practitioners in the group thought the second series aligned with well-child visits. It appeared that the third dose of the initial series was in the 9- to 12-month range, while the return for confirmatory testing would be in the 11- to 14-month timeframe depending upon on when the third dose was administered. When restarting the series, she wondered whether this would align with the 15-, 18-, 24-month period or if these families would have to attend extra visits.

Dr. Moore responded that if everything is done on time, the PVST would be done around 9 or 10 months of age. In general, the minimum age for the PVST is 9 months. If they needed to restart, they could do so potentially at their 1-year visit unless they went in early for the first dose. It roughly aligns. She said she could hear all of the Perinatal HepB Coordinators cheering, because the 1-dose option is a huge step forward in terms of being able to close out the follow-up of these children much more efficiently. The most common scenario is the child does not have their PVST done in a timely manner, so many who were protected will wind up

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having a 3-dose series and additional visits although only 1 dose would be needed to demonstrate protection.

Dr. Schillie (SME) indicated that the current recommendation for post-vaccination testing is 9 to 12 months of age, because there are two well-child visits at those points. The recommendation also states that infants who are delayed in vaccine series completion should be tested 1 to 2 months after the final dose of the vaccine series.

Dr. Hunter asked if it would be possible to have an option in the recommendation stating that the testing can be done at 7 to 8 months if the child happens to present at that time, which should result in fewer children falsely testing negative.

Dr. Messonnier pointed out that some of the details are what Perinatal Hepatitis Coordinators need to know when they implement the recommendations. They can try to differentiate the language of the recommendation verses the practical implementation guidance.

Dr. Sun (FDA) asked whether in the WG's review of the literature there were any studies on the population of infants who received the higher dose who essentially failed the first series and had to receive another series of vaccinations.

Dr. Nelson replied that she was not aware of those studies in the published literature. Some studies have been conducted, which are unpublished, that assessed differences in what the total actually was and how that might indicate how the baby might respond. She did not believe that any of the published studies assessed higher vaccine doses.

Dr. Schillie (SME) added that the majority of infants who receive a full second re-dose series respond at the standard dose.

As Dr. Hunter understood it, for the cost analysis to be correct, an assumption had to be made that 45% of the children who received the extra single dose after they were negative for the antibody hepatitis converted to positive.

Mr. Hall confirmed that this interpretation was correct. The estimate for that was based on a couple of smaller studies. It was estimated at about 0.78, with a wide range of variability.

Dr. Duchin (NACCHO) asked whether anything was known about the risk factors for failure to respond to the first series, if the large proportion of infants born to infected mothers who are not ascertained might have higher or lower risk of failure to respond, and whether that would impact the cost-effectiveness calculations.

Dr. Schillie (SME) replied that low birth weight and pre-term birth are influential factors. Prematurity is a risk factor for non-response, and some limited data suggest that male infants might have a slightly lower response than female infants.

Dr. Nelson added that there may be other factors they are unaware of. They used wide ranges in the sensitivity analysis down to 0.0 in some cases.

Dr. Thompson asked whether the WG had an opinion as to which of the three scenarios is the true scenario, or how those scenarios should be interpreted in the context of what the evidence suggests.

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Mr. Hall responded that they tried to create three very drastic scenarios. The initial scenario, A, assumes a very high efficacy of the first initial series and that everybody receives their PVST on time. That scenario has the highest threshold value for Dose 2a. That is where the 0.45 comes from. Scenario B assumptions were made to be more realistic using data about the proportion of infants in the perinatal HepB prevention program who have a delayed PVST, and the proportion of those who do have antibodies. He would say that Scenario B is probably the most reflective of what would be expected. Scenario C had a very low initial efficacy level of that first vaccine series that basically incorporated all infants who were not receiving the initial vaccine series. It assumed that a lot of them had an initial delayed PVST, and that a similar proportion of those had waned antibodies.

Revaccination for Unprotected Infants Born to HBsAg-Positive Mothers

Noele Nelson, MD, PhD, MPH
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Nelson reported that the WG convened for two teleconference meetings on this topic and reached consensus regarding the proposed update to the hepatitis vaccine statement regarding single-dose revaccination for infants born to HBsAg-positive mothers. They considered the pros and cons of single-dose revaccination verses 3-dose revaccination. The pros of the single vaccine dose are that there are fewer vaccine doses for most infants, there is a short duration of case management, and it is less costly overall. The cons are that those infants who do not respond to the single dose vaccination would need an additional blood draw, and provider/parent decision-making would be necessary because there would be two options (1-dose revaccination and 3-dose revaccination). The existing language states that, “HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine” [[1] Schillie S, et. al. MMWR Morb Mortal Wkly Rep. 2015 Oct 9;64(39):1118-20; Mast EE, MMWR Recomm Rep. 2005 Dec 23;54(RR-16):1-31]. She then presented the revised language presented for a vote as follows:

- HBsAg-negative infants with anti-HBs <10 mIU/mL should be re-vaccinated with a single dose of hepatitis B series and postvaccination serologic testing should be performed 1 to 2 months after the final dose of vaccine.

- Alternatively, these infants may be revaccinated with a single dose of hepatitis B vaccine and retested 1 to 2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine, followed by testing 1 to 2 months later.

- Available data do not suggest a benefit from administering additional hepatitis B vaccine doses to infants who have not obtained anti-HBs levels ≥10 mIU/mL following receipt of two complete hepatitis B vaccine series.

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Discussion Points

Dr. Romero made a motion to accept the language as proposed, which Dr. Moore seconded. The discussion then continued.

Dr. Belongia was unclear about the benefit of having two options. One of the cons mentioned was that parents/providers would have to decide between two options, and the cost-effectiveness analysis made the assumption that the outcomes would be the same for the two strategies. The only difference is a cost issue not an outcome issue. The proposed option incorporates the 3-dose series because if the infant is below 10 mIU/mL, the 3-dose series would be given anyway. As stated, the first bullet of the proposed language added complexity without any additional benefit.

Dr. Kempe concurred, emphasizing that this is likely to be confusing to providers. They should have a blood draw anyway after the second 3-dose series, so this is not necessarily causing another blood draw.

Dr. Nelson clarified that an additional blood draw would be required for infants who are revaccinated with one dose but still do not respond. That is the primary con.

Dr. Walter asked if the suggestion was to flip the bullets in the alternate language.

Dr. Nelson asked for clarity regarding whether that meant the revised language would simply state that they should be revaccinated with a single dose of hepB vaccine and retest at 1 to 2 months later. Basically, the second bullet would replace the first.

Dr. Bennett called on Dr. Reingold to comment on the thinking of the WG in bringing this statement forward in its current form, and whether there were any specific objections to making this a recommendation.

Dr. Reingold replied that it was basically viewed as an evolution and providing two options rather than a stark change.

Dr. Nelson added that there were no specific objections. However, the WG did not specifically address the alternative of only single-dose revaccination. It was not presented as such in the WG calls.

Dr. Moore proposed that the preferred option be the single revaccination dose, followed by PVST, with an alternate option to give the 3-dose series if the single revaccination strategy is not chosen. Dr. Kempe seconded the motion.

Dr. Bennett repeated the amendment on the floor to reverse the proposed revised language such that the primary strategy would be single-dose, with an alternative of the full 3-dose series.

Dr. Riley asked for clarification regarding whether the pediatric outcomes were the same for both strategies in the cost-effectiveness analysis.

Dr. Schillie (SME) replied that they would receive 6 doses regardless, so there would not be any reason at all to think that the outcomes would be different.

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Dr. Nelson added that there is always a risk of infection if the infant does not respond, but that is not expected to differ between the two scenarios. If they respond after 1 dose, they will be less likely to be infected than if they take 3 more doses to respond.

Dr. Atmar thought the initial discussion pertained to including only what was in the second bullet and not even having the first bullet as an alternative.

Dr. Moore clarified that her motion was to leave the 3-dose series as an alternative as part of the evolution of the strategy, versus recommending a sharp change in the recommendation. For example, a family may prefer to avoid a blood draw as they are quite difficult on the child and the family. A back-up strategy is not inferior in any way, and still should be considered acceptable.

Dr. Romero clarified that some parents might object to an additional blood draw on their infant and, therefore, would prefer a straightforward 3-dose series. That has to remain as an option for those parents who have very strong feelings about the number of invasive procedures done to their child.

Dr. Walter pointed out that there also may be logistical issues in terms of getting the blood draw, such as actually getting the child there.

Dr. Byington (AAP) indicated that the AAP would favor the single-dose as the preferred option. Only if that fails would they support the 3-dose option. This would be easier for families overall.

Dr. Nelson presented the following revised language for a vote:

- ❑ HBsAg-negative infants with anti-HBs <10 mIU/mL should be re-vaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1-2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine, followed by PVST 1-2 months after the last dose.
    - ➢ Based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs ≤10 mIU/mL may instead be revaccinated with a second, complete 3-dose series, followed by postvaccination serologic testing (PVST) performed 1-2 months after the final dose of vaccine.
- ❑ Available data do not suggest a benefit from administering additional HepB vaccine doses to infants who have not attained anti-HBs ≥10 mIU/mL following receipt of two complete HepB vaccine series.

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Public Comment

Christina Hildebrand
A Voice for Choice

I am glad to see a reduction of vaccines given to babies. I know that previously there was a 3-dose series. I assume, but I can't assume that the—well, I should go back. The information that was presented today was based on the efficacy of the vaccine as well as the cost of the vaccine, but it didn't go into the risks of the vaccine or look at the outcome of the babies who were not given these doses and what happened in those families. So, I just want to make sure—I just want to comment that, you know, the risk piece of this is also an important piece. The other piece which I find disturbing, which I mentioned the last time I was here, is the fact that this is based on very, very small base sizes. So, you know, you've got 15 babies that you've looked at and you haven't looked at a larger sample size. And I would hope that any recommendation is based on more than 15 people, or 15 babies, and that, you know, I understand that you're voting on this today, but in the future, I would hope you would look at a larger base size. I understand that the percentage of outcome is very high, and so being a statistician, I understand that that would likely replicate and it would likely, you know, be a positive outcome and come to the same conclusion. But, having small base sizes is something that, you know, as a statistician you don't do anything with 15 people other than qualitative responses. You don't base decisions on that. That was my public comment. Thank you.

Vote: Hepatitis B Vaccine Recommendation

Dr. Romero initially made a motion to accept the revised Hepatitis B Vaccine Recommendation language as presented for a vote by Dr. Nelson. Dr. Moore seconded the motion. The motion carried unanimously with 13 affirmative votes, 0 negative vote, and 1 abstention. The disposition of the vote was as follows:

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

Vote: Amended Hepatitis B Vaccine Recommendation

Although an initial vote was made on the above motion, following additional discussion, Dr. Moore motioned to approve the Hepatitis B Vaccine Recommendation as amended such that the preferred option would be the single revaccination dose, followed by PVST, with an alternate option to give the 3-dose series if the single revaccination strategy is not chosen. Dr. Kempe seconded the motion. The motion carried unanimously with 13 affirmative votes, 0 negative vote, and 1 abstention. The disposition of the vote was as follows:

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

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VFC Resolution

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

Dr. Santoli indicated that the purpose of this resolution was to clarify recommendations related to dosing intervals and revaccination. The eligible groups are all children and adolescents from birth through 18 years of age.

The tables below list the acceptable vaccination schedules for children and adolescents from birth through 18 years of age, for which there is no change:

Table 1, Part I: Infants

		Single antigen vaccine		Single-antigen[1] and combination vaccine[2,3]	
Birth weight	Maternal HBsAg status	Dose	Age	Dose	Age
≥2000 g	Positive	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Unknown	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Negative	1	Birth (≤ 24 hours)[1]	1	Birth (≤ 24 hours)[1]
		2	1-2 months	2	2 months
		3	6 -18 months	3	4 months
				4	6 months

Table 1, Part 2: Infants

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

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

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Table 2: Children and Adolescents

Age	Schedule[1, 6]
Children (1 through 10 years)	0, 1, and 6 months[2] 0, 2, and 4 months[2] 0, 1, 2, and 12 months[2,4]
Adolescents (11 through 18 years)	0, 1, and 6 months[2] 0, 1, and 4 months[2] 0, 2, and 4 months[2] 0, 12, and 24 months[2] 0 and 4-6 months[3] 0, 1, 2, and 12 months[2,4] 0, 7 days, 21-30 days, 12 months[5]

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

This clarification is added to address confusion related to single antigen versus combination vaccine schedules. In some cases, more than 3 doses are administered:

Interrupted schedules and minimum dosing intervals

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

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

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

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

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This update reflects the discussion ACIP just participated in related to single dose revaccination:

Revaccination

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

- Infants born to HBsAg-positive mothers
  - HBsAg-negative infants with anti-HBs <10 mIU/mL should be re-vaccinated with a single dose of HepB vaccine and receive post vaccination serologic testing 1-2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine, followed by PVST 1-2 months after the last dose.
    - Based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete 3-dose series, followed by post vaccination serologic testing (PVST) performed 1-2 months after the final dose of vaccine.
- Hemodialysis patients. For hemodialysis patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.
- Other immunocompromised persons. For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. When anti-HBs levels decline to <10 mIU/mL, annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.
- Persons with postvaccination serologic testing results that do not demonstrate protection. This includes children and adolescents through age 18 years who are chronic hemodialysis patients, HIV-infected, otherwise immunocompromised (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), or sex partners of HBsAg-positive persons. Persons in these groups found to have anti-HBs concentrations of <10 mIU/mL after the primary vaccine series should be revaccinated.

Recommended Dosage

Refer to product package inserts.

Contraindications and Precautions

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

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Statement Regarding Update Based on Published Documents

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

Vote: Vote: VFC Resolution for Hepatitis B Vaccine Recommendation

Dr. Hunter motioned to approve the VFC resolution for the Hepatitis B Vaccine Recommendation. Ms. Pellegrini seconded the motion. The motion carried unanimously with 13 affirmative votes, 0 negative vote, and 1 abstention. The disposition of the vote was as follows:

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

Influenza

Introduction

Chip Walter, MD
Chair, Influenza Work Group

Dr. Walter reminded everyone that during the October 2016 meeting, there were two sessions, including an influenza epidemiology and surveillance update and a summary of the clinical data for AFLURIA® Quadrivalent vaccine in adults, which was licensed for persons 18 years of age and older in August 2016.

Since the October 2016 ACIP meeting, the WG has engaged in calls twice a month. The following is a list of highlights from the calls:

- Updates from MedImmune regarding investigations and planned studies related to the lower than expected effectiveness observed with FluMist® against H1N1pdm09 strains during the 2013-2014 and 2015-2016 seasons in the US

- Updates from Seqirus regarding their pediatric development program for AFLURIA® Quadrivalent implications for use in children
  - Their current trivalent vaccine is licensed in the US for those 5 years of age and older
  - During the 2010-2011 timeframe, ACIP recommended that the vaccine be given only to those 9 years of age and older, given that higher rates of fever and febrile seizure were observed in children in Australia during the 2010-2011 season

- Ongoing discussions regarding the effectiveness of Fluzone® High-Dose (HD)

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The topics for the February 2017 session included an influenza surveillance update, influenza VE update, AFLURIA® Quadrivalent vaccine update, and a FluMist® update.

Influenza Surveillance Update

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

During this session, Ms. Brammer provided a brief update on influenza activity for the 2016-2017 season. As of the week ending February 11, 2017, the peak influenza positivity so far was during Week 6 at 24.2% positive. This level is similar to the peak for last season. Thus far from clinical laboratories, 83% of the viruses have been influenza A. Data from public health laboratories show that influenza A (H3N2) viruses are the predominant virus this season. So far, 88% of the viruses tested by the public health laboratories have been influenza A viruses. Among those that were subtyped, 98% were H3N2 viruses. There have been some reports of influenza B, which seemed to be increasing as would be expected for this point in the season. Cumulatively for the season, 56% of the influenza B viruses that have had lineage testing performed have been from the B Yamagata lineage. Prior to the start of 2017, B Victoria viruses had been predominant.

In terms of genetic information on the viruses circulating, the vast majority of viruses have been H3N2. In terms of the breakout of those viruses genetically, 96% tested by public health laboratories were in the 3C.2a genetic group, which is the same genetic group that the vaccine strain belongs to (A/Hong Kong/4801). The remaining 4% were in the 3C.3a group. A/Switzerland, last year's virus, is a representative of that group. All of the H1pmd09 were in the 6B.1 genetic group, all of the B Victoria were in the V1A genetic group, and all of the B Yamagata were in the Y3 genetic group.

In terms of the antigenic characterization of the viruses, all 74 of the A(H1N1)pdm09viruses tested using ferret post-infection antisera were A/California/07/2009-like, the H1N1 component of the 2016-2017 vaccine. Among the A(H3N2) viruses, 311 of the 322 (96.6%) were antigenically characterized as A/Hong Kong/4801/2014-like, the H3N2 component of the 2016-17 vaccine. Among the B/Victoria linage viruses, 71 of 78 (91%) were antigenically characterized as B/Brisbane/60/2008-like, which is included in both quadrivalent and trivalent influenza vaccines for the 2016-2017 season. Among the B/Yamagata lineage, all 67 were antigenically characterized as B/Phuket/3073/2013-like, an influenza B virus included in the quadrivalent influenza vaccines for the 2016-2017 season.

Regarding influenza-like illness (ILI) as reported through outpatient surveillance, 5.2% of visits during the week ending February 11th were for ILI. This is well above the baseline of 2.2%. All 10 HHS regions were above their region-specific baselines. For that week, all regions except 9 and 10 (West Cost) continued to increase. The following map shows ILI activity level for states:

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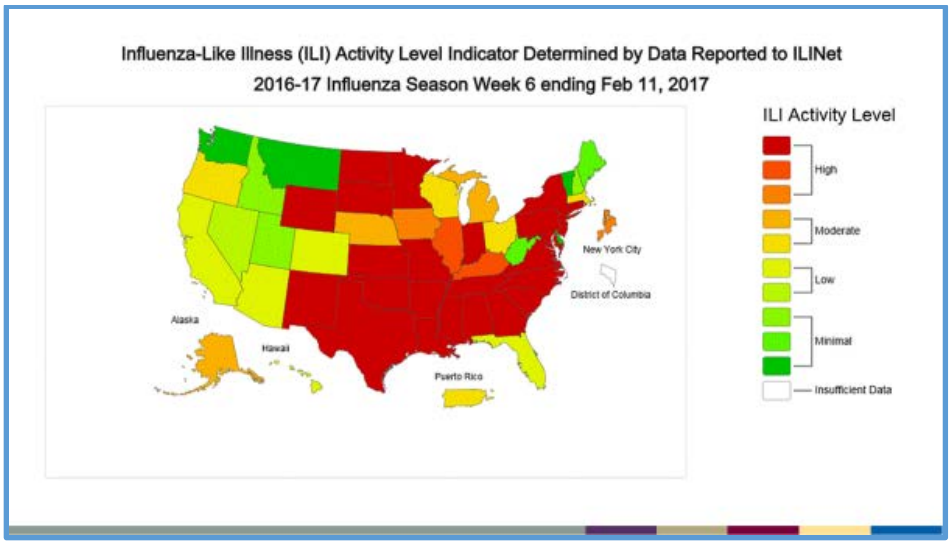

Numerous states were reporting high ILI activity, including 28 states and New York City at high activity and another 7 in Puerto Rico at moderate activity. The Western portion of the US was at a lower activity level, which likely reflects the fact that many of those states, particularly in the Northeast, may already have experienced peak activity and may be declining.

In terms of hospitalization data report through FluSurv-NET, which covers about 9% of the US population, the overall laboratory-confirmed associated hospitalization rate was 29.4/100,000 cumulative through the week ending February 11th. That rate was highest for people 65 years of age and older at 136.6/100,000 followed by people 50 to 64 years of age at 28.5/100,000.

Based on data from the National Center of Health Statistics (NCHS) mortality surveillance system as of the week ending January 28th, 7.8% of deaths filed had pneumonia or influenza listed on the death certificate. This is above the epidemic threshold of 7.5% for that week and was the fourth week above that threshold. This is considered to be excess influenza-associated mortality. Thus far, 29 influenza-associated laboratory-confirmed pediatric deaths have been reported.

Regarding the schedule for vaccine strain selection for the 2017-2018 influenza season, the WHO Consultation on the Composition of Influenza Virus Vaccines for Use in the 2017-2018 Northern Hemisphere influenza season was scheduled for February 27-March 1, with their announcement of their decision anticipated on March 2nd. The FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) was scheduled to meet on March 9, 2017 to make the US-specific vaccine strain decision.

In summary, influenza A(H3N2) viruses have predominated during the 2016-2017 season. However, influenza B activity may be starting to increase as would be anticipated late in the season. So far, influenza activity has been moderate but may not have peaked yet. The majority of circulating stains are similar to those contained in the 2016-2017 vaccine. Vaccine virus recommendations for the 2017-2018 influenza season should be made in the next two weeks.

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Vaccine Effectiveness Update

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

Dr. Flannery reported interim estimates of 2016–2017 seasonal influenza VE against medically attended influenza from the US Flu VE Network. The interim estimates were published in the *Morbidity and Mortality Weekly Report* (*MMWR*) on February 17, 2017. These data come from five US Flu VE Network. The sites and principal investigators are as follows:

- Baylor Scott and White Health (Manju Gaglani)
- Group Health Cooperative (Mike Jackson, Lisa Jackson)
- Marshfield Clinic Research Foundation (Ed Belongia, Huong McLean)
- University of Michigan (Arnold Monto, Emily Martin)
- University of Pittsburgh (Rick Zimmerman, Tricia Nowalk)

The methods are the same as have been used for estimates in the past. The system enrolls outpatients 6 months of age and older with acute respiratory illness defined as having acute respiratory illness with cough of less than 7 days duration. These data include enrollment from November 28, 2016 through February 4, 2017. One of the sites started as early as November, with others starting in January. These data come from a test-negative design. Vaccination odds are compared among influenza reverse transcriptase polymerase chain reaction (RT-PCR) positive cases and RT-PCR negative controls. Vaccination status for the interim estimates is receipt of at least one dose of any 2016–2017 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. One site has medical records in registries only for this interim estimate, two sites have a mixture of medical records and self-report, and two sites that use self-report; whereas, for the end of season estimates, it is documented or plausible self-report. The analysis uses a logistic regression of (1 – adjusted OR) x 100% for VE. The variables used to adjust odds ratios include study site, age, self-rated general health status, race/Hispanic ethnicity, interval (days) from onset to enrollment, and calendar time.

Similar to the surveillance data, the majority of cases for patients enrolled in the network were H3N2. Overall, 24% (744) of the 3144 patients enrolled during the time period of the interim analysis tested RT-PCR positive and 76% (2400) tested influenza RT-PCR negative. There was some B/Yamagata predominantly among the B lineage seen for patients enrolled. About 30% of those enrolled were positive for influenza in more recent weeks.

The overall estimate for all influenza A and B includes all ages. The percentage vaccinated was 45% among the influenza positives and 55% among the influenza negatives. The VE was 48% (CI 37% to 57%). Dr. Flannery stressed that it was too early at this stage to make much of the differences in some of the point estimates by age, though they hope to have better estimates to determine whether VE differs by age group as has been observed in some previous seasons in the end of season estimates. The estimates also were available by H3N2 specifically, which was very similar to the overall estimate. The adjusted VE against H3N2 for all ages was 43% (CI 29% to 54%). There was some variability in the point estimates by age, but only two of the age groups were statistically significant at this point, the 6 months through 8-year-old group at 53% and the 50 through 64-year-old group at 50%. Overall for all ages against influenza B, the VE was 73% (CI 54% to 84%].

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In summary, the interim results for 2016–2017 season through February 4, 2017 indicate VE of 48% against medically attended influenza. This interim estimate is similar to previous seasons when vaccine was well-matched to circulating influenza viruses. There was significant protection against circulating influenza A(H3N2) and B viruses (predominantly B/Yamagata), but VE was not estimated against H1N1pdm09 or B/Victoria due to the small number of cases. Enrollment continues, so end-of-season VE estimates may differ from interim estimates. VE was 43% against A(H3N2), similar to antigenically matched H3N2 viruses. VE was 39% in both 2011-2012 and in 2012-2013. Both of those seasons were judged to be antigenically matched, although in 2012-2013 it was noted that there were egg adaptations in H3N2 viruses that may have affected the VE.

However, a meta-analysis[1] of test-negative VE studies similar to this study looking at VE over a number of seasons found an H3N2 VE weighted average of 33% (26% - 39%). The 43% estimate can be said to be similar to those estimates of H3N2 effectiveness over multiple seasons, which suggests that there is a problem for VE against H3N2 in relation to slightly higher effectiveness than seen against A(H1N1)pdm09, which was an average of 61% in the same meta-analysis, and B viruses with an average of 54%.[1] It is not clear why there is a problem with H3N2 viruses specifically. There are more frequent updates to the H3N2 component, which reflects more rapid antigenic change among H3N2 viruses. Also noted is that the candidate A(H3N2) vaccine viruses are more often affected by egg-adapted changes that result in antigenic difference after the adaptation to growth in eggs. CDC is working on methods and approaches to improve VE against A(H3N2) viruses and better candidate viruses [[1] Belongia et al. Lancet Infect Dis, 2016].

Discussion Points

Regarding the change in the antigenic nature of the vaccine virus in the egg as possibly being a reason that H3N2 VE is lower, Dr. Hunter asked whether there were any data about vaccines administered that have not been produced in egg to know whether they work better against H3N2.

Dr. Flannery responded that there are not yet enough data to be able to have an estimate of VE of either the recombinant or the cell-based vaccine from the CDC network. CDC is dependent on uptake of those vaccines, which has not reached a level at which they have been able to estimate the effectiveness of those vaccines. End-of-season estimates will include vaccine-specific or vaccine type estimates, but being able to get a VE will still be dependent upon uptake.

Dr. Reingold asked whether there were any estimates of vaccine coverage for this season in various groups.

Dr. Flannery replied that estimates through November were published and are included in the *MMWR* on VE. The key question regards the live attenuated influenza vaccine (LAIV) recommendation and effective coverage in children. It is too early to know. The Immunization Services Division (ISD) is doing some work on that. The point estimate for young children is slightly lower than it was in November for the previous season by about 5 percentage points at about 40%.

Dr. Messonnier added that there are some newer data, which would be presented later in the session.

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Dr. Duchin (NACCHO) asked whether any assessment is being done of sequence differences between the vaccine strain selected and the strain produced after egg manufacturing as a way to determine what might explain the reduced VE.

Dr. Katz replied that in the US, the FDA does not require that information. However, in Europe there is a pilot study to examine the sequences after the viruses have been propagated during the vaccine manufacturing process. The regulatory requirements are different in the US and are very stringent. The FDA does an antigenic analysis of the seed virus that goes into the manufacturing process, and that can be passaged only one or two more times. They ensure that the egg propagated vaccine seed virus is antigenically similar within 2-fold to the candidate vaccine virus that the manufacturers receive. They send their seed that they have passaged several times to optimize yield back to the FDA, and the FDA compares the two. This is with ferret antisera raised to the vaccine virus. There are different approaches in Europe.

AFLURIA® Update

Gregg C. Sylvester, MD, MPH
Head of Medical Affairs
Seqirus™ A CSL Company

Dr. Sylvester reviewed the comprehensive investigation on 2010 AEs in the Southern Hemisphere CSL 2010 SH trivalent influenza vaccine (TIV), as well as the staged clinical development program for AFLURIA®. The four trials in the staged clinical development program for AFLURIA® include the following, though Dr. Sylvester focused only on the first and third trials during this presentation given that they were the ones germane to the discussion earlier in the morning pertaining to fever rates:

- Children 5 years <9 years of age: Modified TIV Safety Phase IV
- Adult ≥18 years of age: QIV Immunogenicity & Safety Phase III
- Children 5 years of age to <18 years of age: QIV Immunogenicity & Safety Phase III
- Children 6 months of age to 59 months of age: QIV Immunogenicity & Safety Phase III

AFLURIA® is a purified, inactivated, split virion influenza vaccine. It has been manufactured in Parkville, Australia for the last 40 years. There are two formulations, a thimerosal-free 0.5mL pre-filled syringe and a thimerosal-containing 5mL multi-dose vial. It has an interesting licensure history. In November 2007, CSL was granted approval for the TIV in those ≥18 years. In 2010-2011 season, there was a licensure down to 6 months of age and above. The vaccine was never brought into the US, so in December 2011, the FDA revised the licensure and now it is licensed for the TIV for those 5 years of age to <18 years of age. The FDA approve QIV in those ≥18 years of age in August 2016, which Dr. Sylvester presented on to ACIP in October 2016. A Supplemental Biologics License Application (sBLA) has been submitted to the FDA for use of QIV in those 5 years of age to <18 years of age.

The prescribing information for AFLURIA® is that it is not to be used in children less than 5 years of age. However, ACIP recommends that other age-appropriate influenza vaccine should be used in children through the age of 8 years. There is a different in the licensure versus the recommendation, which is due to the fact that there was an unexpected increase in reports of fever and febrile seizures primarily in children less than 5 years of age compared to previous seasons in the Southern Hemisphere using the CSL 2010 SH TIV. Also noted was that there were increased reports of fever in children 5 years of age to less 9 years of age.

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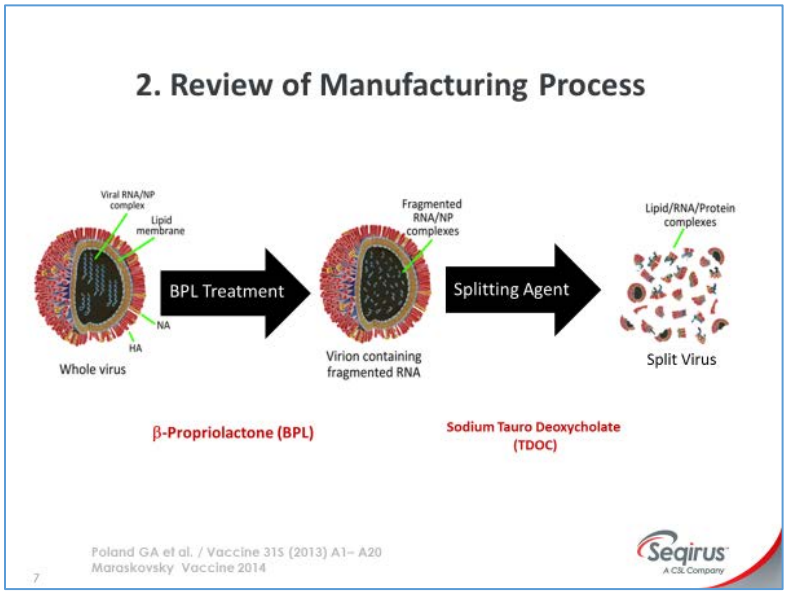
Dr. Sylvester described three discrete programs looking at a systematic and comprehensive investigation:

- Clinical Safety Review
  - Characterize the AEs
  - Identify risk factors and at-risk populations
- Manufacturing & Quality Review
  - Assessment of safety and manufacturing process
  - Assessment of quality (purity and potency)
- Scientific Research Investigation
  - Explore potential indirect surrogate measures (*in vivo* and *in vitro* tests)

The safety review examined the unexpected increase in fever and febrile seizures observed in the Southern Hemisphere in 2010. It would be rare to see a febrile seizure over the age of 5 due to the stage of hypothalamic development in young children. Febrile seizures typically occur in children between the ages of 6 months and 5 years of age. The peak age is about 24 months of age, and they can occur up to 5 years of age. In the Southern Hemisphere, 5 to 9/1000 children vaccinated had a febrile seizure. More than 80% occurred within the first 12 hours of receiving the vaccine. The average duration following seizure onset was 2.5 minutes, with a range from 1 to 6 minutes. In the US, this occurred in a predominance of males at 2/3 compared to 1/3 in females. The highest fever recorded was 40.8° C but the mean was 39° C. There also were increased fever reports in children 5 to less than 9 years of age. Within a month of this investigation, the regulatory agency in Australia, the recommending body in Australia, and the company CSL withdrew the vaccine but continued post-marketing surveillance throughout the entire season. At that time, FDA, CDC, and ACIP were notified. As early as July 2010, the recommendation was made on AFLURIA®.

Dr. Sylvester showed the following schematic of the CSL manufacturing process, asking everyone to focus on the two arrows:



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After the whole virus is grown in egg, there is an inactivation state, the β-propiolactone (BPL) treatment. That inactivates the vaccine, creating the virion in the middle, which contains the fragmented ribonucleic acid (RNA). The splitting agent is created by sodium tauro deoxycholate (TDOC), which creates the lipid/RNA complexes. Dr. Sylvester focused further on the TDOC and the lipid RNA complexes.

A detailed review was made of all manufacturing aspects starting at the seed all the way to fill and finish, including raw materials, facilities, utilities, and processes. No deviation or change was found from previous seasonal formulations. All batches met specification and there was no evidence of batch-specific issues. Laboratory testing ruled out chemical contamination, bacterial contamination, and viral contamination. There was no evidence of agglomeration as a contributing factor. However, there was one major change of note. The WHO had recommended three new virus strains for inclusion in the 2010 influenza vaccines for the Southern Hemisphere. There was a complete strain change for TIV in 2009. The strains for those two years were:

TIV 2009

- A/Brisbane/59/2007 (H1N1) – Like
- A/Uruguay/716/2007 (H3N2) – Like
- B/Florida/4/2006 – Like

TIV 2010

- A/California/7/2009 (H1N1) – Like
- A/Perth/16/2009 (H3N2) – Like
- B/Brisbane/60/2008 – Like

The scientific investigation was then performed. An attempt was made to find an animal model that could create febrile seizures. Non-human primates, ferrets, rabbits, and newborn rats were considered. However, febrile seizures were not induced in any of the *in vivo* models examined with any TIV. Therefore, assays were created for *in vitro* models. The published literature suggested that increased cytokine levels were observed after febrile seizures. Thus, cytokine and chemokine models were explored as correlates of in vivo pyrogenicity. Mapping these cytokines and chemokines *in vitro* may act as an indirect surrogate measure of the reactogenic potential of the TIVs. CSL 2010 SH TIV was found to stimulate the release of cytokines and chemokines in whole blood assays more robustly than previous CSL TIVs or other manufacturers' TIVs. The difference between the CSL 2010 SH TIV and other TIVs suggested that the manufacturing process may have played a role. The difference between the CSL 2010 SH TIV and previous CSL TIVs suggested that the new influenza strains may have played a role.

The investigation revealed that the CSL manufacturing process resulted in more residual lipid and RNA complexes with the CSL 2010 SH TIV than other licensed influenza vaccines. These complexes induced a stronger than expected inflammatory signal. It turned out that the splitting agent, or TDOC, plays a key role in the number of lipid/RNA complexes. The higher concentration of TDOC and lower reduction of lipid/RNA complexes resulted in lower reduction in the assays or in the signal. By increasing the concentration in TDOC levels, CSL showed that there was a significant reduction in the inflammatory response, shown in these two graphs:

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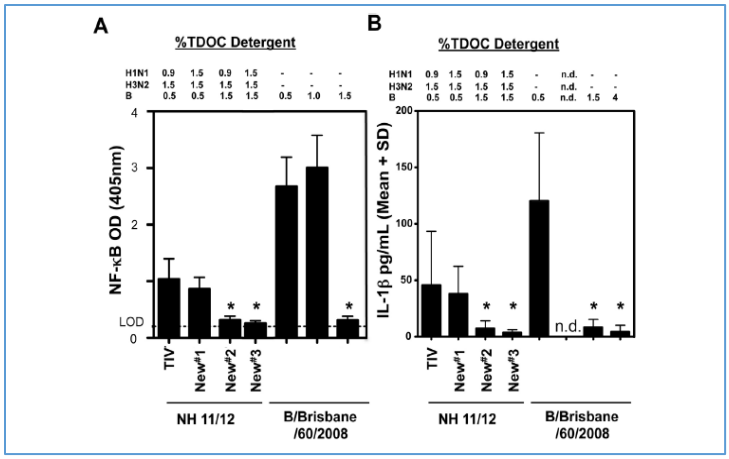

The two graphs represent two assays. The standard TIV was split for A(H1N1) at 0.9%, H3N2 at 1.5%, and B at 0.5%. The inflammatory signal can be seen on both of the above assays. H1N1 was then increased to 1.5% and H3N2 and B were left the same (New #1). That resulted in a reduction in the pyrogenicity. Then H1N1 was 0.9% and H3N2 and B were 1.5% (New #2), which resulted in a marked reduction. There was a belief that B was creating the AEs. Then all three were assessed at the concentration of 1.5% (New #3) within the manufacturing process allowance, which showed an even further reduction. These *in vitro* models demonstrated that lipids and degraded RNA fragments "preserved by the standard TDOC manufacturing process" as well as the three new strains were the contributing factors of the CSL 2010 SH TIV pediatric AE profile. The investigation demonstrated that increasing the levels of TDOC attenuated the pro-inflammatory signals *in vitro*. These conclusions led to the staged approach for a new clinical development program for AFLURIA®.

The Pediatric Phase 4 Safety Study focusing on children 5 years to <9 years of age was modified within registered conditions because the B strain was split at 1.5% TDOC. There were 400 subjects in whom safety and tolerability were evaluated. Hopefully, the results will inform the QIV pediatric clinical development program and can be used as an indirect comparison with historical data and comparator QIV. The comparator QIV is a licensed US vaccine. This study showed an overall fever rate for the CSL TIV modified vaccination in children 5 years of age to <9 years of age was 8.2%, with the vast majority being mild or moderate at <39° C compared to the reference QIV, which was 9.2%. The confidence intervals overlap and the fever rates are similar to the licensed QIV product. By increasing the TDOC in the B strain, the point estimates are now much lower than the historical TIV as well as the comparator QIV. The confidence limits do overlap. In terms of severe fever rates, fever intensity of >39° C, the point estimates hover at about 2% and once again, below the comparator QIV and historic TIV from past experience at CSL.

The conclusion was that the CSL TIV fever rates observed in this study were similar to the comparator QIV vaccine in children 5 years of age to <9 years of age. Due to this, the TDOC concentrations are now incorporated for splitting all A and B strains. This informed the staged approach for the QIV program. As mentioned earlier, the FDA has already approved the licensure for the QIV in those ≥18 years. The Phase III Study for those 5 years to <18 years of age has been submitted to the FDA, with the hope that it will be licensed in 2017. The Phase III Study in those 6 months to 59 months of age is now an ongoing study.

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The trial in children 5 years to <18 years of age was an immunogenicity as well as a safety trail, and all 8 co-primary endpoints were met. AFLURIA® QIV demonstrated non-inferior immunogenicity for all strains to the comparator QIV (Fluarix® QIV) in children 5 years to <18 years of age. Descriptive secondary immunogenicity endpoints overall, and by age subgroups (5 years to <9 years, and 9 years to <18 years inclusive) were robust and were consistent with expectations for these age groups, and this is similar with the comparator QIV.

AFLURIA® QIV following vaccination were similar to the comparator QIV in both age groups, with 5 years to <9 years of age at 4.5% (95% CI: 3.2, 6.1) compared to 3.6% (95% CI: 1.8, 6.6), and in 9 years to <18 years at 2.1% (95% CI: 1.3, 3.4) compared to 0.8% (95% CI: 0.1, 2.7). The vast majority of fever in both vaccines were mild to moderate. In terms of historical fever rates, the point estimates are even lower than the TIV study with 400 subjects and historical TIV. For severe fever, AFLURIA® QIV hovers just over 1% for >90° C and slightly higher than the comparator, but well within the same confidence limits.

In summary, AFLURIA® TIV and QIV safety profiles in those 5 years to <18 years of age is acceptable. Fever rates for those 5 years to <9 years of age are similar to the comparator and less than historical vaccines. Both AFLURIA® TIV and QIV will be offered in the US during the 2017-2018 influenza season. As mentioned, the sBLA for the 5 years of age through 18 years of age was submitted in 2016 and is anticipated to be licensed before the end of the year.

Discussion Points

Dr. Belongia asked whether TDOC is routinely used for split virus vaccines across manufacturers, and what kind of guidance the FDA provides to manufacturers in terms of the TDOC concentration.

Dr. Sylvester replied that every vaccine manufacturer has different proprietary methods. TDOC is used only for AFLURIA® and not in other influenza vaccines.

Dr. Sun said that he had nothing to add, but that if the other manufacturers wished to comment on their splitting agents, they may do so.

Dr. Stephens noted that it raised the question about mechanism. He wondered if Dr. Sylvester could offer any more specificity about how they are modifying the immune response by increasing the TDOC and changing the lipid and RNA fragment concentrations.

Dr. Sylvester responded that that what they do know is that when TDOC was at 0.5% for the B strain, there was a lot of residual lipid that was connected to the messenger RNA (mRNA). Increasing the TDOC clears out much of the lipid component that was believed to be causing much of the AEs and leaves the RNA, and there is still nice immunogenicity.

Dr. Walters asked whether there were plans to continue the assessments on an ongoing basis as vaccines are produced and differ annually.

Dr. Sylvester replied that the two assays they created have been validated and are now part of the manufacturing process, so that as the four strains are created, they are tested throughout the system and at the end product to ensure that the reactogenicity is much lower than previously.

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Based on the data, Dr. Foster (APhA) asked whether the WG was considering removing the recommendation for those 5 years of age to <8 years of age.

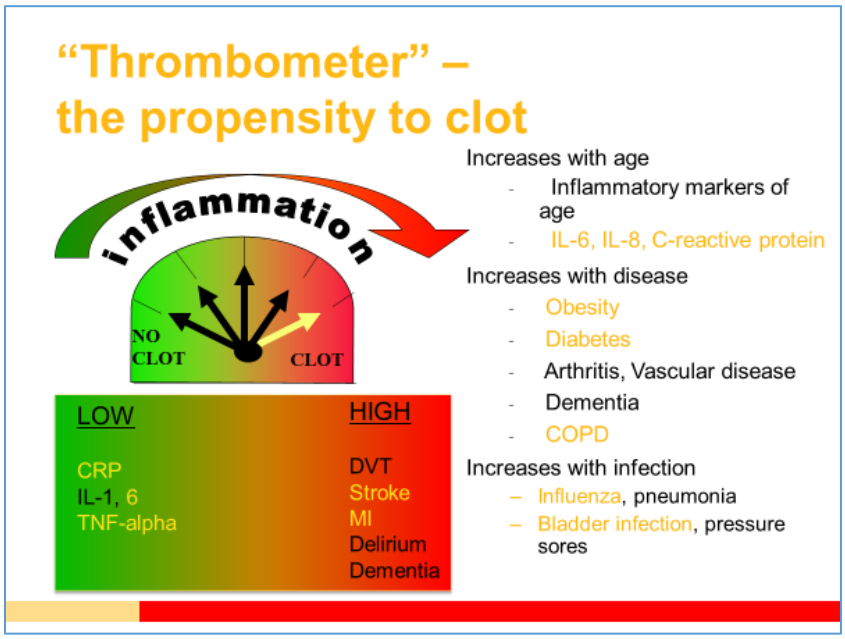
Dr. Cohn indicated that a summary of the WG discussion would be presented later in the session.

Fluzone® High-Dose (HD) Update

Stefan Gravenstein, MD, MPH, CMD
Professor of Medicine
Director, Center for Geriatrics and Palliative Care
University Hospitals and Case Western Reserve University
Adjunct Professor of Medicine, Brown University
Clinical Director, Healthcentric Advisors

Dr. Gravenstein presented results from a Fluzone® HD versus standard-dose (SD) cluster randomized trial in US long-term care facilities (LTCF). He said that as a geriatrician, he would frame this around the way he thinks about older patients and the value of vaccines as distinguished from children. A study by Smeeth examined first heart attack or first stroke after an inflammatory event, in this case systemic respiratory tract infection (SRTI) or urinary tract infection (URI). The study showed that in the weeks and months following the inflammatory event, there is an increased risk for first heart attack or first stroke that is 2- to 4-fold higher. That increased risk persists out for a few months [Smeeth, L. et al. N Engl J Med 2004; 351: 2611-2618].

When Dr. Gravenstein talks about this with his health staff, he talks about inflammation and the risk of vaso-occlusive event. In this case, it is framed as thrombosis, and he uses a "thrombometer" that he contrived to help explain this:



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When people are born and are young, the inflammatory mediators or markers of inflammation are relatively low. On the Thrombometer, young people would be at low-risk for propensity to clot. With increasing age, inflammatory markers start rising and the propensity to clot increases as well. If underlying diseases (obesity, diabetes, arthritis, vascular disease, dementia, chronic obstructive pulmonary disease (COPD)) are added on top of that, the markers increase further and the propensity to clot is even higher. In terms of the risk for complications from infectious events, vaso-occlusive risk rises with age and disease. Add to that infections (bladder, respiratory), the risk goes even higher. One outcome that might be expected with administration of an effective vaccine that reduces the amount of inflammation with an infectious event such as influenza or pneumococcal disease is a reduction in these types of events. Older individuals become immune senescence, have a lessor immune response that is more permissive for infection and often more permissive for severe infection that can result in hospitalization. This also lowers the vaccine response, so better vaccines are needed to overcome declining response. This also slows recovery from infection and changes symptom presentation with age [Lambert Nathaniel D et al. Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach. Expert Rev. Vaccines. 2012 August; 11(8): 985-994; and Taub D, Longo D. Insights into thymic aging and regeneration. *Immunol Rev*. 2005;205(1):72-93. (Abstract only)].

Studies with HD compared to SD influenza vaccine have been presented to ACIP previously. In an RCT published by DiazGranados and colleagues of an elderly population of approximately 32,000 people showed a 25% reduction in laboratory-confirmed influenza and a 30% reduction in hospitalizations.[1] A meta-data analysis study published by Izurieta and colleagues in collaboration with CDC, NIH, and FDA examined individuals diagnosed and treated for influenza and observed a similar reduction in these diagnoses (22%) and hospitalizations (22%) with an influenza diagnoses[2] [[1]Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., *Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults*, N Engl J Med 2014; 371:635-645|August 14, 2014|DOI: 10.1056/ NEJMoa1315727; [2]SIzurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, Franks R, Pratt D, Forshee RA, MaCurdy T, Worrall C, Howery AE, Kelman J., *Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis*, Lancet Infect Dis 2015 Mar;15(3):293-300. doi: 10.1016/S1473-3099(14)71087-4. Epub 2015 Feb 9].

What these studies did not answer are questions about the people who are the sickest and least likely to respond to vaccine and whether a benefit can still be achieved in this group, such as the group that is in the long-term care setting. Case Western Reserve University's (CWRU) approach to this was a pragmatic large-scale cluster RCT on comparative effectiveness of HD versus SD influenza vaccine in long-term care specifically in the long-term care setting. Two studies were conducted. The first was a pilot/feasibility study undertaken in 39 nursing facilities for the 2012-2013 predominantly A/H3N2 influenza season. The second was the full cluster RCT of HD influenza vaccine versus SD influenza vaccine in 823 nursing homes (NHs) for the 2013-2014 predominantly A/H1N1 influenza season.

Of the 39 facilities enrolled in the pilot study, 19 were in the HD group and 20 were in the SD group. Approximately 12,000 people were admitted to these facilities during the influenza season. As of October 1, 2012, there were 4400 residents living in the facilities. Of those, 3800 were over the age of 65 who qualified for the analytic group and 3000 were in the long-stay population. The long-stay population had to have been living there for at least three months. Those were the analytic samples with roughly an even split of just under 1500 in each of the HD and SD group. There was no difference in the outcome of death for this season. There was a

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30% reduction in hospitalization, which was the primary outcome and satisfied the investigators that this was feasible to do in a long-stay population. The absolute hospitalization rate between the two groups for ever being hospitalized during the season was just under 21% for the SD and 13.5% for the HD. This gave the signal to move forward to the large trial.

For the pragmatic cluster RCT of HD versus SD influenza vaccine in NHs, NHs were recruited in areas adjacent to 122 cities in the CDC influenza surveillance system. Federally mandated nursing home resident Minimum Data Set (MDS) assessment to identify permanent NH residents with selected demographic and functional characteristics and to measure the outcomes. Medicare Fee-For-Service (FFS) resident hospital claims were used to measure the outcome of hospitalization for influenza cardiovascular exacerbations of influenza.

Facilities were recruited within 50 miles of CDC cities. Facilities were excluded that already were using HD as standard of care, had fewer than 50 permanent residents, were hospital-owned NHs, or in which >20% of residents were under 65 years of age.

Individual residents could still decline vaccine or ask for a different vaccine, and the facility could do whatever they typically would do as its standard of care. If a facility had already been offering HD as its standard of care, they were excluded to the study. Facilities had to be indifferent to the type of vaccine that was going to be given to their residents.

The facilities were randomly assigned to 4 groups:

- High-Dose for NHs residents
  - Free Staff Vaccine
  - No Free Staff Vaccine

- Standard Dose for NHs residents
  - Free Staff Vaccine
  - No Free Staff Vaccine

Provision of free or no free vaccine for staff did not affect any outcomes. Facility staff were educated on influenza and the study procedures. There were some 200,000 hits to the video for this education. Facility data were linked to the Online Survey Certification & Reporting System (OSCAR) that nursing homes submit to describe themselves; the federally required MDS, which includes demographic information and information about the facility; and Medicare Part A data for the FFS and diagnoses; MDS discharge data, which indicates where someone leaving the NH went (hospital, other setting); and vital status files to determine who died. Vaccination data reports were collected directly from the facilities. The facilities faxed these to the investigators monthly, and the investigators conducted an onsite audit. Patient eligibility was at least 3 months of residency, over 65 years of age on November 1, 2013, and Medicare FFS.

The first analysis examined all-cause hospitalization per person-year, which is all that can be acquired out of the MDS; mortality; and functional decline. The qualifying period was through September, the vaccination period until November, and the outcome period from November through March. The pre-specified primary outcome for FFS was the risk of hospitalization due to pulmonary and influenza-related illness defined by these International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 460–466, 480–488, 490–496, 500–518.

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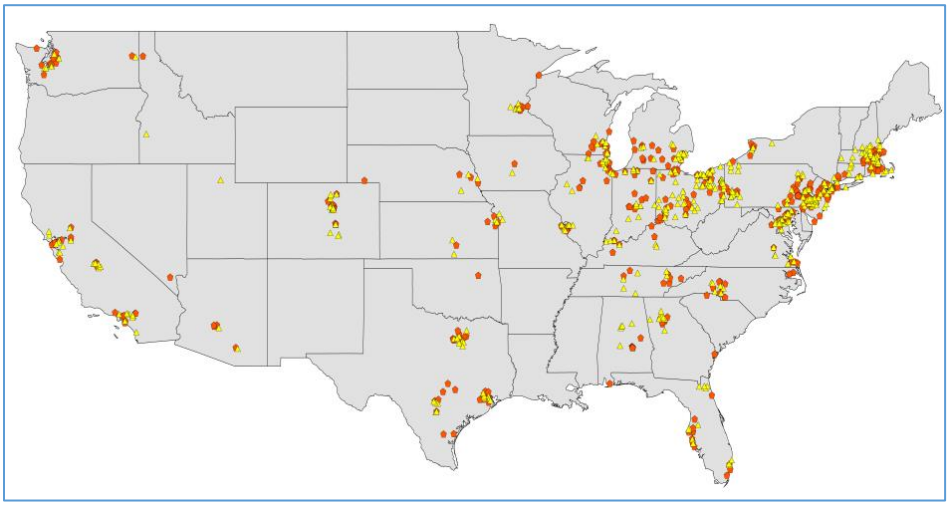
The 823 participating facilities across the country are relatively well-distributed, as shown in the following map (yellow = HD vaccine facilities; red = SD vaccine facilities):



Within the 50-mile radius, there are 9200 facilities of which 10% were screened. Of those, 166 were excluded leaving 823. About half were HD and half were SD. In that allocation, there were approximately 45,000 residents in each of the HD and SD facilities. There were approximately 54 to 60 residents per NH in the analytic sample for the MDS, leaving approximately 25,000 residents per group.

Based on the OSCAR and Medicare claims data, the facilities were relatively similar between the groups with about 118 residents per home, 80% of residents vaccinated, 78% long-stay residents, about 86% of the long-stay residents vaccinated, about 55% of staff vaccinated across all facilities, about the same number of patients on Medicaid, about the same ratio of Registered Nurse (RN) or RN plus Licensed Practical Nurse (LPN) staffing, and about the same level of functional disability.

Approximately 92,000 residents were living in the study NHs on October 1, 2013. Approximately 76,000 of these were over the age of 65; about 53,000 were long-stay; about 52, 000 were in the MDS analytic sample; and about 38,000 were in the FFS sample. The MDS sample included all-cause hospitalizations and all residents were included in that. The FFS sample included only those who were on Medicare FFS, which reduced the sample by about 20%. In terms of the demographics of the individual residents, the groups were similar by age, gender, ethnicity, and underlying conditions.

The influenza season during the study timeframe was predominantly A/H1N1, with a little A/H3N2. It was an interesting season because it often is said that A/H1N1 is not such a big deal in older people. The unit of analysis for the analytic approach was individual residents, which was adjusted for clustering by NHs using robust variance estimates. Multivariable logistic, Poisson, and Cox regressions were used. The initial model assessed interaction between treatments, and was adjusted for pre-specified NH- and resident-level covariates. The analysis was Intention-To-Treat (ITT), so the 15% who were not vaccinated were still included. The Number-Needed-to-Treat (NNT) was also calculated.

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Based on a seasonal index of hospitalizations by month from November 2013 through May 2014, about 20% of the population was hospitalized. There were more hospitalization in the SD group versus the HD group in all months except May. Because these are index hospitalizations, the typical epidemic curve expected is not seen because this includes only the first hospitalization for any one individual.

This is the calculation for the NNT:

NNT = 1/ARR where ARR* = CER – EER
1/(0.2090-0.1967) = 81.3 (CI: 53, 182)
*Using unadjusted event rates

There was a 21% hospitalization rate in the SD and a 19.67% in the HD. That 1.2% difference generates a NNT to prevent hospitalization of about 81. With the adjusted numbers, it is a little higher than that at 82.6.

For the unadjusted Medicare FFS data diagnosis-related hospitalizations of a smaller population of only 38,000), all-cause hospitalizations was 7.4% relative difference or an absolute difference of about 280 hospitalizations from any cause. Looking at the diagnoses with which people were diagnosed, if cardiac or cerebrovascular was in any position, there was about a 10% difference. If a cardiac diagnosis of heart attack, heart failure, atrial fibrillation, or a respiratory diagnosis was in any position, it was about a 10% difference. Cardiac, cardiovascular, or respiratory can account for the entire difference in the all-cause hospitalization. If a respiratory condition is by itself in any position, it only accounts for about 10% difference or two-thirds. If the discharge diagnosis is required to be a cardiac condition in the first position, it also accounts for about two-thirds of hospitalizations. In the case of respiratory in the first position, it is a difference of 92 or about 12%, so about one-third have a diagnosis with a respiratory condition in the first position. With pneumonia in the first position, it is a difference of 31 or only 10% of the total difference seen in all-cause. As the numbers get smaller, the statistical and clinical meaningfulness is less. While there was a 70% lower likelihood of having an influenza diagnosis, only 27 people had an influenza diagnosis in these claims. Of those, 6 received HD and the remainder received SD. This is a frequency plot, not an adjusted plot.

In terms of the unadjusted and adjusted marginal Poisson regression analysis outcomes accounting for clustering by NHs, a nearly 7% reduction was observed for all-cause hospitalization in the MDS cohort. In the smaller FFS cohort (N=~38,000), in the adjusted group all-cause, there was a similar size reduction estimated of about 8.5%. For hospitalization for respiratory issue, there was a 12.5% reduction in hospitalizations.

To summarize, hospitalization reductions by diagnoses listed at discharge were as follows:

<u>Unadjusted</u>

- ❑ Any cause: 7.4%
- ❑ Any cardiac or cerebrovascular event: 9.7%
- ❑ Any heart failure, heart attack, atrial fibrillation or respiratory diagnosis: 9.7%
- ❑ Any respiratory diagnosis: 10.3%
- ❑ As primary diagnosis, a cardiac condition heart attack, heart failure or atrial fibrillation: 9.0%
- ❑ As primary diagnosis, a respiratory condition: 11.8%
- ❑ Pneumonia: 26.2%

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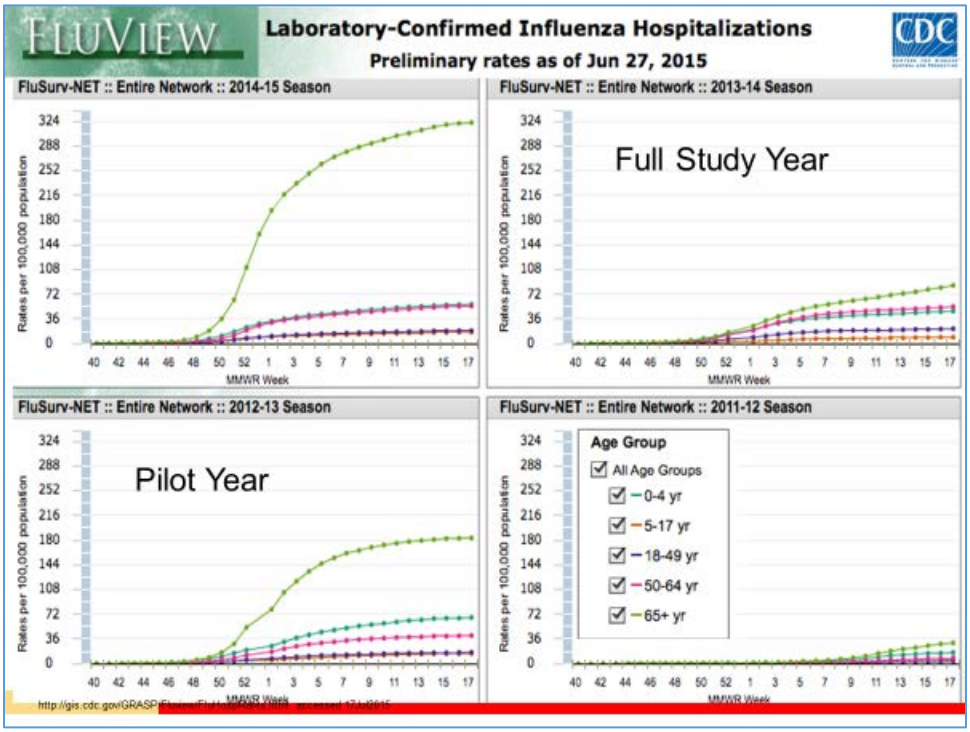
Adjusted
- All cause: 8.5 %
- Respiratory first: 12.7%

The following offers some context between the two study years:



In the bottom left is the pilot year, during which there was a large hospitalization rate that was almost twice as high is the top right, which is the full study year. The year that followed the full study year was much higher. There was a relatively light influenza season compared to the pilot year or the year after.

In summary, HD vaccine has been shown to reduce laboratory confirmed influenza among outpatient elderly. NH residents have higher event rates (e.g., hospitalization) than other settings, which enables health services impact studies; cluster-randomized approach; and overcomes selection biases such as access. All residents had equal access to vaccine. The 2013-2014 season is of special interest because it offers a conservative estimate of relative benefit in this population. It was an A(H1N1) predominated season, and the relative benefit of HD vaccine for this strain in a NH population has yet been unknown. It was a relatively mild season compared to other seasons, so the opportunity for greater effect is also not seen, but is suggested by the pilot study. The FFS claims differences are consistent with the biologic plausibility of effect on hospitalization-based diagnoses and the cardiorespiratory outcomes.

To recap the primary findings, the pilot and full study support the idea that HD influenza vaccine reduces hospitalization risk for institutionalized elderly compared to standard dose. In the pilot among nearly 3000 people divided between HD and SD, 197 (13.5%) versus 302 (20.2%) were hospitalized, or an adjusted RR of 0.701 (0.543-0.905), in an A/H3N2 predominant season. In the full study among approximately 53,000 people divided between HD and SD, 5239 (19.7%) versus 5517 (20.9%) were hospitalized, or an ARR of 0.933 (0.884-0.985) in an A/H1N1

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predominant season. The differences in hospitalization rates can be largely accounted for by differences in cardiorespiratory event diagnoses.

These estimates may be conservative due to the severity of the influenza season, the ITT approach with nearly 15% residents not being vaccinated, and the type of influenza virus circulating (A/H1N1), and the assessment only of reduced hospitalization which likely underestimates the net benefits to nursing home residents' health outcomes. When approximately 20% of the population is hospitalized, even a 1% absolute reduction in hospitalization can be cost-effective (e.g., 81 vaccines at ~$30/vaccine = $2430, or less than the average cost of hospitalization).

There are some limitations of the study. There are no laboratory data to confirm influenza. The HD:SD relative benefit on A(H1N1) may underestimate difference when other strains dominate, such as A(H3N2). The relative difference to no vaccine was not estimated, though it could be larger.

Discussion Points

Dr. Atmar observed that other studies that have examined this population have shown that vaccination of the healthcare workers in these facilities has a greater effect than vaccinating the residents. He found it disappointing that only 26% of the workers in these facilities were vaccinated. He wondered whether they examined the effect of higher versus lower vaccination acceptance within facilities on outcomes and, if so, how that compared to HD versus SD.

Dr. Gravenstein responded that they wondered if by offering free vaccine they would see a skew in vaccine uptake to prospectively settle the question of whether vaccinating staff could reduce risk. By offering free vaccine, nothing was skewed. Therefore, it is not possible to tell whether there was a difference in HD versus SD based on staff vaccination from a randomization perspective. The hazard of the other studies that assessed staff vaccination, though he believes them to reflect truth, is that the percentages of facilities with the highest staff vaccination often are making many other efforts that help the residents potentially do better. It is hard to know for sure how much the difference is, because the facilities are just better. Facilities that have higher uptake among the residents are more likely to have higher uptake among the staff, have infection control policies in place, have an Infection Preventionist to implement isolation, and other types of measures. It is difficult to speak specifically to whether staff vaccination would actually help in this case.

Dr. Kempe asked whether any self-selection was involved in residents who chose to get the HD vaccine in those facilities.

Dr. Gravenstein replied that there is not. In any facility, when residents are asked what vaccine they got for anything, they typically do not know. The 10% of residents who refuse may be the subset who might know what they are getting. This is an unblended study allocated at the facility level, but even the nursing staff do not know what they gave three weeks later. Expecting that the residents are skewing the results is unlikely.

Dr. Reingold pointed out that Dr. Gravenstein had not mentioned anything about pneumococcal vaccine coverage in these NHs. He was curious as to whether that information was available, and if it made any difference.

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Dr. Gravenstein responded that they do not have that information, and he was not sure whether the information available to them through the MDS record is reliable. In terms of whether it would be in the administrative data, this would have to go back five years and they were looking at the data only for one year.

Dr. Messonnier asked who funded the study.

Dr. Gravenstein replied that Sanofi Pasteur funded the study.

Dr. Duchin asked whether there was any information about medications that patients were taking, such as statins or others with an anti-inflammatory effect.

Dr. Gravenstein responded that they did not yet have the Part D claims, but they do plan to examine this in the future.

Dr. Schmader (AGS) said it struck him that perhaps the name “pilot” should be removed for the pilot study. He found both studies to be equally valuable. There were positive findings for H3N2 in the pilot, so it was adequately powered. There is no Type 2 error there. The study is even positive against the obstacles of a weak season with H1N1, so the results are impressive.

Dr. Thompson (NVAC) suggested examining cost in a more significant way. In reality, the cost savings could be quite significant.

Dr. Gravenstein indicated that they have begun the cost-effectiveness work.

Dr. Maldonado (AAP) asked whether it was possible to examine AEs with HD, which has been raised as an issue in the past.

Dr. Gravenstein replied that because this was a standard of care, they used the VAERS reporting system, and there were no differences in the reports.

FluMist® Update

Helen Bright, PhD
Raburn Mallory, MD
MedImmune

Drs. Bright and Mallory presented an update of the 2015-2016 vaccine effectiveness data, including recently published data on the effectiveness of LAIV against pediatric influenza hospitalization. In addition, they provided an update on the non-clinical root cause investigation, and work that MedImmune has been doing to help optimize the A/H1N1 strain selection for the 2017-2018 vaccine formulation, and insights into ongoing clinical studies and timelines for data availability.

Revisiting the data from the 2015-2016 influenza season, Dr. Bright reminded everyone that the data from this outpatient setting showed six vaccine effectiveness studies with a consolidated estimate. Looking across the studies, the point estimates are generally similar. The consolidated estimate is 48% for LAIV and 60% for IIV. For the B strains, there is an additional dataset from a test negative study published last year. LAIV has a consolidated vaccine effectiveness point estimate of 66%, while IIV is 49%. [1. Ambrose C. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 2. Flannery B.

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Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 3. Caspard H et al. Presented at International Society for Influenza and Other Respiratory Virus Diseases (ISIRV) Options IX for the Control of Influenza Conference; August 25, 2016; Chicago, IL. 4. Nohynek H et al. Euro Surveill. 2016;21(38):pii=30346. 5. Pebody R et al. Euro Surveill. 2016;21(38):pii=30348. 6. Helmeke C et al. http://www.verbraucherschutz.sachsen-anhalt.de/fileadmin/Bibliothek/Politik_und_Verwaltung/MS/LAV_Verbraucherschutz/hygiene/influenza/Effektivitaet_der_Influenzaimpfstoffe_2015-16.pdf 7.Caspard H. Abstract Accepted for Publication PAS, May 6-9, 2017; San Francisco, CA].

In terms of LAIV and IIV effectiveness estimates for A/H1N1pdm09 strains for the 2015-2016 influenza season[1,2] in the outpatient setting from the US and the rest of the world, the consolidated overall VE was 32%, demonstrating low but significant effectiveness. The IIV effectiveness was 72% [[1]Caspard H et al. Abstract accepted for presentation at: Pediatric Academic Societies Meeting; May 6-9, 2017; San Francisco, CA; [2]Helmeke C et al. [poster]. Presented at: European Scientific Conference on Applied Infectious Disease Epidemiology; Nov 28-30, 2016; Stockholm, Sweden.

Despite overall low effectiveness against the predominating circulating H1N1 strain outpatient setting, there are data from the same season which demonstrate moderate to good VE in the inpatient setting. Data on the impact of LAIV use on inpatient hospitalization due to influenza was recently published on the 2015-2016 influenza season in the UK. These data demonstrated meaningful endpoints for the reduction of severe disease resulting in hospitalization. Effectiveness in the prevention of laboratory-confirmed influenza hospitalization in children was 55% in England and 63% in Scotland. These are both populations in which LAIV is almost exclusively used [[1] Peabody R et al. *Euro Surveill.* 2017; 22(4):pii=30450. [2] Health Protection Scotland. http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5529. Accessed 16 February 2017].

Turning to the progress made in the non-clinical root cause investigation, this investigation is currently focused on two potential hypotheses. The first is reduced replicative fitness of H1N1pdm09 LAIV strains in human cells, and the second is vaccine virus interference in the quadrivalent formulation. Studies to address the second hypothesis are currently ongoing. During this session, Dr. Bright presented an update on the first hypothesis. The approach has been to characterize and define the biological profile of the effective vaccine strains and compare these to recent H1N1 strains that had lower than expected VE. This presentation focused on a comparison between the following pdm09 H1N1 strains:

Pre-Pandemic Strains	Post-Pandemic Strains
New Caledonia 1999 (NC99)	California 2009 (CA09)
South Dakota 2007 (SD07)	Bolivia 2013 (BOL13)
	Slovenia 2015 (SOLV15)
	Pandemic (pdm)

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NC99 is particularly relevant as it was in the vaccine for many years and has a high level of efficacy and effectiveness of clinical data. MedImmune has profiled its LAIV strains through the influenza virus life-cycle and also developed a novel primary human nasal cell model in which their performance can be evaluated. An important feature of their LAIV strains is that they only differ biologically in their external surface glycoproteins, hemagglutinin (HA) neuraminidase (NA). These are taken from the wild-type circulating strain each year, and they provide the antigenic match to the vaccine. The remaining internal components of the vaccine virus remain the same every year and provide the attenuated phenotype. The HA protein is responsible for cell binding and cell fusion of the virus, while NA is responsible for virus release and spread.

The physiological role of HA is to help the virus enter the cell. At a pH of approximately 5.5, the HA changes its shape and allows the virus to uncoat its genome. However, high temperature from the external environment can also have an effect on the HA shape and this could reduce virus infectivity. Initial findings with the California strain in the 2013-2014 vaccine indicated an HA protein at a lower than expected stability. Based on this, Bolivia was selected as it demonstrated higher HA thermostability, which is much more similar to previous H1N1 LAIVs. However, this may have made the HA too acid-stable. The Bolivia strain has a much lower activation period in terms of the pH at which HA changes it shape. This can result in a prolonged uncoating stage for the virus, which would also impact virus replication fitness.

HA is also responsible for the binding of the virus to the cell. Assays have been developed to compare binding of the viruses to α2-6 human cell receptors. These studies indicate that the pandemic CA09 and BOL13 strains may have decreased binding to the human receptor compared to NC99.

The late stage of viral replication was also evaluated, which affects cellular release and spread. This was done by comparing replication using two assays. The Fluorescent Focus Assay (FFA) measures a single cycle of replication. The Tissue Culture Median Infectious Dose (TCID50) measures multiple rounds of replication and relies on proficient release of the virus and efficient spread. For the pre-pandemic H1N1 viruses, the two assays gave similar results. However, for the pandemic09 strains, there is a discrepancy between the FFA titer and the $TCID_{50}$ titer. This suggests that H1N1pdm09 viruses are less able to support multiple rounds of replication. Post-pandemic H1N1 LAIV strains have reduced replication in primary human nasal epithelial cells.

Regarding the update on A/H1N1 strain selection for 2017-2018 season, as was the case for all previous effective vaccine strains, A/California and A/Bolivia were selected based on characteristics and characterization data from a range of assays. This culminated in immunogenicity studies in ferrets. However, based on the lower than expected vaccine efficacy seen with these two strains, several new assays have been added into the strain selection process. Using these assays, a lead H1N1 candidate was identified, A/Slovenia 2015 for inclusion in the 2017 vaccine.

The preliminary data show that A/Slovenia has improved HA properties. It has an activation period that is very similar to the pre-pandemic H1N1 strain and to other effective vaccines strains. Preliminary receptor binding data suggest that A/Slovenia has improved receptor binding compared to Bolivia. Measuring A/Slovenia's replication by FFA and $TCID_{50}$, the assay values are very similar. Again, this profile matches vaccine with previous effective LAIV strains. When evaluated in the primary human nasal cell model, the new A/Slovenia strain showed significantly improved replication kinetics compared to the previous A/Bolivia vaccine strain, though not quite to the level of NC99.

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To summarize the non-clinical dataset, the initial findings indicated that there was reduced replicative fitness with H1N1pdm09 viruses. The underlying mechanism for this is likely to be multi-factorial (e.g., HA stability, HA activation pH, receptor binding, NA). MedImmune has identified a lead H1N1 candidate, A/Slovenia, for inclusion in its 2017-2018 LAIV composition. A/Slovenia has no deficiency with multiple rounds of replication. Its FFA and $TCID_{50}$ titers match, and it is much more similar in this regard to previous LAIVs. It has a higher HA activation pH compared with A/Bolivia, and looks much more similar to previous effective LAIVs. It has a much higher replication in the primary human nasal epithelium model versus the A/Bolivia strain. Investigation is ongoing and is now focusing on cell and ferret studies evaluating interference and formulation. There is a planned clinical study with the 2017-2018 LAIV.

Dr. Mallory described a planned pediatric study to further characterize the A/Slovenia strain that likely will be included in the vaccine for the 2017-2018 influenza season, and to further compare the new A/Slovenia strain to the previous A/Bolivia strain that was previously included in the vaccine. This will be a randomized, double-blind, study that plans to enroll approximately 200 children 24 to <48 months of age. Subjects will be randomized with approximately 65 subjects per group at a 1:1:1 ratio to receive two doses of one of the following vaccines:

- ❑ LAIV4 2017-2018
  (A/H1N1 Slovenia strain)

- ❑ LAIV4 2015-2016
  (A/H1N1 Bolivia strain)

- ❑ LAIV3 2015-2016
  (A/H1N1 Bolivia strain)

Having trivalent and quadrivalent versions of the 2015-2016 will allow for evaluation of what interference might be occurring between these two strains. This issue is being addressed with the A/Bolivia strain because it has reduced replicative fitness compared to the A/Slovenia strain, and these results will be more likely to show this. The primary endpoint of the study is HAI antibody seroconversion rates after each dose. The secondary endpoints include neutralizing antibody seroconversion rates after each dose, mucosal immunoglobulin A (IgA) increases after each dose, shedding after each dose, and safety.

In terms of the timelines for data availability from ongoing studies, final 2017-2018 H1N1pdm09 A/Slovenia strain characterization and 2016-2017 VE H3N2 data (UK, Finland, Canada) should be available for presentation during the June 2017 ACIP meeting. Data should be available on US pediatric shedding/immunogenicity from the new H1N1pdm09 strain and from the Japan 2016-2017 pediatric efficacy study data on A/H3N2 for presentation during the October 2017 ACIP meeting.

In conclusion, LAIV demonstrated overall effectiveness in most studies conducted in 2015-2016. However, H1N1 effectiveness was more variable and lower than IIV in all studies. Effectiveness against influenza hospitalization has been published recently. Initial findings from the investigation indicate that post-pandemic strains have reduced replicative fitness compared to pre-pandemic strains. Based on the findings of the investigation, new assays were introduced into the strain selection process. A replacement A/H1N1 Slovenia strain has been selected for 2017-2018 that has characteristics similar to pre-pandemic strains. Final non-clinical strain

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characterization data for the new A/Slovenia strain are expected to be available by the end of the second quarter in 2017.

Discussion Points

Dr. Reingold asked whether the prior vaccination histories will be known for the participants in the US and Japan, and if they believe it matters whether they have been primed with IIV.

Dr. Mallory replied that for the Japan study, that is being conducted by MedImmune's marketing partner, they will be collecting five years of vaccination history. In the study MedImmune plans to conduct, vaccination history will be collected on the 2 to 3-year-old children.

Dr. Walter noted that in the pediatric study, children will receive two doses of vaccine. He asked whether blood draws would be done after the first dose on all of those children. Referring to Slide 6, he also asked what was driving the consolidated estimate. It seemed to be the data from Finland. The confidence interval for all of the effectiveness for LAIV crosses zero for every other study but the Finland study and the consolidated estimate.

Dr. Mallory replied that immunogenicity blood draws will be done at baseline, 28 days after the first dose, and 28 days after the second dose. The second dose is an attempt to assess vaccine shedding after the second dose to determine whether there is a reduction in shedding after the second dose compared to the first dose. In terms of what was driving the consolidated estimates, he said he thought in general with the consolidated estimates was that there are more subject cases, the confidence intervals are narrow in general. He deferred to Dr. Caspard who is conducting the study for more details.

Dr. Atmar asked which of the countries used LAIV3 versus LAIV4.

Dr. Mallory reported that for 2015-2016, all countries were using LAIV4.

Referring to slide 22, Dr. Savoy (AAFP) said she thought the CA09 strain was the reason the US stopped offering LAIV in the US. It appeared that the new strain is somewhat better, but was pretty much the same as the SLOV15 line. It was not clear to her how that would help to make a decision about LAIV in the US.

Dr. Mallory replied that these are *in vitro* data. They proposed the pediatric study, which will be examining pediatric data on the shedding and immunogenicity of that strain. That study will be able to directly compare the previous BOL13 strain that was in the vaccine with the new strain to determine whether there are differences in immune responses in the shedding of that strain.

Dr. Gorman (NIH) asked whether all of the children in the proposed pediatric study will be naïve to influenza vaccine when they begin, or if previously vaccinated children will be accepted.

Dr. Mallory replied that the goal for the proposed pediatric study is for about half of the children to be naïve to previous vaccination.

Dr. Hunter asked whether the A/Bolivia strain was used in the MedImmune vaccine and that was why it was emphasized so much.

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Dr. Mallory clarified that the A/Bolivia vaccine strain was in the 2015-2016 influenza season, for which there are all of the H1N1 effectiveness estimates. It is in the vaccine this year. However, because H3N2 has been circulating predominantly, there are no effectiveness estimates for that strain for this year. The vaccine strain was selected primarily on improved stability properties compared to the previous California strain. Effectiveness has still been lower than IIV, which is what they are attempting to solve now.

Dr. Kempe observed that if half of the 200 children to be included in the proposed pediatric study are naïve and half are primed, it seems like the study would be underpowered to examine the issue of whether this was related to priming.

Dr. Mallory clarified that overall the study has the power to detect difference around 20% to 25% in either shedding rates or immune responses. The power will be lower for the subgroup analysis. They struggled with which type of subjects to enroll because they also want a subject population that is somewhat representative of the people who would be receiving the vaccine.

Dr. Bennett said she remained somewhat confused about the interference issue. It appears that the only way this will be addressed is in the study of children, some of whom will receive trivalent versus quadrivalent.

Dr. Bright indicated that they have been using an optimized ferret model to compare mono, versus trivalent, versus quadrivalent with Bolivia and the NC99, which was a very effective vaccine strain. NC99 was given only as a trivalent, so now it is being compared to determine how it would have performed had it been in a quadrivalent. In addition to pre-clinical ferret models, they have some assays using and are using the primary human nasal epithelial cell model as well for pre-clinical to determine whether these models can translate into the clinic for future use.

Dr. Byington (AAP) said she shared some of the concerns and confusion of others. She still had not heard stated directly what MedImmune believes the definitive mechanism to be for the failure, and the focus on the thermal and pH stability. The lack of emphasis on human trials for interference and priming make her believe that MedImmune eliminated those or that they do not think those are viable causes for the failure.

While the study is ongoing, Dr. Mallory emphasized that the data presented during this session show that the post-pandemic strains have reduced replicative fitness compared to the pre-pandemic strain, and that a strain has been selected that looks better in that regard. There are extensive ongoing ferret studies to try to elucidate whether interference may also be playing a role. That also will be assessed using the human nasal epithelial cells. Some information will be collected from the clinical study as well. In terms of prior immunity, the previous effectiveness studies conducted did not show an effect of prior immunity in lowering vaccine effectiveness estimates. In terms of whether prior immunity is completely eliminated, additional data will be available from the ongoing studies. Throughout the development of FluMist®, effectiveness has been examined in different age groups of people exposed to either vaccination or wild-type influenza, prior immunity has not shown an impact on VE in children. Slide 31 shows that the VE estimates in children immunized previously did not change compared to those who were not.

Referring to slide 22, Dr. Romero said his understanding was that the $TCID_{50}$ represented multi-cycle replication and the FFA represents single cycle replication. He wondered how the two could be compared.

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Dr. Bright said that both values were given as a titer or as a log value. FFA is an infectivity assay that tells how much virus is getting into a single cell, and it has to be tittered out. $TCID_{50}$ relies on the NA efficiently working. It is a 6-day assay that requires multiple rounds of replication and amplification. If those two titers do not match, it suggests that while some viruses can get in quite efficiently and start the replication cycle, what they are not able to do so efficiently is multiple rounds of replication and amplification over a number of days. That is when the pandemic H1N1s struggle. This offers a clue to the biology of the virology behind these strains that says something about the difference between the pandemic H1N1 strains compared to the seasonal influenza viruses they have worked with previously. It gives them clues as to what might be mechanistically happening. Because only the HA and NA differ each year, it has to be something about what the HA and NA are doing.

Dr. Decker (Sanofi Pasteur) questioned whether the response earlier that the Y axis scale on the right half of slide 22 was linear arithmetic logarithmic. On the left hand side there is 10^8 and 10^9 $TCID_{50}$, while on the right-hand side there was 2 to 8. Not 10^2, but simply 2.

Dr. Bright replied that it is a log scale.

Dr. Moore said she still hears concerns about repeated use of LAIV year over year and whether that would contribute in any way to the US results being lower than some of the others observed elsewhere. She wondered whether any of the studies assess not only prior season use of vaccine, but also year over year use of LAIV as seen in the US.

Dr. Mallory replied that they do not have those data readily available. What will be interesting are the data that come out of the UK for the past season, because children in the UK are enrolled in a vaccination program year after year. So, they are beginning to look more like US children in terms of their prior vaccination history. The other data that can address this will be from the Japan efficacy study. Those children will have up to five years of vaccination history, so it will be possible to assess VE in heavily vaccinated children compared to VE in less heavily vaccinated children.

Ms. Pellegrini noted that she had not seen anything to account for the geographic variation observed during that season, and she wondered whether there were theories that would account for variation in VE from country to country during that season.

Looking at the overall data for A and B strains, Dr. Mallory pointed out that there was less variation from country to country than there actually is within the US. In the B strain data, there is some variation but the confidence intervals are very wide because there was not a lot of B strain circulating in the 2015-2016 season. There are not clear explanations for the differences that occurred in the US and in other countries. MedImmune is doing some work with CDC to combine the data from the MedImmune study and the CDC study to determine whether some of the differences can be further elucidated. The differences were observed in the US and other countries, so this is not a US-specific finding.

Dr. Bennett asked whether there was any explanation for why the Finland data, which is the outlier, looked different.

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Dr. Mallory responded that the Finland study was a cohort study while the rest of the studies were test-negative. In addition, a limited age group was enrolled in Finland of children 2 years of age.

Dr. Walter requested clarification about what additional strain characterization data will be presented during the June 2017 ACIP meeting.

Dr. Bright replied that in June, they will present ferret data from their interference studies.

Dr. Mallory added that they presented the data on the A/Slovenia strain with the expectation that that strain will be selected at the March WHO meeting and the subsequent VRBPAC meeting. If a different strain is selected, they will present final data on the new strain. Most of the strain characterization data from the *in vitro* assays has been presented, but there will be some additional *in vivo* ferret data.

Regarding the effect or prior immunity, Dr. Belongia emphasized that it is important to recognize that the VE studies do not have the ability to assess children under 4 years of age. They typically assess children 2 years to 17 years of age, which perhaps could be stratified down to 2 years to 8 years of age, but there are a lot of children in that analysis who are older who certainly have been previously infected. In the trial, there will be children under 48 months of age. Thus, he would not rule out the possibility that they will see priming effects or differences between those children who have been previously vaccinated and those who have not. If those effects are present, then they will be down to stratification with perhaps 30 to 35 children in each group. If both of those effects are operating, this could be very difficult to tease out.

Dr. Duchin (NACCHO) added that there are some data in adults with IIV that suggested that repeat vaccination with the same vaccine strains results in reduced VE against a drift strain. In the context of previous vaccination, he wondered if MedImmune was considering the impact of the vaccine strains that a child was vaccinated with in previous seasons and the specific strain that is circulating that season to draw conclusion about the impact of prior vaccination.

Dr. Mallory replied for the proposed study the children will be young and the investigators will know which vaccines they received and thus which strains are in them. In the Japan study, there will be five years of vaccination history, so they should be able to assess the specific effects to the extent that they are powered to do that. On the question of prior immunity, this seems to be more specific to the A than the B strains if it is occurring. B strain effectiveness continues to look good. If it is occurring for the A strain, it may be in the setting of reduced replicative fitness for that particular strain.

Dr. Bennett emphasized that what she was hearing from the ACIP was that they have concerns about the power calculations and whether they will be able to tease out the impacts.

Dr. Mallory replied that they struggled to enroll very young children to receive a vaccine that is not approved for use in the US.

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Influenza Summary and WG Considerations

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Regarding plans for the 2017-2018 ACIP influenza recommendations that will be published sometime during the summer, Dr. Grohskopf indicated that no new policy language was proposed for consideration at the time of this meeting. The 2017-2018 statement will reiterate the core recommendation that annual influenza vaccination is recommended for all persons aged 6 months of age and older who do not have contraindications.

In terms of the vaccines discussed during this session, the WG had the opportunity to hear presentations on AFLURIA® Quadrivalent pre-licensure data for adults prior to the October 2016 meeting. The WG presented to ACIP on these data during the October meeting. Since that time, the WG has heard data on the safety evaluation presented during this session and pre-licensure data for children 5 years of age and older. At this time, the WG has proposed no change in the language for AFLURIA® Trivalent specifically related to the issue of children 5 years of age and older versus 9 years of age and older and awaits licensure of a quadrivalent for an age ≥5 years.

Regarding WG discussion about Fluzone HD® and because there are related vaccines (Fluad® and Flublok®) that have been examined specifically for this high-risk group of 65 years of age and older, the WG had an opportunity to listen in and ask questions about the Gravenstein long-term care facility data presented during this meeting. Currently, two vaccines are licensed specifically for age ≥65 years. Data heard previously by ACIP include Fluzone HD® data that were noted to have superior VE to standard-dose IIV3 against protocol-defined ILI-associated with laboratory-confirmed influenza in a two-season RCT of almost 32,000 persons age ≥65 years. ACIP also recently heard data for Fluad®, which is the adjuvanted IIV3 that was shown to have superior VE to unadjuvanted IIV3 against lab-confirmed influenza in an analysis of 227 participants in a one-season observational study of persons age ≥65 years.

In addition to that and although it is not licensed for 65 years of age and older, ACIP previously heard data from a 2014-2015 season randomized trial of Flublok® Quadrivalent, which was licensed by the FDA last fall but is not available this season. These data compared Flublok® Quadrivalent to IIV4 in a randomized study of subjects 50 years of age and older, and noted superiority over IIV4 during that season. During that season, there was notable drift. There have not been any direct comparisons of these vaccines with one another. Currently, ACIP expresses no preference for one vaccine over another. The WG proposes no change in language, and looks forward to further discussion of the efficacy and effectiveness data for these vaccines in this high-risk population. Data for vaccines for this population will be summarized in upcoming 2017-2018 ACIP Influenza Statement.

In terms of influenza vaccine coverage among children, CDC has updated early season influenza vaccination coverage estimates from NIS-Flu to evaluate potential impact of the recommendation to not use LAIV for the 2016-2017 season. The preliminary estimates reflect reported vaccinations received by the end of December 2016. Coverage among children ages 6 months through 17 years increased from 37% by early November to 50% by the end of December. This end of December coverage was similar to coverage through December last season, which was 51%. Comparing by age group, there was no statistically significant differences for 2016-2017 compared to the 2015-2016 season. The differences in the various

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age groups ranged from 2.7% for ages 13 through 17 years to -2.8% for ages 5 through 12 years. As in past seasons, coverage was higher in younger children at 66% for ages 6 through 23 months, 56% for ages 2 through 4 years, 50% for ages 5 through 12 years, and 40% for ages 13 through 17 years. In past seasons, influenza vaccination of children continued to be reported past December. For 2015-2016, coverage increased from 52% by the end of December 2015 and 59% by end of May 2016. It is important to note that these are very new data.

To summarize influenza division activities related to VE and more specifically to LAIV, there continues to be ongoing evaluation of vaccine effectiveness via the US Influenza Vaccine Effectiveness Network, which Dr. Flannery presented data from at the beginning of the session. There is also discussion of an intra-seasonal waning and decision tree analysis regarding timing of vaccination, as well as research studies ongoing to assess immunologic effects of repeat vaccination. Regarding specific LAIV activities, the division has embarked on a systematic review of the literature and meta-analysis of efficacy and effectiveness of LAIV since 2010-2011, the first season post-pandemic, as well as a combined US individual patient-level LAIV effectiveness analysis that will include CDC, DoD, and MedImmune data. In addition, data continue to be gathered for review and publication of the annual ACIP influenza statement.

In terms of WG considerations regarding FluMist®, the best evidence to support recommendation for use would be effectiveness data for LAIV containing a new H1N1 component against H1N1 viruses. Anticipated data timelines include the 2016-2017 effectiveness data for H3N2 from the US, UK, and Finland by June 2017; and efficacy data on H3N2 from Japan and US pediatric shedding/immunogenicity by October 2017. That said, this is a predominantly H3N2 season, so effectiveness against H1N1 cannot be assessed from the current season's data in any of these countries. Unfortunately, it is not possible to predict when the next H1N1-predominant season will occur. Therefore, it could be several years before there is an H1N1-specific season so that effectiveness/efficacy data would be available.

In the absence of effectiveness/efficacy data for FluMist® with a new H1N1 component, the following would be reassuring: 1) Demonstration that the new virus exhibits improved fitness in animals (ferrets), and particularly in human shedding and immunogenicity studies; and 2) Demonstration that performance (e.g., replicative fitness) is similar to that of pre-pandemic H1N1 viruses, which were demonstrated to be effective in previous studies.

A caveat, there is no adequate correlate of protection for LAIV against influenza viruses. Shedding and antibody levels do not always correlate with effectiveness. Shedding is an indication of replicative fitness and vaccine "take." However, lack of shedding has not always correlated with poor effectiveness. Therefore, there is inherent difficulty in interpreting a negative (poor shedding) result. However, the human shedding and antibody (immunogenicity) data anticipated by October 2017 are probably the most constructive data that can be collected within a 1- to 2-season timeframe. The question regards whether the ACIP feels that these data will be sufficient to re-consider whether to recommend LAIV.

Discussion Points

In terms of the immunological effects of repeat vaccination, Dr. Kempe wondered whether the data exist to allow them to examine priming and repeated LAIV versus IIV adequately.

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Dr. Grohskopf reminded everyone that the Japan study would have five years of data collected, which could potentially address this. However, the current season is predominantly H3N2. If there is a differential effect, it will be more difficult to determine if the problem is H1N1-related.

Dr. Reingold asked whether there was an expectation of having effectiveness data from other countries and, if so, is it possible that they will be useful in the US context in terms of number of prior doses, priming, and other potential issues.

Dr. Grohskopf indicated that this has been a common theme of discussion. For example, the European data have differed from the US data even for H1N1. Although it does appear consistently that generally, the inactivated vaccine has done better. CDC will continue to communicate with colleagues overseas to find out what they are observing. There is always going to be a question about comparability, given the fact that the US has routinely recommended vaccination for the entire pediatric population since 2008. This is relatively new in other countries. Granted US coverage is not perfect, but pediatric vaccination was phased in age stepwise between 2003 and 2008. That is a longer period of time than most other countries have been vaccinating healthy children annually on a routine basis. They will just have to try to determine how comparable the data are to the best extent they can.

Dr. Bennett added that not only is it important to understand the context in which the studies are conducted, but also it is important to understand the study methods. Because there are significant differences, ACIP would like to hear about the methods in some detail.

Dr. Belongia noted that there is consideration of a human challenge study with H1N1. While there are differing opinions about whether that would be helpful, because by necessity it would have to be done in adults. Adults are different from children and may respond differently. However, if it did work in adults, there might be reasonable inference to say that it is likely to work in children as well. Since it looks like that is not planned, they will be left with the data from the proposed study. He expressed his hope that the results would be clear and conclusive, at least in terms of shedding and serologic response, to give ACIP sufficient confidence. If it is more equivocal, it could be a tough decision.

Dr. Riley recalled that when this was discussed previously, one of the concerns when this was removed as an option regarded whether a major decrease would be observed in the number of children being vaccinated. This made her think that something is better than nothing if only 20% of children will be vaccinated. The fact that it is 50% versus 51% made her think that if there was not a significant decrease in the number of children being vaccinated, it certainly is important to ensure that what they are being given works.

Dr. Hunter said he was not familiar with the methodologies of the various countries for which VE for H1N1 was presented. He was curious to know whether there was something about the methodology used by CDC that would explain why it is so much lower than everyone else.

Dr. Grohskopf replied that the majority of studies are test-negative case-control designs. The Finland study was a cohort design. The definitions of infection are not universal across all of the studies.

Dr. Flannery added that the short answer is that there is no explanation for the difference in the point estimates. There are wide confidence intervals around the estimates from the CDC data. There is some heterogeneity in the point estimates, but there are overlapping confidence intervals. Except for the Finland study, the studies all included zero for the H1N1-specific

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effectiveness in 2015-2016. All of the studies except Finland used a test-negative design. CDC's inclusion criteria are slightly more sensitive. They do not include ILI specifically. It is acute respiratory illness. It is helpful that the MedImmune also showed the B estimates, which were different, but the heterogeneity was less. It is expected that if there was a methodological problem, it would not just apply to H1N1 over several seasons. Other than that, there is no explanation for why CDC's estimate seems to be the lowest point estimate by far.

Dr. Moore emphasized that the virus does continue to drift. It could be that in just one more season, it will be necessary to move on from A/Slovenia to something else. She asked whether in the future the ACIP could anticipate that MedImmune would perform these same pH, thermostability, and replication studies and present them to the committee in order to be able evaluate future strains. Because that question arises, she wondered if it would be valuable to assess those same studies on the past H3N2 strains that have been effective so that future changes in H3N2 strains also could be assessed in the same type of way, given that there are not good laboratory correlates of protection.

Dr. Bresee replied that MedImmune is planning to conduct these replicative fitness studies with the assays they used to understand these strains better each year going forward. As the strains and antigens change, they will understand replicative fitness going forward and will make sure that it does not drift back again to the A/Bolivia phenotype.

Dr. Mallory indicated that the new assays described by Dr. Bright described to their strain characterization on an ongoing basis, and they will be assessing H3N2 and B strains with these assays. There is ongoing work to assess past H3N2 strains that were known to work. The priority is to examine the new A/Slovenia strain and H1N1, but data are being gathered for the H3N2 strains.

Dr. Gemmill (NACI) reported that there are numerous studies underway in various centers in Canada on VE for influenza vaccine. He is certain that those data will be available through the Canadian Immunization Research Network (CIRN) as part of their collaboration. He shared Canada's frustrations with trying to get a handle on influenza vaccine. Fifteen years ago, there was one vaccine. Now there are many vaccines and everyone is trying to figure out how they compare to each other. VE seems to be a "moving target" as well. A think tank was planned for February 24, 2017 to consider how best VE can be used to make recommendations. This has been a terrible frustration for them. A silver lining for Canada of the recommendation by ACIP in June 2016 not to use LAIV in America was that it gave Canada the ability to pull back from its preferential recommendation on LAIV in Canada for young children. He was not confident that he could make a preferential recommendation for any of the vaccines. When one looks somewhat better, they are using statements such as "If you use this vaccine, it is expected that you may have better protection."

Dr. Gellin (NVPO) asked how long MedImmune would continue, given that it is unknown how long before the season would be right to develop VE data.

Dr. Mallory responded that MedImmune and AstraZeneca place the highest priority on patient health and the overall impact of its products to public health. They remain committed to FluMist® as they believe it provides an important option for vaccination and for pandemic preparedness. They are committed to investigation and to providing FluMist® as an option for patients.

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Dr. Walter pointed out that the WG seemed to be struggling with what level of data they need to bring before the ACIP in order to help make a decision (*in vitro*, *in vivo*, effectiveness, efficacy, which season).

Dr. Kempe emphasized that there are some very large issues immunologically here that probably cannot be answered by MedImmune or a company. There are natural experiments comprised of cohorts of people who have received yearly LAIV for four to five years and other children who have received none. It seemed to her that some basic science would be helpful in answering portions of this that should be funded other than by the companies. Portions of this should not be related to a particular vaccine, but that are important for ACIP to understand in the context of how they consider each new vaccine.

Dr. Atmar expressed concern about potentially having to withdraw a recommendation again if they recommend LAIV based on the data that are or will be available, but then it still did not demonstrate effectiveness in the US. This could lead to loss of confidence in this group. Without really understanding the reason for the lack of effectiveness, despite some good hypotheses, he urged ACIP to have VE data for H1N1 going forward though it probably would have to be developed in other countries.

Ms. Pellegrini pointed out that the issues raised during this session were not exclusive to influenza. The same types of issues are being observed with the inability to get to a vaccine for Ebola and Zika as strains or viruses burn themselves out, abruptly reemerge, and disappear again. This field as a whole is going to have to continue grappling with the idea of what kind of data is acceptable at different points in an epidemic or the natural rise and fall of these viruses.

Dr. Stephens would like to see effectiveness data, given that it is most powerful in human populations. This may not be available for a while. He said that he was troubled that the *in vitro* studies were proposed to be a correlate based on some of the discussion about slides 20 and 22 and the new A/Slovenia strain. Even those data were not very convincing to him at this point.

Dr. O'Leary (PIDS) noted that in some of the data from other countries, VE was still less than IIV. Some questions for the WG and ACIP is: What is the threshold? Is it better than zero? Is it overlapping confidence intervals? If they had good VE studies, what would be the threshold for consideration of another recommendation?

Dr. Atmar said he did not know whether a threshold could be defined at this point, but he reminded everybody that LAIV was superior to IIV in many of the early studies. He still believes that this is potentially an important vaccine, particularly for young children. Understanding why it did not work in the US for the three seasons it did not is important so that this can be overcome and it can be used again. It is a valuable tool even if IIV is accepted by parents and children in this age group.

Ms. Stinchfield (NAPNAP) said that anecdotally in clinical settings in hospitals, clinics, and school-based influenza programs, they did not see a lot of rejection of the injectable vaccine this year. There was initial sadness without having intranasal vaccine, but people dealt with that and went on. Those who wanted to be vaccinated were taking the injectable.

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Herpes Zoster Vaccines

Introduction

Edward Belongia, MD
Chair, Herpes Zoster Work Group

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 herpes zoster vaccines. The WG will:

- ❑ Consider vaccine and programmatic performance of currently licensed vaccine (Zostavax®)
- ❑ Consider the efficacy, safety and duration of protection of HZ/subunit (HZ/su) vaccine that is currently in review at FDA
- ❑ Identify programmatic options for both vaccines that incorporate cost effectiveness analyses and impact on disease burden

Recently, the WG reached consensus on important and critical outcomes to consider pertaining to vaccination for HZ, received presentations by manufacturers and researchers on the safety and immunogenicity of HZ vaccines, and considered the body of evidence supporting HZ/su vaccine.

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). During this session, there were presentations on the safety summary of HZ/su vaccine by GSK; and Grading of Recommendation Assessment, Development and Evaluation (GRADE) of HZ/su vaccine and considerations for policy by CDC. In June 2017, presentations are anticipated on a cost-effectiveness analysis, Zostavax® GRADE, and considerations for policy. A vote is anticipated in October 2017.

Safety Summary of Candidate Vaccine HZ/su

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Global Medical Affairs Lead, Zoster
GSK

Dr. Colindres noted that he would be presenting on behalf of a very large team at GSK and many study investigators across the world on the safety summary for GSK's adjuvanted HZ/su vaccine candidate. To place this presentation into context, he reminded everyone that ZOE-50 and ZOE-70 results were previously presented at ACIP sessions in 2015 and 2016, and also have been published in the *NEJM*. ZOE-50 and ZOE-70 are the Phase III clinical trials that enrolled subjects greater than 50 years of age and greater than 70 years of age respectively, and demonstrated a remarkable VE of greater than 90% independent of age, even in those greater than 70 years of age and 80 years of age who are most at risk for zoster disease. GSK is also pleased because this efficacy has been demonstrated to last at least 4 years post-vaccination. The presentation during this session focused on a broad overview of HZ/su vaccine safety.

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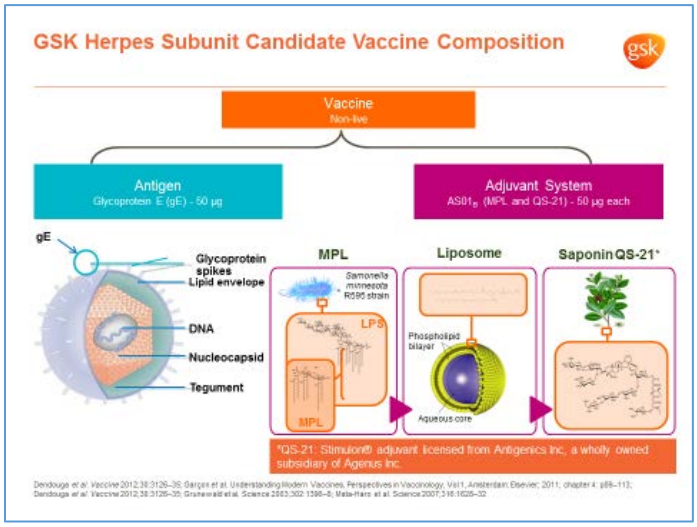
During this session, Dr. Colindres presented information on the vaccine composition; the adjuvant used in HZ/su vaccine; the incidence of solicited local and systemic events, including some new data on frequency of reactions between doses; detailed safety analyses and conclusions; and new data on 9-year immunogenicity for HZ/su vaccine.

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



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

AS01 was chosen for the zoster program because of its ability to increase both humoral and cellular response to the co-administered antigen. This is important in the context of zoster because of the VZV-specific cellular decline that can lead to increased susceptibility of zoster disease in individuals over 50 years of age. AS01 works by inducing a local and transient inflammatory response similar to other adjuvants in licensed vaccines. This transient inflammation, while often associated with local or systemic symptoms, promotes a faster, stronger, and longer lasting VZV-specific response[1,2] [[1]Didierlaurent et al, J. Immunol, 2014;. Didierlaurent et al, Exp Rev Vac, 2016. [2]Leroux-Roels G, et al. Clin Immunol. 2016 May 25;169:16–27].

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There is now a large amount of clinical experience with AS01 covering a wide range of populations with several antigens in over 40,000 subjects. Of course, the largest experience is with the HZ/su vaccine candidate in which over 28,000 adults have been exposed. The second largest population is greater than 12,000 infants and toddlers who received $AS01_E$, a smaller dose of the same adjuvant, together with a malaria antigen. There is a series of other vaccines in earlier phase development such as tuberculosis (TB), human immunodeficiency virus (HIV), and hepB in which the adjuvant has been combined with the antigen and applied to several populations such as children, adolescents, and adults. Importantly, all of these vaccines have been well-tolerated with no major safety concerns. Additionally, independent of antigen adjuvant combination, AS01 has been shown consistently to stimulate a strong T-cell response.

The safety data presented during this session were drawn from a large pooling of over 14,000 subjects from the ZOE-50 and ZOE-70 Phase III clinical trials which were conducted at multiple sites across 18 countries. A comparative analysis was performed between the vaccine group and a placebo group, including all of the safety endpoints: local and systemic reactions, SAEs and potential immune-mediated diseases (pIMDs).

In terms of how safety data were collected in these clinical trials, subjects received 2 doses of either vaccine or placebo at a 2-month interval. Solicited local and systemic symptoms were proactively collected via diary cards for 7 days post-each dose. SAEs were collected for up to 12 months post-second dose. SAEs considered related to vaccination by the investigator, any fatalities, and pIMDs were tracked for the entire time of the study, which had a mean follow-up of 4.1 years. As a note, because of the potential concern between adjuvanted vaccines and autoimmune diseases, GSK closely monitors pIMDs in all clinical trials with adjuvanted vaccine.

Turning to the results for solicited local symptoms of any grade post-vaccination in a comparison between the vaccine and placebo group, the solicited local symptoms were more common among vaccine than placebo recipients as might be expected with an adjuvanted vaccine. Pain was by far the most common solicited local symptom. The majority of these symptoms were reported as moderate to mild in intensity and had a median duration of 2 to 3 days. Looking specifically at Grade 3 solicited local symptoms reported during the 7 days post-vaccination, Grade 3 is defined as “redness and swelling at the injection site were scored as grade 3 for those more than 100 mm. All other symptoms were scored as 3 for preventing normal activity.” Subjects experienced 8% or less Grade 3 reactions for local symptoms, and these were still more common among vaccine than placebo recipients. The median time for these Grade 3 reactions was 1 to 2 days.

In terms of solicited systemic symptoms of any grade 7 days post-vaccination, for any grade fatigue, headache, myalgia, and shivering were the most common. All symptoms occurred more frequently in vaccine compared to placebo recipients. Most of these were mild to moderate in intensity, with a median duration of 1 to 2 days. Grade 3 solicited systemic symptoms 7 days post-vaccination were reported in 6% or less of study subjects and were still more frequent in the vaccine versus placebo group specifically for fatigue, headache, myalgia, and shivering. The median duration for these symptoms was 1 to 2 days.

Regarding some new data from an ad hoc analysis of systemic and local reactions by dose, GSK sometimes receives the question, “What is the frequency by grade between Dose 1 and Dose 2?” This analysis attempted to answer these questions. Looking at subjects’ intensity of reaction at Dose 2 for those individuals who had a Grade 0 or 1 reaction at Dose 1, 3650 subjects reported having a Grade 0 or Grade 1 pain following the first dose. Approximately 85% of the 3650 subjects had a similar Grade 0 or Grade 1 reaction following the second dose. If

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this is extended to look at the remaining systemic symptoms, the trend is similar with the proportion of subjects who had a Grade 0 or Grade 1 specific symptom at Dose 1 experiencing a similar intensity of reaction for the same symptom at Dose 2 ranges between 85% and 92%. A similar analysis looked specifically at Grade 3 reactions at Dose 1 to determine what occurred with Dose 2. There were 155 subjects who reported Grade 3 pain on the first dose. Approximately two-thirds of the 155 subjects experienced Grade 2 or less reaction on the second dose. Extending to the other systemic symptoms, the trend is similar with the proportion of subjects who had a Grade 3 specific symptom at Dose 1 experiencing a lower intensity of Grade 2 for the same symptom at Dose 2 ranging from 66% to 76%.

Regarding 2-dose compliance, 96% of subjects complied with the second dose in ZOE-50 among vaccine and placebo recipients. For ZOE-70, 94% and 95% received a second dose respectively for the vaccine and placebo groups. Overall in these clinical trials, there was very high second dose compliance. In terms of the impact of a Dose 1 reaction on Dose 2 compliance, of the 268 subjects ZOE-50 and ZOE-70 who experienced a first-dose Grade 3 local reaction, 23 received Dose 1 only and 245 (91%) received both Dose 1 and Dose 2. Of the 251 subjects who experienced a first-dose Grade 3 systemic reaction, 27 received Dose 1 only and 224 (89%) received both Dose 1 and Dose 2. While Dose 1 reaction may be a factor in subjects not receiving the second dose, the large majority of subjects in this study, including those who had a Grade 3 reaction on the first dose, still received the second dose.

Shifting to the main safety analysis, in the first 30 days post-last vaccination there was no difference between the vaccine and placebo groups for SAEs, fatalities, or pIMDs. At 1 year post vaccination, SAEs were well-balanced between the vaccine and placebo groups with a frequency of 10.1%. There also were no differences between groups for deaths or pIMDs, with pIMDs having an incidence of 0.7% in both groups. The most frequent SAEs by preferred term were cardiac conditions such as atrial fibrillation and myocardial infarction (MI), as well as infections such as pneumonia. These frequencies are as would be expected for the study population. More importantly, for the individual rates of these frequent SAEs, there was no difference between the vaccine and placebo groups.

Regarding fatal SAEs by time period, for all time periods evaluated, there were no differences between the vaccine or placebo group. The majority of the deaths occurred greater than 1 year post-last vaccination. In terms of the most frequent fatal SAEs during the whole post-vaccination time period overall, cardiac conditions, infections of the respiratory track, and neoplasms were common. This aligns with the most frequent causes of death among this aged population. Once again, these most frequent fatal SAEs were equally balanced between the vaccine and placebo groups. As expected, fatal SAEs were more common in subjects 70 years of age or older.

For all time periods evaluated, the pIMDs were seen in equal frequency among the vaccine and placebo groups, with a frequency of 1% for the entire study period in both groups. Approximately half of the pIMDs were reported greater than one year after the last vaccination. The most frequent pIMDs in the entire study were polymyalgia rheumatic, rheumatoid arthritis, psoriasis, and autoimmune thyroiditis. These are some of the most frequently reported pIMDs in the general population. There were no differences for these between the vaccine and placebo groups.

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In conclusion for local and systemic solicited symptoms, as may be expected with an adjuvanted vaccine, local and systemic solicited symptoms were higher in the HZ/su vaccine versus placebo group. However, the majority of symptoms were mild to moderate intensity and of short duration of 1 to 3 days. In an ad hoc analysis, it was observed that subjects with Grade 3 reaction at Dose 1 were likely to experience a lower grade reaction at Dose 2 for the same symptom. Compliance for the second dose was quite high overall at 95%, and ≥ 89% even among subjects who had Grade 3 reaction at Dose 1. With regard to general safety conclusions, a large safety database with over 14,000 subjects with greater than 60,000+ person years of active follow-up was available for the evaluation of the safety of HZ/su candidate vaccine. Safety data from the HZ/su vaccine clinical program has not detected any safety concern. The overall incidence of SAEs, deaths, and pIMDs is equal between the vaccine and placebo groups. Based on the data available, the current benefit/risk profile for this vaccine remains positive.

The new data on the 9-year immunogenicity of HZ/su vaccine come from the Zoster-060 study, which is an extension to a Phase II immunogenicity and safety study (Zoster 003). Subjects in the original study received 2 doses of HZ/su vaccine at a 2-month interval. A subset of subjects from this original study were followed through 6 years post-vaccination, and these data were published previously. Zoster-060 included 70 subjects for evaluation of immune response at year 9 post vaccination. The endpoints assessed included antigen-specific humoral and cell-mediated immune response.

The 70 subjects received 2 doses of HZ/su vaccine and had a mean age of 72.3 at the time of the initial vaccination. The mean age 9 years later is 81.3 with the oldest subject in the study being 90 years of age. There was a predominance of female subjects and all subjects were White-Caucasian, which is not surprising considering that the study was conducted in Germany, Sweden, and the Czech Republic.

In terms of the sustained cellular immune response overall 9-years post-vaccination, the cellular immune response persists well above pre-vaccination baseline values. At month 108, or 9 years post-vaccination, there was a 3.4-fold increase over pre-vaccination. This fold increase was sustained since month 48, or 4 years post-initial vaccination. Similar results were observed when stratified by age categories of subjects 60 through 69 years of age and 70 years of age or older. Independent of age and including the subjects who were 70 years of age or greater at initial vaccination, there was a modest decrease in immune response during the first few years that seems to have plateaued by Year 4 and remained stable through Year 9, still above the pre-vaccination levels. Looking at sustained humoral immune response for the same two age categories, the trends for humoral immunity closely followed those of cell-mediated immunity with persistent immune response at Year 9 well-above baseline levels, a larger fold than the cell-mediated immune responses. The humoral immune response also remained stable between Year 4 and Year 9 and applied to all age groups, including those individuals 70 years and older at initial vaccination.

In conclusion, 9 years post-vaccination, immune responses to HZ/su vaccine were above baseline values (median 3.4-fold increase) in healthy older adults. Stable, persistent immune responses were observed between Year 4 and Year 9. Immune responses were maintained in the oldest age cohort (≥ 70 years). Additional Year 10 data will be available in the first quarter of 2018.

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In summary, the HZ/su candidate vaccine has a well-characterized safety profile with no concerns observed to date. The majority of local and systemic reactions were of mild to moderate intensity and of short duration. As might be expected with an adjuvanted vaccine, these were higher among HZ/su vaccine than placebo recipients. However, this same adjuvant in combination with the gE antigen contributes to robust immunogenicity, persisting through 9 years post-vaccination. The unique combination of adjuvant and antigen in HZ/su vaccine has led to unprecedented VE of greater than 90% independent of age, largely overcoming the natural decline in cell response that can lead to increased zoster in older adults. This VE extends at least 4 years post-vaccination and may very well last for much longer.

Discussion Points

Dr. Reingold asked whether there were any studies of immunogenicity and safety data in people who have previously received another zoster vaccine, and whether GSK would be seeing an indication for use in that population.

Dr. Colindres responded that GSK is currently conducting a revaccination study among subjects 65 years of age and older who received or did not receive the currently licensed vaccine. This study will evaluate immunogenicity and safety, and the results should be available in the upcoming months.

In terms of the 4% to 5% who did not return for the second dose, Dr. Hunter asked how hard the research assistants worked to get them to come back. He wondered how this would work in actual practice outside of a research setting.

Dr. Colindres replied that the reasons for not returning were quite varied, but as expected in most clinical trials. The number one reason was withdrawal of consent not due to an AE. Other reasons included loss to follow-up, moving from the area, unsolicited AEs, SAEs, pIMDs, and protocol violations. While there are no real-world data yet, in the clinical trial settings in the US, at the lowest percentile of compliance in individual sites, the lowest 2-dose compliance was 85%. Worldwide, the lowest compliance was approximately 68%. GSK is currently working with its own health economic teams as well as health economic teams at CDC to determine how to best estimate 2-dose compliance in a real-world setting.

Dr. Walter observed that about 5% to 6% of participants had Grade 3 reactions per event, and wondered what total percentage had a Grade 3 reaction.

Dr. Colindres replied that for specific symptoms, 8% or less experienced Grade 3 injection site symptoms and 6% or less experienced Grade 3 systemic symptoms. It is about 8% to 9% for all of the symptoms combined. An analysis is being performed now to interpret what exactly is the experience of a patient with a Grade 3 reaction. By definition a Grade 3 for most of the symptoms was preventing daily activity. A Grade 2 was interfering with daily activity and a Grade 1 was tolerable.

Dr. Duchin (NACCHO) asked whether there was any variability in the incidence AEs or SAEs according to the race or ethnicity of the subjects.

Dr. Colindres responded that the patterns of safety and reactogenicity among minority populations, such as African Americans or Hispanics, did not differ significantly from the general population as a whole. Of the North America subjects, 8% were African American. Based on the US Census data from 2016, African Americans above 50 years of age is about 10%. They

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realized that they were modestly below the representation of the general population, but GSK always strives to have a diverse population in its studies.

Dr. Decker (Sanofi Pasteur) asked whether they had followed the Zoster 003 population over time to look at zoster-free survival curves.

Dr. Colindres replied that the current plan for the Zoster-060 study as an extension of the Zoster 003 study is to follow those subjects through Year 9. Currently, the only subjects still being followed are the 70 presented during this session. The placebo recipients have not been followed.

GRADE of HZ/su Vaccine

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Dr. Dooling presented the results from the GRADE analysis of HZ/su vaccine. She reminded everyone that the GRADE process is to develop policy questions, consider critical outcomes, review and summarize evidence of benefits and harms, evaluate quality of evidence, assess population benefit, and evaluate values and preferences. The subsequent steps involving the review of health economic data, considerations for formulating recommendations, and GRADE category will be presented during a future meeting.

The policy question for consideration is, “Should HZ/su vaccine be routinely used to prevent herpes zoster?” The population of interest is immunocompetent adults aged 50 years or older. The intervention of interest is a 2-dose series of HZ/su vaccine consisting of the current formulation of 50 µg gE and the adjuvant $AS01_B$ administered intramuscularly at 0 and 2 months. The WG looked for studies that compared this intervention to placebo or no vaccine. The outcome the WG considered most important included the following:

- ❑ HZ
- ❑ Post herpetic neuralgia (PHN)
- ❑ Duration of protection against HZ
- ❑ SAEs
- ❑ Reactogenicity (Grade 3)

Outcomes included in the evidence profile can be divided into both benefits and harms. The benefits of prevention of HZ and PHN were deemed critical and duration of protection considered important. The harm category of SAEs was deemed critical and reactogenicity was considered important.

The WG completed a systematic review of studies from PubMed, Embase, CINAHL, Cochrane, Scopus, and clinicaltrials.gov in any language. Efforts also were made to obtain unpublished or other relevant data. Initial search terms included: “herpes zoster” and “subunit,” or “HZ su ADJ5 subunit,” or “HZ su,” or “GSK 1437173A.” Articles were included if they presented data on the HZ/su vaccine and involved the relevant population of immunocompetent adults aged 50 years or older, included data for the relevant intervention, included data relevant to the outcome measures being assessed, and reported primary data.

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Working with an expert in Library Sciences, the WG identified 116 references via database searches. An additional 32 references were identified from clinicaltrials.gov. Title and abstracts were then screened for all 148 references, and records were excluded if there was no primary data or if the study did not include the population or intervention of interest. Following that step, 29 full text articles were reviewed and 19 were excluded because either the study was still ongoing, the reference was a duplicate, the population under study was immunocompromised, or multiple vaccines were co-administered as an intervention. Ultimately, 10 studies were included in this GRADE analysis.

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

Outcome #1 was the incidence of HZ. Two manuscripts were included for assessment. Lal et al reported an RCT in adults 50 years of age and older, also known as ZOE-50. This Phase III clinical trial compared HZ/su vaccine to placebo and reported vaccine efficacy against HZ. Cunningham et al reported an RCT in adults 70 years of age and older known as ZOE-70, which also reported vaccine efficacy against HZ compared to placebo. These GSK-funded studies were performed in parallel at the same study sites in 18 countries. After enrollment in the study, participant 70 years and older were randomized either to ZOE-50 or ZOE-70. Study protocols were consistent in both study arms. While the results were reported separately, for GRADE purposes these were considered as one study.

For HZ, the estimates of effect were as follows: For adults over 50, VE was 96.6%. For adults in their 60s, it was 97.4%. For adults 70 years of age and older, VE was 91.3%. The type of evidence supporting the prevention of HZ is Type 1. ZOE-50 and ZOE-70 are considered one RCT with an initial evidence level of 1. The WG determined that there was no serious risk of bias. As there was only one study, inconsistency could not be assessed between studies. There were no serious concerns regarding indirectness of the study with respect to the central policy question, and no concerns regarding imprecision of the study.

Outcome #2 was the incidence of PHN. Cunningham et al described previously pooled data from pooled data from ZOE-50 and ZOE-70 studies to report VE against PHN. Regarding incidence of PHN, the estimates of effect were as follows: For adults 50 years of age and older, VE was 91.2%. For adults in their 50s and 60s, there actually were no cases in the vaccinated group. Thus, there was a VE of 100% with wide confidence intervals. The study was powered to assess PHN in adults 70 years of age and older. For this group, VE was 88.8%.

The type of evidence supporting incidence of PHN is type 1. ZOE-50 and ZOE-70 are considered one RCT with an initial evidence level of 1. The WG determined that there was no serious risk of bias. As there was only one study, inconsistency could not be assessed between studies. There were no serious concerns regarding indirectness of the study with respect to the central policy question, and no concerns regarding imprecision of the study.

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Next, the WG considered outcome #3, duration of protection against HZ. Again, Cunningham et al was the only manuscript to report on this outcome and was derived from pooled ZOE-50 and ZOE-70 data. For the duration of protection against HZ, estimates of effect in adults 70 years of age and older were as follows: During the first year following vaccination, VE was 97.6%. In the second, third, and fourth years, VE was 92.0%, 84.7%, and 87.9%, respectively.

The type of evidence supporting the duration of protection against HZ is type 1. ZOE-50 and ZOE-70 are considered one RCT with an initial evidence level of 1. The WG determined that there was no serious risk of bias. Inconsistency was not applicable. There were no serious concerns regarding indirectness of the study with respect to the central policy question, and no concerns regarding imprecision of the study.

Turning to the evidence for potential harms, outcomes #4 and #5 were SAEs and reactogenicity. Four studies were included. Cunningham and Lal were discussed earlier in this presentation. Chlibek et al in the *Journal of Infectious Diseases* (*JID*) in 2013 was an RCT that included adults 50 years and older and compared HZ/su vaccine to placebo and assessed SAEs as well as reactogenicity. Another study by Chlibek et al published first in 2014 and then followed up in 2016 was an RCT that compared HZ/su vaccine to an unadjuvanted glycoprotein vaccine. Poder, Leroux-Roels, and Vink were RCTs in the target population that administered HZ/su vaccine but did not have a non-vaccine comparison group. Godeaux and Lal 2013 were not randomized, nor did they have an adequate comparison group. All studies assessed SAEs as well as reactogenicity, and all were funded by GSK.

Outcome #4 was SAEs. Among the over 29,000 participants followed through the entire study period, almost equal numbers of SAEs were observed in the placebo and vaccine groups. This was true for all SAEs as well as AEs considered by the independent safety committee to be possibly related to vaccination. The remaining 7 studies that administered HZ/su vaccine to a total of 616 participants found no SAEs related to vaccination. The type of evidence for SAEs is type 1. There were two RCTs with an initial evidence level of 1. The WG determined that there was no serious concerns regarding risk of bias, inconsistency, indirectness, or imprecision. The four RCTs with no placebo group and the two non-randomized trials were non-blinded, open-label trials and therefore were downgraded for risk of bias and indirectness. They were downgraded for indirectness because they did not have a comparison group. The two non-randomized studies started at a lower initial evidence type. Given that the top two listed RCTs contributed type 1 evidence and the other studies were consistent with their findings, the evidence type assigned to this outcome is type 1.

Outcome #5 was reactogenicity, specifically Grade 3 reactions. In ZOE-70 studies, symptoms were solicited from almost 10,000 participants for 7 days following vaccination. Any Grade 3 reaction was noted in 3.1% of the placebo and 16.5% of the vaccinated group for a difference of 13.4%. Grade 3 reactions at the injection site showed 9.1% excess in the vaccinated group, and Grade 3 systemic reactions showed an excess of 8.4% in the vaccinated group. Four additional studies reported any solicited Grade 3 reactions after vaccination among participants who received HZ/su vaccine. Those estimates are 3.4% (Godeaux, 2017, n=96), 9.3% (Chlibek, 2013, n=150), 11.5% (Poder, 2016, n=119), and 40% (Lal, 2013, n=10). The remaining three studies that administered HZ/su vaccine to a total of 241 participants reported Grade 3 reactions by symptom and had findings consistent with the previous studies. The type of evidence for reactogenicity was type 1. There were two RCTs with an initial evidence of type 1. The WG determined that there was no serious risk of bias in these studies and there were no concerns about inconsistency, indirectness, or imprecision. The four RCTs with no placebo group were non-blinded, open-label trials and were downgraded for risk of bias and

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indirectness. The two non-randomized studies had an initial evidence level of 2 and were downgraded for risk of bias and indirectness. Given that the two RCTs contribute type 1 evidence and that the other studies are consistent with those findings, the evidence type assigned to this outcome was also type 1.

There were limitations to the ZOE-50 and ZOE-70 study as with any study. Reactogenicity of the vaccine itself may have resulted in effective un-blinding of some vaccine recipients, leading to opportunities for bias in reporting of AEs and possibly case ascertainment. With regard to generalizability, only 18% of the participants were from North America and only 1% of overall participants were black. The study excluded those with a history of HZ, previous Zostavax® recipients, and those taking immunosuppressant or immuno-modifying drugs.

In summary, the critical outcomes of HZ, PHN, and SAEs are all supported by at least one good quality, large RCT. To recap, the findings were that HZ/su vaccine is significantly efficacious in preventing HZ and PHN. No differences were detected between the vaccinated and placebo groups for SAEs. Grade 3 reactions were more commonly reported in vaccinated groups compared to placebo. Overall, HZ/su vaccine was significantly efficacious in preventing HZ 4 years following vaccination. The overall evidence type supporting the critical outcomes is 1. In other words, the WG's level of certainty of the estimate of effect for these outcomes is high.

Consideration for HZ Vaccine Policy

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Dr. Dooling emphasized the importance of considering vaccine policy in the context of the epidemiology in the US. The annual rate of HZ is approximately 4 cases per 1000 population or roughly 1 million cases annually[1,2]. The incidence increases with age, ranging from <1 case/1000 children to >15 cases/1000 population 80 years and older[2,3]. For adults 50 years and older with HZ, 10% to 18% will go on to develop PHN. Similar to HZ, the incidence increases with age[3]. The incidence of HZ is decreasing in children, increasing in younger adults, and has plateaued in adults ≥65 yrs[4] [[1]Jumaan et al., JID, 2005, 191:2002-7; [2]Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9; [3]Insinga et al., J Gen Intern Med. 2005, 20:748-53; [4]Hapaz et al, IDWeek 2015].

Zostavax®, a live attenuated vaccine for the prevention of HZ, was recommended by ACIP in 2008 for immunocompetent adults ≥60 years. Phase III clinical trials demonstrated a VE of 51% against HZ and 67% against PHN[5]. The duration of protection against HZ[5,6] was 62% in Year 1, 45% by Year 4, and 7% by Year 9. In terms of AEs following immunization[5], there was no significant difference between placebo and vaccine. However, non-serious AEs were seen more frequently in the vaccinated group. In 2015, 31% of adults ≥60 years had been vaccinated with Zostavax[7] [[5]Oxman et al. 2005, NEJM, [6]Morrison et al. 2015, CID; [7]CDC 2015 Adult Vaccination Coverage General Population Report.

Therefore, the key factors to consider when formulating policy recommendations can be summarized as thus: The evidence type for both harms and benefits is evidence type 1. In terms of balance between benefits and harms, HZ and PHN were significantly less frequent in the vaccinated group. That finding persisted 4 years following vaccination. SAEs occurred at

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similar rates in vaccinated and placebo groups. Grade 3 reactions occurred more frequently in vaccine recipients. Ultimately, the WG concluded that benefits of disease prevention outweigh harms of reactogenicity. With respect to values, the WG placed high value on prevention of HZ and PHN. Studies have shown that community members also place high value on prevention of HZ and PHN[8]. Patients who had experienced herpes zoster consistently placed the highest value on avoidance of the disease[8] [[8]Lieu, Pharmacoeconomics 2009]. Of course, cost-effectiveness will be an important factor to consider. That analysis is ongoing.

The WG has identified a number of information gaps for policy-making. For example, 2-dose compliance was 95% in Phase III clinical trials. It is not known what 2-dose compliance will be under real world conditions, or whether non-completion of the series will have an effect on vaccine effectiveness and/or duration of protection. The protection that HZ/su vaccine can provide beyond 4 years is not clear. Though no data are yet available to assess vaccine efficacy in immunocompromised persons, fortunately Phase III trials of 2 vaccines, HZ/su and V212, are ongoing. The efficacy and safety data from these trials will inform vaccine policy in this high-risk group. Importantly, there are no head-to-head comparisons of VE between HZ/su and Zostavax®.

Based on the review of the evidence for critical and important outcomes, the WG's interpretation is that the vaccine is safe, efficacious, and maintains high protection against HZ 4 years following vaccination among immunocompetent adults aged 50 years and older. The issues under active consideration by the WG are as follows:

- ❑ Should recommendations for routine vaccination start at age 50 or age 60? The substantial disease burden in the 50 through 59-year-old cohort must be weighed against increasing disease incidence with age, possible waning of immunity, and incremental cost/benefit.

- ❑ Should persons previously vaccinated with Zostavax® be revaccinated with HZ/su and if so, when? As mentioned earlier, Zostavax® recipients account for over 30% of the population 60 years of age and older. The known waning of immunity of Zostavax® must be considered and the forthcoming safety and immunogenicity studies that address revaccination. More information will be presented on this during the June ACIP meeting.

- ❑ What policy recommendations may prevent the greatest burden of HZ and PHN if 2 licensed vaccines are available for use? Given the differing VEs, duration of protection, reactogenicity profiles, and dosing regimens, how can we prevent the most disease?

- ❑ What is the most cost-effective vaccine program? The price of HZ/su vaccine is not yet known, but that will factor into each of the above considerations. ACIP will hear cost-effectiveness analyses during the June and October 2017 meetings.

Next steps for the WG include cost-effectiveness analyses for HZ/su in the context of the current vaccine program, as well as a GRADE for Zostavax®. Forthcoming data for consideration include co-administration of HZ/su with other adult vaccines and expanded dosing schedules, immunogenicity and safety in adults who have previously received Zostavax®, and immunogenicity and safety in Zostavax® versus HZ/su.

To recap and review the intended timeline, after today's review of safety and GRADE HZ/su, in June 2017 ACIP will hear a GRADE review of Zostavax®, as well as safety and immunogenicity data that will compare HZ/se and Zostavax® and revaccination. Cost-effectiveness and considerations for policy also will be presented in June. In October 2017, summaries of

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GRADE, cost-effectiveness, and policy considerations will be presented. With that in mind, she asked whether there are additional data that would be helpful to ACIP to inform a recommendation for the use of HZ/su in immunocompetent adults.

Discussion Points

Dr. Hunter thought there were times when there were lower quality evidence that would diminish higher quality evidence, such that the final quality score would be lower.

Dr. Dooling clarified that within any individual outcome, the GRADE level applied is not necessarily the arithmetic average of the GRADEing of the studies. In fact, if there is strong level 1 evidence, that carries the most weight. For the outcomes she presented, the lower quality of evidence showed similar effect sizes as the higher quality of evidence; therefore, the higher quality of evidence prevailed.

Dr. Hunter asked which would have prevailed if the higher and lower quality of evidence had not agreed, and if there is ever a decrease in the final quality score of the evidence when there is only one study from one source.

Dr. Dooling replied that the overall quality of evidence would have been downgraded for inconsistency. Therefore, the highest quality would not have been assigned to any outcome that demonstrated inconsistency of estimates. In terms of only one study, one of the areas of assessment is heterogeneity or inconsistency between studies. With only one study, that particular parameter cannot be assessed. This raises a good philosophical point in terms of whether it should count against the body of evidence that there is only one large study. So far, the guidance has been to not downgrade if there is one well-done, large RCT.

Dr. Patricia Whitely-Williams (NMA) asked if the group discussed whether having additional data on the use of zoster vaccine in a more heterogeneous population, particularly African Americans, would be beneficial. The disparity gap is large for this vaccine and is probably even worse for some of the other vaccines. Not that they could predict that there would be an adverse health outcome. However, if there is, it is important to avoid having any other more negative effect or reasons for African Americans not to become immunized, particularly as the population ages.

Dr. Dooling responded that the WG agrees that diversity in the population under the study is extremely helpful and essential to be able to generalize the results to the entire American population for whom ACIP would be making recommendations. Worldwide, it was only 1% of the study population. Specifically within the US population, the percentage was greater as was previously indicated by Dr. Colindres. Could the study populations achieve better diversity to reflect the populations for whom we want to make public health recommendations? Absolutely. The WG has consistently reinforced that in its discussions and has asked for specific ethnicity- or race-based breakdowns of safety.

Dr. Bennett asked whether there were any additional data that would be helpful to the ACIP. No other data were requested.

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Meningococcal Vaccines

Introduction

David S. Stephens, MD
Chair, Meningococcal Work Group

Dr. Stephens reported that the Meningococcal WG has been engaged with a number of activities, including reviewing newly available data for meningococcal B (MenB) vaccines, including antibody persistence and response to a booster dose, considering booster doses of MenB vaccine for persons at increased risk, and recently hearing an update on the discontinuation of the meningococcal polysaccharide vaccine Menomune® (MPSV4).

The policy option under consideration pertains to booster doses of MenB vaccines for persons at increased risk, which states that:

- Booster doses of MenB vaccine should be administered every 5 years throughout life to persons aged ≥10 years in each of the following groups:
  - Persons with persistent complement component deficiencies including persons taking eculizumab
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis* (as long as exposure continues)

- Booster doses of MenB vaccine should be administered to persons identified as at increased risk because of a serogroup B meningococcal disease outbreak if it has been ≥6 months since their last MenB dose
  - When multi-year or prolonged outbreaks occur, CDC should be consulted and recommendations for additional booster doses will be considered on a case-by-case basis

The agenda for this session focused on considerations for MenB booster doses in groups at increased risk for serogroup B meningococcal disease; and an update on the epidemiology of meningococcal disease and guidance for the control of meningococcal disease outbreaks in the US.

As mentioned, Sanofi Pasteur is discontinuing production and supply of the meningococcal polysaccharide vaccine A, C, Y, W Menomune® (MPSV4) in the US. The last remaining lots will expire in June through September 2017. Letters to health care providers were sent on February 8, 2017.

The updated guidance for use of meningococcal vaccines in persons aged ≥56 years is as follows:

- Meningococcal vaccines that are licensed for use in persons aged ≥56 years are not currently available in the United States

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- Persons aged ≥56 years who are recommended meningococcal vaccination because they are at increased risk for meningococcal disease should receive MenACWY conjugate vaccine
  - This includes, meningococcal vaccine-naïve persons aged ≥56 years who anticipate requiring only a single dose of meningococcal vaccine (e.g. travelers and persons at risk as a result of a community outbreak)
  - And persons who were vaccinated previously with MenACWY conjugate vaccine and are recommended for revaccination or for whom multiple doses are anticipated (e.g., persons with asplenia, HIV, and microbiologists)

A Policy Note regarding the updated recommendations for the use of MenB-FHbp (Trumenba®) is soon to be published in the *MMWR*.

Considerations for Serogroup B Meningococcal (MenB) Vaccine Booster Doses in Persons at Increased Risk for Serogroup B Meningococcal Disease

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

Ms. MacNeil presented the WG's considerations for MenB vaccine boosters in persons at increased risk for serogroup B meningococcal disease. As a reminder, MPSV4 polysaccharide vaccine was first recommended for groups at increased risk in 1980. MenACWY conjugate vaccine was recommended for persons 11 through 55 years of age at increased risk when licensed in 2005, which was the original age indication for licensure. Recommendations for children 2 through 10 years of and infants at increased risk were then made as the licensed indication expanded. However, during this time, MPSV4 was available for use in persons at increased risks who were outside of the licensed age indication of the conjugate vaccine. In 2010, booster doses of MenACWY conjugate vaccine were added for certain groups who remain at increased risk for meningococcal disease.

The rationale for ACIP recommending booster doses of MenACWY for persons at increased risk included that persons at increased risk for meningococcal disease represent small targeted groups with a demonstrated increased risk for meningococcal disease. There is evidence of waning functional antibody 3 to 5 years after a single dose of MenACWY and evidence of a booster response to revaccination. There is a low-risk for SAEs following additional doses of meningococcal conjugate vaccine, and vaccination is the accepted standard of care for high-risk groups. Based on these considerations, ACIP recommended booster doses of MenACWY every 5 years throughout life for certain persons who remain at increased risk for meningococcal disease.

In 2014 and 2015 two MenB vaccines were licensed in the US for persons aged 10 to 25 years of age. MenB-FHbp (Trumenba®, Pfizer) contains two components. It can be administered either as a 3-dose series administered at 0, 1–2, and 6 months among persons at increased risk for serogroup B meningococcal disease or as a 2-dose series at 0 and 6 months when administered to healthy adolescents who are not at increased risk. MenB-4C (Bexsero®, GSK) contains four components and is administered as a 2-dose series at 0 and ≥1 month of age. MenB-4C is also licensed in a number of other countries for use in persons ≥2 months of age.

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Shortly after the licensure of the MenB vaccines, in 2015 ACIP recommended routine use of MenB vaccine for persons aged ≥10 years at increased risk for serogroup B meningococcal disease. During its February 2015 meeting, ACIP recommended routine MenB vaccination for persons with complement component deficiencies, persons with anatomic or functional asplenia, microbiologists routinely exposed to isolates of *Neisseria meningitidis*, and persons identified as being at increased risk because of a serogroup B meningococcal disease outbreak. In June 2015, ACIP recommended that adolescents and young adults 16 through 23 years of age may receive a MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. To date, ACIP has not discussed or made recommendations for booster doses of MenB vaccine.

It is known that certain people, including the groups outlined above, who are increased risk for meningococcal disease are likely to remain at increased risk throughout their lifetime. Further available data suggest waning of antibodies shortly after vaccination with MenB vaccines among healthy subjects. There are currently limited data available on the immunogenicity of the MenB primary series among immunocompromised subjects, the duration of protection of MenB vaccines, and the efficacy of MenB booster doses among persons at increased risk. It is unlikely that more data for these groups will become available. However, there is a need to optimize protection for persons at increased risk for meningococcal disease.

During this presentation, Ms. MacNeil reviewed the groups at increased risk for serogroup B meningococcal disease who are currently recommended MenB vaccination, and discussed the WG's interpretation of the available data on immunogenicity of MenB-4C among immunocompromised subjects and data on the antibody persistence and response to a booster dose following a primary series with MenB-FHbp (Trumenba®) or MenB-4C (Bexsero®) among healthy subjects. In addition, she reviewed the proposed policy option for MenB booster doses among persons at increased risk for serogroup B meningococcal disease.

In terms of the groups at increased risk for serogroup B meningococcal disease currently recommended for MenB vaccination, persistent or genetic deficiencies in the complement pathway are well-known to increase risk for meningococcal disease. Individuals with persistent complement component deficiencies are at up to 10,000-fold increased risk for developing meningococcal disease often develop recurrent infections. Complement component deficiencies are rare and only affect about 0.03% of the US population[1]. Complement component deficiencies are often recognized as a result of a meningococcal infection or recurrent meningococcal infection. In the US, it is estimated that between 7% and 25% of meningococcal cases have a complement component deficiency[2] [[1]Densen R. Clin Exp Immunol. Oct 1991; 86(Suppl 1): 57-62; [2]Figueroa JE. Clinical Microbiology Reviews. July 1991; 4(3):359-95].

Persons who take eculizumab (Soliris®), which is a monoclonal antibody that is indicated for treatment of atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH) are also at elevated risk for developing meningococcal disease. This is because the monoclonal antibody binds to C5 and inhibits the terminal portion of the complement cascade. Data presented to the FDA Drug Safety and Management Advisory Committee showed that 16 cases of meningococcal infection occurred among persons taking eculizumab during 2007–2014, including one death.[1] These 16 cases occurred out of 5200 person years of eculizumab exposure, which means that these patients have 2000 times the occurrence of meningococcal disease when compared to the general US population. Among those 16 cases, 1 was serogroup B, 2 were serogroup C, and 2 were serogroup Y. In 11 cases, the serogroup was unknown[1]. All of the patients had been vaccinated with a MenACWY

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vaccine.[1] Additionally, the first known MenB vaccine failure was recently reported in the UK in a person taking eculizumab.[2] The number of patients taking eculizumab is unknown, but both aHUS and PNH are rare conditions [[1]http://www.fda.gov/ downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf; [2]Abstract O54: http://neisseria.org/ipnc /2016/ IPNC2016 AbstractBook.pdf; [3]http://atypicalhus.ning.com/page/what-is-ahus; [4]http://imgjp1. pnhsource.jp/Downloads/pdf/UnderstandingPNHBrochure.pdf].

Asplenic persons are also at increased risk for invasive infection caused by many encapsulated bacteria, including *Neisseria meningitidis*. The asplenic population is quite heterogeneous and notably includes patients with sickle cell disease which affects ~100,000 persons of all ages[1]. Importantly, people with asplenia have a higher case-fatality ratio when they do develop meningococcal disease (40%–70%)[2] compared to the US population.[3] In one study from the UK, persons with asplenia were shown not to respond as well to 1 dose of MenC vaccine[4] [[1]http://www.cdc.gov/ncbddd/sicklecell/data.html; [2]MMWR. January 28,2011; 60(3): 72-76; [3]Cohn AC. Clin Infect Dis 2010;50:184-91; [4]Balmer P. Infection and Immunity, Jan 2004, 332-337].

Microbiologists are also at increased risk of developing meningococcal disease, with an attack rate that was found to be 13/100,000 among those who work with *Neisseria meningitidis* compared to 0.1 to 0.2/100,000 among the general US population. Microbiologists have been shown to have a higher case fatality ratio, possibly due to exposures to higher concentrations of the organism or to highly virulent strains. However, the majority of cases that have occurred in clinical microbiologists occurred in those who were not using respiratory protection at the time of the exposure [Sejvar JJ. Journal of Clinical Microbiology. Sept 2005;43(9):4811-14].

Meningococcal disease outbreaks are rare and only account for 2% to 3% of US cases.[1] However, when they do occur, they cause significant anxiety and are devastating for the communities in which they occur. There were 5 serogroup B meningococcal disease outbreaks on college campuses during 2008–2014. During those outbreaks, students were found to be at between 200- and 1400-fold increased risk for meningococcal disease during the outbreak period. In 2015 and 2016, there have been an additional 6 serogroup B meningococcal disease outbreaks on college campuses [[1]National Notifiable Diseases Surveillance System].

In the US, data on the number of cases that occur among persons in these groups at increased risk are limited. Through the Active Bacterial Core surveillance (ABCs) system, information was collected on two of these groups, persons with anatomic or functional asplenia and complement component deficiencies. ABCs is an active laboratory- and population-based surveillance system that operates in 10 states and covers approximately 43 million persons, or 13% of the US population. ABCs collects data information from the medical record for all meningococcal cases reported in the surveillance area, and has collected information on whether cases had asplenia or sickle cell disease since 1995 and complement component deficiencies since 2005. One limitation that is of particular relevance for the information on the diagnosis of complement component deficiencies is that these deficiencies may not be diagnosed until after hospitalization for meningococcal disease and therefore may not be captured in ABCs during the medical record review for the acute meningococcal hospitalization.

In terms of the estimated number of people and the reported number of cases reported in each group, approximately 270,000 individuals fall into three groups of people at increased risk for meningococcal disease. Although only a handful of cases have been documented in ABCs or the published literature, these groups are known to be at increased for meningococcal disease

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and are currently recommended to be vaccinated with both MenACWY conjugate vaccine and MenB vaccine. Looking at the outbreak at-risk populations, approximately 180,000 students attend the universities where the 11 serogroup B university outbreaks occurred during 2008-2016. This translates into approximately 20,000 students at risk per year or 16,000 students at risk on average per outbreak. During these outbreaks on college campuses, a total of 50 cases of serogroup B meningococcal disease and 3 deaths were reported.

In summary, persons at increased risk for serogroup B meningococcal disease represent small targeted groups with a demonstrated increased risk for meningococcal disease. For persons with complement component deficiencies or anatomic or functional asplenia and most microbiologists, the increased risk for meningococcal disease is ongoing. For persons at increased risk because of a serogroup B meningococcal disease outbreak, the risk period may be more limited.

In terms of the immunogenicity among immunocompromised subjects for MenB-4C vaccine, Bexsero®, the only available data for MenB vaccine response in immunocompromised persons comes from a study that looked at the immunogenicity of a 2-dose series of MenB-4C among subjects with complement component deficiency or asplenia compared to healthy controls. This study was a Phase IIIb, open label, controlled, multi-center study that evaluated the safety, tolerability, and immunogenicity of 2 doses of MenB-4C administered to 152 subjects 2 through 17 years of age with complement deficiency or asplenia compared to 87 healthy controls. Subjects received vaccine at 0 and 2 months.

Immunogenicity was assessed as the proportion of subjects who achieved an hSBA titer ≥1:5 using an exogenous complement source for each of the 4 selected serogroup B strains tested. An exogenous complement source means that a complement derived from healthy adult sera is added during the hSBA assay. When comparing baseline to post-dose 2, after receiving 2 doses of MenB-4C, there was an increased immune response to all 4 strains tested in subjects with complement deficiency and asplenia. However, the response was generally lower in subjects with complement deficiency compared to subjects with asplenia or healthy controls.

Immunogenicity was also assessed as an hSBA titer ≥1:4 using an endogenous complement source for each of the 4 selected serogroup B meningococcal strains tested. Endogenous complement means that the source of the complement for the hSBA assay is the test serum itself. After receiving 2 doses of MenB-4C, all three groups had an increased response. However, the hSBA responses were lower among those with complement deficiency when an endogenous complement source is used.

Subjects with complement deficiency were broken down into 3 separate groups, including 7 subjects who were taking eculizumab, 4 subjects with terminal complement deficiencies, and 27 subjects with other deficiencies compared to 85 healthy controls. After receiving 2 doses of MenB-4C, there was an increased response among all three groups, but the subjects taking eculizumab had the lowest response.

In summary, in the only available data assessing immunogenicity of a 2-dose series of MenB-4C among persons 2 through 17 years of age at increased risk of for meningococcal disease, there was an increase in hSBA responses in subjects with complement component deficiency and asplenia, and in subjects receiving eculizumab after two doses of MenB-4C. Comparable responses were observed in healthy subjects and subjects with asplenia. The lower responses were reported in subjects with complement component deficiencies, especially if endogenous

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complement was used in the hSBA assay. Subjects receiving eculizumab showed an increase in hSBA titers, but had the lowest response.

Regarding MenB antibody persistence and response to a booster dose among healthy subjects, based on the available data, for healthy adolescents, antibody persistence and booster response data are available up to 48 months for MenB-FHbp and up to 11 through 24 months for MenB-4C. Among children 4 through 7 and 8 through 12 years, there are antibody persistence and booster response data for MenB-4C up to 24 to 36 months.

In terms of the persistence of hSBA responses ≥1:4 against 4 selected serogroup B meningococcal strains up to 48 months in adolescents aged 11 through 18 years following completion of a 2- or 3-dose series of MenB-FHbp, 1 month post-completion of the primary series for persons who completed both the 2- and 3-dose series, there was an initial increase in the percentage of persons with hSBA titers ≥1:4. However, the percentage of subjects with protective antibodies dropped sharply at 12 months post-completion of the primary series and then remained stable through 48 months post-vaccination.

Regarding antibody persistence up to 48 months in adolescents 11 through 18 years of age after completion of either the 2- or 3-dose of primary MenB-FHbp series and hSBA responses to a booster dose at 48 months post-primary series, for each strain tested there was an initial increase in the percentage of persons with hSBA titers ≥1:4 at 1 month post-primary series. This was followed by a decline at 48 months post-completion of the primary series, then followed by another increase in the percentage of persons with hSBA titers ≥1:4 1-month post-booster dose.

Looking at the percentage of adolescents with hSBA titers ≥1:4 or ≥1:5 1 month after a 2-dose primary series of MenB-4C, between 99% and 100% of adolescents had an hSBA titer of ≥1:4 or ≥1:5 1 month after a 2-dose primary series of MenB-4C. At 11 months or 18 through 24 months for each of the strains tested, antibody persistence declined over time.

Among children 4 through 7 years of age and 8 through 12 years of age who received a primary series of MenB-4C, there was an initial increase in the percentage of persons who had hSBA titers ≥1:4 1 month post-primary series, followed by a decline at 24 to 36 months post-completion as a primary series, followed by another increase in the percentage of persons with hSBA titers ≥1:4 at 1 month post-booster dose at 24 to 36 months.

The WG anticipates reviewing one additional study before the June 2017 ACIP meeting. Four-year antibody persistence and booster response data for adolescents from Canada and Australia after completion of primary series of MenB-4C are anticipated within the next few months. Data are anticipated to be available for ACIP to review during the June 2017 meeting.

The WG also reviewed the available safety data for both the primary series and a single booster dose for the MenB vaccines. As described to ACIP previously, MenB vaccines are more reactogenic than other vaccines given during adolescence, with the most common AE reported being pain at the injection site. However, the overall safety and tolerability profiles are similar for the primary series and one additional booster dose.

In summary, the available data demonstrate that there is evidence of waning antibody for both MenB vaccines as early as 12 months after completion of the primary series. However, different waning rates were observed for antibodies to each vaccine antigen or strain tested. The data from the two MenB vaccines are not directly comparable, as each was evaluated against

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different strains at different intervals following the primary series, and in subjects of different ages. These data also demonstrated that there is evidence of a booster response to revaccination among previously vaccinated subjects at intervals varying from 24 to 48 months, and there is a low-risk for SAEs following additional MenB doses.

Overall, the WG's interpretation of the data presented during this session is that persons at increased risk for serogroup B meningococcal disease represent small targeted groups with a demonstrated increased risk for meningococcal disease. MenB vaccines are immunogenic in persons at increased risk for meningococcal disease. Waning of antibody is observed as early as 12 months post-vaccination, and booster response is observed in previously vaccinated subjects following one additional MenB dose.

Similar to the rationale behind the recommendations for booster doses of MenACWY conjugate vaccine, the WG supports MenB booster doses among persons at increased risk because persons at increased risk for meningococcal disease represent a small targeted group with a demonstrated increased risk for meningococcal disease. Evidence of waning antibody is observed as early as 12 months after MenB vaccination, and there is evidence of a booster response to revaccination. There is also a low-risk for SAEs following additional doses of MenB vaccine, and vaccination is the accepted standard of care for high-risk groups.

The WG discussed the appropriate timing or interval for MenB booster doses extensively for persons who remain at increased risk for serogroup B meningococcal disease and in the setting of an outbreak. There is a desire to harmonize the timing of the booster recommendations with MenACWY for persons who remain at increased risk if possible to improve compliance with booster doses of both vaccines, and to ensure that some level of protection is maintained over time in these individuals. There was recognition that there is evidence of waning antibody as early as 12 months after the MenB primary series. However, the WG felt that harmonization of the booster doses made sense at the time given the currently available data. Outbreaks represent quite a different scenario, and there may be additional benefit to an individual if a booster dose is given at a shorter interval to a person previously vaccinated to ensure that antibody and potential protection is maximized during the outbreak period.

The overall consensus of the WG was to support routine MenB booster doses for persons at increased risk of serogroup B meningococcal disease, and to harmonize the timing of the booster doses with MenACWY boosters for groups at prolonged increased risk for meningococcal disease. In outbreak settings, the WG supported providing booster doses if it has been at least 6 months since their last MenB dose. Based on this, the WG proposed the following policy option:

- ❑ Booster doses of MenB vaccine should be administered every 5 years throughout life to persons aged ≥10 years in each of the following groups:
  - ➢ Persons with persistent complement component deficiencies including persons taking eculizumab
  - ➢ Persons with anatomic or functional asplenia
  - ➢ Microbiologists routinely exposed to isolates of *Neisseria meningitidis* (as long as exposure continues)

- ❑ Booster doses of MenB vaccine should be administered to persons identified as at increased risk because of a serogroup B meningococcal disease outbreak if it has been ≥6 months since their last MenB dose

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- When multi-year or prolonged outbreaks occur, CDC should be consulted and recommendations for additional booster doses will be considered on a case-by-case basis

A GRADE evaluation of the evidence supporting MenB booster doses is currently underway and will be presented to the ACIP in June 2017. In addition, an ACIP vote will be proposed during the June 2017 on routine MenB booster doses in persons aged ≥10 at increased risk for serogroup B meningococcal disease.

Ms. MacNeil posed the following questions on which the WG desired feedback:

- ❑ Are there additional data that ACIP would like to review?

- ❑ Does ACIP agree with the proposed policy option language and timing for booster doses in persons with complement component deficiencies, asplenia, and microbiologists?

- ❑ Does ACIP agree with the proposed policy option language and timing for booster doses in outbreak settings?
  - For persons previously vaccinated who later are in an outbreak?
  - For persons within a prolonged outbreak scenario?

Discussion Points

Dr. Atmar requested further information about the relative risk of MenB disease in high risk groups versus the groups involved in outbreaks at a population level.

Ms. MacNeil replied that increased risk varies for each group. For complement deficient people, it is up to a 10,000-fold increased risk, and is also extremely high for eculizumab. For asplenics, the risk is primarily for *streptococcus pneumoniae*, though there is also increased risk for *Neisseria meningitidis*. The primary risk for that group is increased mortality when they do become infected. For microbiologists, it is 13/100,000 and in outbreaks there is about a 200- to 1400-fold increased risk.

Dr. Atmar observed that the recommendation was for outbreak, which on a population-based level seemed to have a lower risk than the total complement deficient patients. Boosting at a shorter interval seemed like it should be the other way around, or it should be a shorter interval for all of them. He questioned the 5-year interval. While he understood that this made it easier, it would potentially leave more than 75% to 80% at risk during that 5-year period if immunity is waning by a year.

Ms. MacNeil indicated that the WG discussed this extensively and felt that based on the data available, it made sense to harmonize with the MenACWY recommendation for the groups at increased risk. There remains a question for the outbreak setting about whether the appropriate interval is 5 years or a shorter period.

Dr. Szilagyi requested additional information about the extent of waning after the booster dose.

Ms. MacNeil replied that there are data for only 1-month post-booster dose currently, but it is hoped that there will be additional data eventually.

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Dr. Kempe requested a reminder about the duration of immunity after ACWY, which she recalled was in the 4- to 5-year range.

Ms. MacNeil indicated that the vaccine begins to wane within a few years after vaccination. The waning curve is slightly different for ACWY in that it wanes somewhat more slowly. Decreases were observed in protection in the hSBA and effectiveness data as early as a few years after vaccination with only a single dose.

Dr. Messonnier noted that routine revaccination was included on the same slide with the outbreaks, but routine revaccination of people with complement deficiency is every 5 years across their entire lifespan as opposed to the outbreak recommendation which has occurred once a year in a limited population. This is the question faced from a public health perspective when a university calls CDC in the middle of an outbreak and is trying to decide what to do. Putting them together on the slide mixed the messages. Those on eculizumab are a small number of people, but they are at exceedingly high risk. However, the data with at least one vaccine do not look reassuring. She asked whether there was certainty that vaccination would help them, or if there is any other information that would help to make a data-based recommendation for that group of people.

Ms. MacNeil responded that the data reviewed so far suggested that vaccine may not protect these individuals. The WG is considering whether there are additional measures that should be used in this population to ensure protection. The WG felt that vaccination should be recommended for this group based on the chance that there would be some protection since the risk is so high. However, other interventions probably should be considered for that group as well.

Regarding Dr. Atmar's comments, Dr. Moore reported that there was not consensus about this issue among the WG members and there was a lot of concern about the 5-year benchmark because they recognized that the evidence of waning immunity showed that they would not be protected for a good portion of that time. While there was not an agreement, what people were weighing and the dilemmas they faced included the fact that there was a concern about people not getting the vaccine at all if it was recommended at a high frequency and also concern about trying to understand cost-benefit or the cost per case prevented among these high-risk populations, acknowledging that the population is very small and the absolute case count among that population is very small. It is very difficult to get a sense of how much would have to be spent and how many doses would have to be administered in that population to prevent a single case of MenB. There was a tension in those issues of trying to harmonize with the schedule that exists and how frequently doses would have to be given in order to provide consistent MenB protection at the highest level, and whether it would be worth it in terms of the potential for cases prevented. She did not believe the WG concluded with a firm answer on that, and would like to have ACIP's input into that dilemma.

Dr. Stephens added that it is unclear what will happen with a subsequent booster. It could provide a much longer period of protection, but those data are not available at this point in terms of making a specific recommendation. Regarding the terminal complement component inhibitor, these are people at very high risk. There is previous experience with polysaccharide and conjugate vaccine in complement deficient individuals. Even though ESBT cannot be boosted, which is what the data are based on, some protection is observed even though they persistently have complement deficiency. So, there may be other advantages to optimization of other components that may be simulated by a vaccine that would not necessarily be reflected in an

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SBA type of assay in that instance. There may be other considerations for this particularly very high-risk group that they need to focus on.

Regarding the question about additional data, Ms. Pellegrini pointed out that typically when discussing meningitis, ACIP hears data on cases and deaths. It is known that for the people who survive, there are often dramatic and life-altering, lifelong health consequences. It would be helpful in the future to capture some of that nuance, because it would help ACIP get a clearer picture of cost-benefit in that there is more than preventing just death. There are disabilities and other issues involved.

Dr. Thompson (NVAC) Requested clarity about the term “microbiologist” regarding how the WG was using it and how that might be interpreted with respect to laboratory personnel, more broadly, and routinely or just in the context of an outbreak.

Ms. MacNeil reminded everyone that two years ago when the recommendation was made, the WG engaged in considerable discussion about how to define that group. The original language was kept, which was that employee health or microbiologists will have to determine who fits that category. The research microbiologists who routinely work with *Neisseria meningitidis* clearly fit. The clinical microbiologists are somewhat more challenging to define. Those who work on outbreaks should be vaccinated already, because those who routinely work with *Neisseria meningitidis* would be in a public health or in a clinical laboratory. The WG has not discussed microbiologists in that setting in particular.

It was not clear to Dr. Savoy (AAFP) what data the WG reviewed to make them feel comfortable to spread out the timeframe for a booster to 5 years, when the vaccine wanes in a year. She values harmonization because family doctors have to deal with so many things already, but not at the risk of someone’s life. Given that this pertains to a very small number of people, the cost cannot be that much.

Dr. Romero pointed out that exposure by clinical microbiologists is not uncommon. His institution had an exposure this year, and it has happened at three times in the 10 years he has been at his institution. They are not cavalier. These people are very careful in what they are doing, but there are exposures in the clinical laboratory.

Dr. Hunter suggested that perhaps ACIP should say they cannot make a change because there are no data to support doing so.

Dr. Messonnier pointed out that the way the language is currently written, a dose is recommended every 5 years for the rest of one’s life. This requires a lot of investment and decision-making. She suggested that the WG think about the short-term versus obliging something for which there are no data across the lifespan. The recommendation already states that duration of protection is not known after one booster dose.

Dr. O’Leary (PIDS) expressed confusion about the process situation since the most someone could have had since the vaccine has been in use in the US is 2 years. With only 2 years of data, it was unclear to him why they were talking about 5 years. He suggested waiting a few years before deciding on a 5-year booster.

Dr. Reingold inquired as to what the current policy is in the military in terms of revaccination for people who are living in a barracks for 20 years, and if there are any data from the DoD that might be accessed.

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A DoD representative indicated that for regular inductees, this has not been included.

Dr. Moore asked what additional information the WG might consider to make a different recommendation, such as the concept of a range.

Dr. Stephens replied that it is known that there is significant waning at 12 to 18 months with the primary series. For individuals at risk, it is because of that waning that the WG is recommending the booster dose. The other question pertains to what should be done after that, and there are no data for that. Perhaps as Dr. Messonnier suggested, the recommendation should be narrowed in the hope of hearing additional data on persistence after the booster dose for future recommendations.

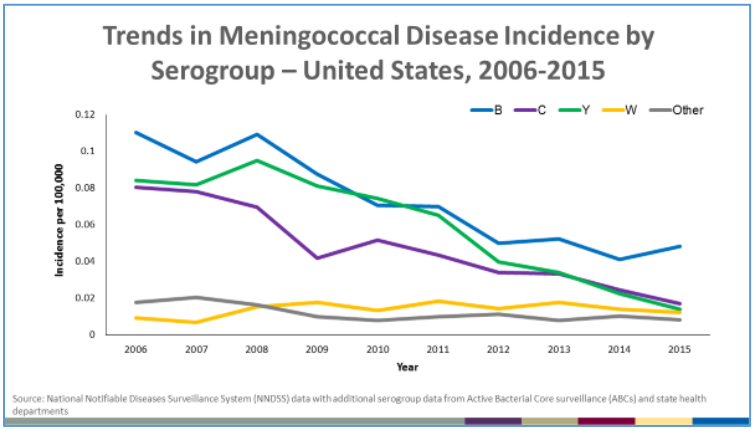
Dr. Atmar noted that an economic analysis had been alluded to, and it may be beneficial to see what the cost would be with various assumptions that might inform the WG's deliberations. He agreed with the suggestion to consider 1.5 to 2 years, but even for that an economic analysis could be beneficial.

Update on the Epidemiology of Meningococcal Disease and Guidance for the Control of Meningococcal Disease Outbreaks in the US

Sarah Meyer, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Meyer described the epidemiology of meningococcal disease and outbreaks in the US, reviewed the current guidance for the evaluation and management of meningococcal disease outbreaks, described the proposed updates to CDC's meningococcal disease outbreak guidance, and discussed the next steps.

Since the late 1990s, a sustained decline in the incidence of meningococcal disease has been observed in the US, decreasing from 1.3 to 0.12 cases per 100,000 population from 1996 to 2015. This decline in incidence began prior to the introduction of a quadrivalent meningococcal conjugate, or MenACWY, vaccine in adolescents or the availability of serogroup B, or MenB, vaccines. Incidence has decreased in all three primary disease-causing serogroups, B, C, and Y, shown in the blue, purple, and green lines in the graph below, with incidence of serogroup W and other serogroups remaining stably low:



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Incidence and serogroup distribution vary by age group. The highest incidence is observed in children aged less than 2 years and adults aged greater than 85 years. A peak in incidence is also observed among adolescents and young adults aged 16-25 years. Serogroup B is the predominant serogroup in children aged less than 5 years. In children and adolescents aged 5 through 20 years, serogroup B accounts for approximately half of cases, and in adults aged greater than 20 years, serogroups C, W, or Y cause the majority of disease.

Although information on outbreak-associated cases is collected through the National Notifiable Diseases Surveillance System (NNDSS), reporting is likely incomplete. In 2014, CDC and state health departments conducted a retrospective review of all meningococcal disease cases from 2009-2013 to identify and characterize clusters/outbreaks. For the purpose of this analysis, clusters were defined as 2 cases of the same serogroup within 3 months. Outbreaks were defined according to the current outbreak threshold as 3 or more cases of the same serogroup with an attack rate of >10 cases/100,000 population within 3 months. Clusters and outbreaks were classified as either organization-based in which there is a common affiliation other than a shared geographic space, or community-based in which there is no affiliation other than a shared geographic space. From 2009-2013, among the 3,683 cases reported to NNDSS, 195 primary cases from 41 clusters that met criteria were identified.

Regarding the epidemiologic features of these clusters, among the 41 clusters or outbreaks, 22 were community-based and 19 were organization-based. Among the community-based clusters or outbreaks, 2 occurred among men who have sex with men (MSM) during this time period. Compared to other community clusters or outbreaks, these clusters had higher cumulative attack rates. The other community-based clusters or outbreaks generally had low attack rates, with a median of 1 case per 100,000 population, with only 2 of 38 clusters meeting the outbreak threshold. Among the 19 organization-based clusters, 9 occurred among university populations and 10 occurred among other organizations such as a correctional facility, health-care facility, high school, et cetera. In general, organization-based outbreaks had high cumulative attack rates. Cases associated with organization-based clusters and outbreaks are primarily due to serogroup B; whereas, those associated with community-based clusters are primarily serogroup C. In contrast, sporadic cases are primarily due to serogroups B and Y, followed by serogroup C.

Dr. Meyer examined in more detail two commonly reported cluster or outbreak types in the US: serogroup B organization-based clusters among university populations and serogroup C community clusters among MSM.

From 2008-2016, 11 serogroup B university-based clusters or outbreaks were reported in the US. The epidemiology of these clusters or outbreaks varies, with duration lasting from a few days to nearly 3 years, with a cluster size of 2 to 13 cases and undergraduate university sizes ranging from 4,000 to 35,000 students. MenB vaccine was first used in response to a serogroup B university outbreak in 2013 prior to licensure of the vaccine in the US. Since that time, 7 of 8 universities implemented MenB vaccination in response to a cluster or outbreak of meningococcal disease.

Since 2010, 5 clusters or outbreaks of serogroup C meningococcal disease among MSM have been reported. To date, these clusters have ranged in duration from 4 months to two and a half years, with 3 to 22 cases reported. MenACWY vaccination has been implemented in four of these clusters or outbreaks.

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In summary, rates of meningococcal disease have declined from approximately 1 to 0.1 cases per 100,000 population in the past 20 years, with a decline seen in all serogroups, including serogroup B. Each cluster or outbreak is unique, with a range in number of cases, population size and characteristics, and duration. This creates challenges in applying guidance for the control of meningococcal disease outbreaks that is applicable to a wide variety of outbreak situations. In recent years, several serogroup B outbreaks in universities and serogroup C outbreaks among MSM have been reported.

Regarding the current guidance for the evaluation and management of meningococcal disease outbreaks and proposed updates to this guidance, guidance was originally developed in 1997 and updated in 2013 in Appendix B of the ACIP "Prevention and Control of Meningococcal Disease" statement. Interim guidance was developed in 2014 for the control of serogroup B outbreaks in organizational settings prior to the licensure of serogroup B vaccines in the US, specifically to guide use of unlicensed serogroup B vaccines under a CDC-sponsored Investigational New Drug (IND) program [Centers for Disease Control and Prevention. Prevention and Control of Meningococcal Disease; Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(No. RR-#2): 1-28].

The key components of these meningococcal disease outbreak guidance documents include the following:

- ❑ Cases to be included in the case count for vaccine decision-making,
- ❑ The affected population, classified as organization or community-based
- ❑ Outbreak thresholds and the decision to vaccinate
- ❑ Defining the vaccination group
- ❑ The role of molecular genotyping
- ❑ Other control measures, such as mass chemoprophylaxis

The current guidance was originally developed under a different epidemiologic context and prior to the availability of conjugate MenACWY or MenB vaccines. Several recent outbreaks have identified challenges in managing outbreaks using the current guidance. As a result, state and local health departments expressed a need for updated guidance better adapted to the current situation.

The objective of the revised guidance is to update and harmonize guidance for the investigation and public health management of suspected outbreaks of meningococcal disease due to all serogroups, accounting for the changes in the epidemiologic situation and available outbreak response measures. To develop this guidance, subject matter experts (SMEs) were consulted from September 2015 to March 2016 to review the current guidance and available data, and discuss challenges in managing outbreaks using the current guidance. A review of the literature also was conducted to describe the use and impact of meningococcal vaccines in outbreak settings.

CDC, with input from SMEs, reviewed all components of the current guidance previously mentioned. However, this presentation focused on a few key areas: cases to be included in the case count for vaccine decision-making, outbreak thresholds and the decision to vaccinate, and the role of molecular genotyping as it pertains to defining outbreak-related cases. Two additional topics were added to the updated guidance document: serogroup B vaccine selection based on expected vaccine coverage against an outbreak strain, and re-evaluation of outbreak status.

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Regarding the cases to include for vaccine decision-making and the role of molecular genotyping, this presentation was limited to the discussion on the role of genotyping in terms of its application in defining outbreak-related cases. In the current guidance, only primary cases of the same serogroup are included in the case count for vaccine decision-making, as primary cases indicate ongoing transmission within a population. A primary case is defined as a case that occurs in the absence of previous known close contact with another patient. Co-primary and secondary cases are those that occur among close contacts of a primary case, with co-primary cases occurring within 24 hours of the primary case and secondary cases occurring more than 24 hours after the primary case.

There are several challenges to the current guidance. Determining whether cases had close contact may be challenging in some populations, such as homeless or MSM populations. In addition, there are differences in the community versus public health perception of what constitutes an outbreak. It may create confusion and communication challenges when some cases "don't count." In some situations, serogroup alone may not be sufficient to determine whether cases are related. New tools for molecular typing are available. Whole genome sequencing (WGS) provides the highest resolution for determining relatedness of strains. The role of WGS is becoming increasing important, particularly with the availability of serogroup B vaccines. However, there will continue to be cases in whom an isolate is not available for WGS.

In the updated guidance, cases will no longer be classified as primary, co-primary, or secondary. In addition, evidence of related or identical strains by WGS will not be required for inclusion of cases in the case count. However, if sequencing demonstrates that a case is unrelated to others in the outbreak, this case should not be included. Thus, in the proposed guidance, all cases of meningococcal disease of the same serogroup are included in the case count unless there is evidence of genetically distinct strains by WGS.

In terms of the outbreak thresholds and the decision to vaccinate, in the published guidance, the outbreak threshold is 3 cases of the same serogroup with an attack rate of greater than 10 cases per 100,000 population in 3 months. In the interim guidance, which applies only to serogroup B organization-based outbreaks, the outbreak threshold is 2 cases of the same serogroup in a population of less than 5000, and 3 or more cases of the same serogroup in a population of greater than or equal to 5,000 in 6 months.

There are many challenges to the current guidance. Meningococcal outbreaks are not "one size fits all." There is a need for flexibility in the guidance to evaluate each outbreak on a case-by-case basis. The threshold of 10 cases per 100,000 population is a hundred times higher than the current US national incidence. However, in the absence of data, it is difficult to define a more appropriate threshold. This creates challenges in situations in which the outbreak threshold is not reached despite a clear need for intervention, such as in the 2016 serogroup C outbreak in Southern California in which 21 cases among MSM were reported but the cumulative attack rate reached only 6 cases per 100,000 population. In addition, there is little tolerance for additional cases that are viewed as preventable, and many communities and health departments are not comfortable with watchful waiting for additional cases. Finally, attack rates are challenging to calculate in community outbreaks and those occurring among special populations due to difficulty in defining the denominator.

While calculation of an attack rate is useful for comparison against baseline trends in the affected population, in the proposed guidance, the threshold for vaccination would not be determined through a specified attack rate. Rather, each outbreak should be evaluated on a

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case-by-case basis to determine the appropriate threshold for implementing vaccination. General guidance includes the following:

- For organization-based outbreaks: 2 to 3 cases of meningococcal disease of the same serogroup within 3 months

- For community-based outbreaks: Incidence of meningococcal disease of the same serogroup that is above expected in the affected community during a 3-month period.

The guidance will provide some flexibility in how an increase above expected is defined, such as comparison against a historical baseline in the community or, in the event that the community baseline is 0 cases, a comparison against national incidence. Considerations for vaccine decision-making include the size of the population, the ability to define a target group for vaccination, whether ongoing transmission is likely, or rather, if cases likely represent a single transmission event (for instance, among household contacts, roommates, boyfriend/girlfriend), the feasibility of a vaccination campaign, and timing of potential vaccination in relation to cases.

Currently there is no guidance related to selection of MenB vaccines for use during an outbreak, as no MenB vaccines were available at the time of writing. Unlike conjugate MenACWY vaccines which target the polysaccharide capsule, MenB vaccines induce an immune response to subcapsular proteins, which vary by strain. While WGS can identify the presence of MenB vaccine antigens in the outbreak strain, it cannot determine expression of the antigen or expected coverage by MenB vaccines. Furthermore, there are challenges to conducting additional testing to determine coverage of a MenB vaccine against the outbreak strain in real-time during an outbreak. Thus, in the proposed guidance, identification of MenB vaccine antigens by molecular characterization should not drive the choice of MenB vaccine during an outbreak of meningococcal disease at this time. No vaccine preference is stated for outbreak control; however, the recommended schedule will be 2 doses if MenB-4C is used and 3 doses if MenB-FHbp is used.

Regarding re-evaluation of outbreak status, there currently is no guidance on when to declare an outbreak as being “over.” Meningococcal disease epidemiology is dynamic and unpredictable, with outbreak-associated cases sometimes reported months after the last known case. Nevertheless, public health officials need guidance on how long to continue vaccination and other interventions following the declaration of an outbreak. For instance, after vaccinating undergraduates at a university with MenB vaccine, do incoming freshman the following year need to be vaccinated? Prematurely declaring an outbreak as being “over” can erode public trust if further cases are identified.

Because of the unique epidemiology of meningococcal disease outbreaks, it is difficult to predict the course of the outbreak and risk of further cases. Thus, the proposed guidance does not provide criteria for determining when to declare an outbreak as being over. However, for public health decision-making, after one year without any new reported cases, the risk of meningococcal disease likely returns to baseline.

In summary, all cases of meningococcal disease of the same serogroup are included in the case count for vaccine decision-making unless there is evidence of genetically distinct strains by WGS. Each outbreak should be assessed on a case-by-case basis to determine the threshold for implementing vaccination, though in general organization-based outbreaks are defined as 2 to 3 cases of meningococcal disease of the same serogroup within 3 months. Community-based outbreaks are defined as incidence of meningococcal disease of the same serogroup

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above expected in the affected community during a 3-month period. No preference is stated for MenB vaccine selection at this time, regardless of molecular typing results. After one year without any new cases, the risk of meningococcal disease likely returns to baseline.

The next steps are the finalization of the CDC guidance document for control of meningococcal disease outbreaks.; publication of the updated guidance document on CDC's website, to replace current guidance in Appendix B of ACIP's Prevention and Control of Meningococcal Disease" statement and the interim guidance for MenB outbreaks; and continued efforts to improve reporting and collection of epidemiologic data of meningococcal disease outbreaks.

Discussion Points

Dr. Szilagyi requested further information about how "community" is defined for a community-based outbreak, and noted that the incidence above a baseline is 1 case.

Dr. Meyer replied that defining "community" was probably the topic with the most discussion among WG members while trying to revise these guidance documents. A community would be defined as the geographic area and cases in space and time that are related. That would be defined at the local level. Typically, this would include the smallest area for which a border could be drawn around the cases. That could be a neighborhood, town, or county and depends upon the epidemiology of the cases. With the incidence of disease being so low in the US, many communities will not have had any cases of meningococcal disease in recent years. This is where the idea to compare against other sources such as national incidence to offer an example of where that has been applied recently. In some of the MSM outbreaks that have occurred in communities, often it is pretty difficult to compare against a baseline because data are just starting to be collected in those populations. The incidence of disease among adult men has been used as the baseline comparison to help health departments make those decisions. That is why there is an emphasis on making these decisions on a case-by-case basis, because the situations are all unique, especially in terms of the community outbreaks. One case would not be considered an outbreak.

Dr. Moore added that in thinking about organization- or community-based outbreaks, in the past the organization or community has not been considered if the cases were clearly epidemiologically linked one to another (girlfriend/boyfriend, household contact). Having a secondary case in a household contact would not define the organization within which that household resides as an organization-based outbreak. It is the identification of cases that are matched where epidemiologic links are lost.

Dr. Meyer responded that this was discussed while revising the guidance. In a lot of cases, it was communicated that it is sometimes difficult to define epidemiological links in real-time, especially among certain populations where it is not clear whether there were any epidemiological links. For the purposes of broad general guidance, in expert consultations and through various outbreaks, it was felt that having this extra layer of classification of cases often can create confusion and may not be necessary, but describing a sample situation could be helpful. For example, if two roommates both had meningococcal disease and there were no other cases, that would not necessarily prompt a 30,000-student university to launch a multi-dose MenB vaccination campaign. This is where the flexibility in the guidance and some of the considerations for vaccine decision-making should be taken into account.

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Dr. Reingold asked what the implications would be upon declaring that an outbreak is over (no longer vaccinating, no further chemoprophylaxis), and how the WG arrived at 1 year.

Dr. Meyer replied that the purpose of having something in the guidance document is for vaccine decisions and public health interventions. The goal is not necessarily to be able to announce this or for communication messaging. This is especially relevant in university or community outbreaks when trying to determine when to stop, and whether vaccine should be given to new people entering the population. Regarding how the WG arrived at the 1 year cut point, the epidemiology of all of the outbreaks of which CDC is aware were assessed. Things varied by outbreak, but this conservative approach was taken to feel relatively confident that the risk has decreased to baseline. The intent was not to say that an outbreak is over, because there can be additional cases.

Dr. Kempe asked whether based on that, the recommendation invariably would be to vaccinate all incoming Freshmen.

Dr. Meyer responded that this type of decision is typically arrived at after consultation with CDC, and that type of language would be included in the guidance document to maximize flexibility. Vaccinating all incoming Freshmen has occurred in some situations.

Dr. Even (ACHA) pointed out that one issue which arises is media and media requests and how to address those, because there is a lot of interest in whether an outbreak is ongoing. The distance between cases in a meningococcal outbreak can make it appear like there is something new happening when it may be part of the same situation. Being able to say that an outbreak is back to baseline helps to clarify the decision about advanced preparation for immunization for incoming students, whether it is incoming Freshmen or students who are new to a campus. This helps to have some frame of reference for outbreak activity.

Ms. Hayes (ACNA & ANA) asked for clarification about the risk factor that is linked to being a gay man and getting this disease, as she was grappling with why this is not occurring among other people who are having sex.

Dr. Meyer replied that this is an area CDC is still trying to understand better. There have been a couple of clusters in the US, and sporadic cases among MSM. HIV is believed to play a role, and there is a growing belief that HIV creates an increased risk for meningococcal disease. That does not explain the whole picture. CDC is actively investigating this area, but has not yet identified risk factors. It is known that meningococcal disease is spread through close contact, which is often observed with people sharing close spaces, going to clubs, smoking, all of which increase risk. Therefore, it could be assumed that some of that plays a role. This area is still being investigated.

Ms. Hayes (ACNA & ANA) asked whether a specific questionnaire has been developed to be used specifically to collect data on these outbreaks among MSM, and what risk factors are being examined.

Dr. Messonnier recalled that there was a discussion about this a couple of ACIP meetings ago. There was a 20-minute presentation from the WG specifically on this issue.

Dr. Sun (FDA) pointed out that both of the available vaccines were licensed based on immunogenicity, and that it is still conceivable that for a particular outbreak, one vaccine may be better than the other in terms of bactericidal activity. He wondered whether consideration had

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been given to examining this type of evidence, and selection of a particular vaccine for a specific outbreak.

Dr. Meyer said the reason they were saying that molecular genotyping should not drive vaccine selection at this time is because they do recognize that more work is ongoing to try to correlate identifying vaccine antigens by WGS with immunologic responses. These data are not currently available to make recommendations in this guidance, but that work is ongoing. Molecular genotyping is used in the management of these outbreaks, but they are saying that this should not drive vaccine selection at this time. As new data become available, consideration will be given to whether that data can be used.

Dr. Gorman (NIH) asked whether there is any role for nasal carriage surveillance after an initial case to inform vaccine decision making for an outbreak, or if data are being collected for the isolated cases to see if they are surrounded by people who carry even if they do not have the disease.

Dr. Meyer responded that this is not part of current public health practice. In general, there are logistical challenges and utility issues that play into that. One is that the priority is to provide chemoprophylaxis to persons who are close contacts of patients. Swabbing them for carriage delays the whole process. Also, carriage is dynamic and transient. Someone could have been a carrier, but by the time they are swabbed they could no longer be a carrier or at the time of swabbing, was not a carrier, only to subsequently become a carrier. This has not been identified as being very useful for active public health management during an outbreak.

Dr. Hahn (CSTE) said that as a state epidemiologist, she like the proposed language and thought it would be a very helpful tool.

Dr. Stephens indicated that WGS is being used as an approach, but it is not necessarily predictive based on the sequence data in terms of what the immune response is going to be and what will be protective. Work is ongoing and they will continue to learn more about the relationship between the antigens present, whether they are expressed or not, and immunogenicity.

Global Measles/Rubella Elimination Initiative

Global Polio Eradication Initiative

Abhijeet Anand, MBBS, MPH
Polio Eradication Branch
Global Immunization Division
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Dr. Anand presented a status update on polio eradication, reviewing the four key objectives as described in the endgame strategic plan. The objectives are: 1) detection and interruption, which is essential to the core set of eradication objectives; 2) oral polio vaccine (OPV2) withdrawal, inactivated polio vaccine (IPV) introduction, immunization system strengthening; 3) containment and global certification; and 4) legacy planning.

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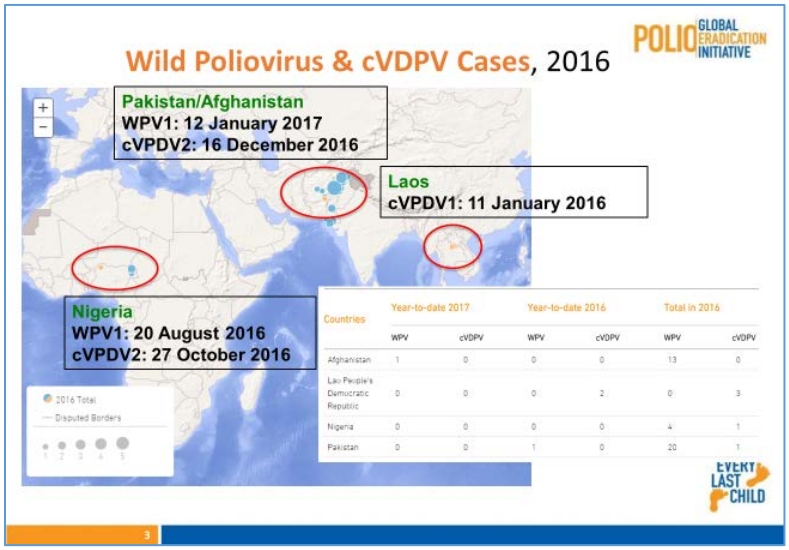
The following map and the table lay out the number of cases that have been observed in the three endemic countries where there is polio transmission (Nigeria, Pakistan/Afghanistan, Laos). The table lists the number of cases in 2016 and 2017:



The total case count in 2016 was down to the lowest point ever seen. In Afghanistan, there were 13 cases and in Nigeria there was 1 case of Wild Poliovirus Type 1 (WPV1). There were 3 cases of circulating vaccine-derived polioviruses 1 (cVDPV) in Laos in 2016. There were more cases in 2015. In Nigeria, there was one cVDPV Type 2 case reported in 2016 and another was reported much later. In Pakistan, there was 1 cVDPV Type 2 case. The key message is that in 2016, the only type seen was Type 1. The last time Type 3 virus was seen was in November 2012.

There has been a tremendous amount of progress in Pakistan and Afghanistan, with the lowest number of cases that have been seen. There has been a dramatic reduction in the total number of cases for Type 1 virus, which is unprecedented in terms of the total number of cases that have been seen in Pakistan. It is not only a reduction in the total number of cases, but also a reduction in the geographical distribution of these cases. The number of districts that have been affected is much lower, the genetic diversity of the virus is reduced, and there has been an improvement in the program quality in the transmission zones in Pakistan, which has essentially led to the virus being seen outside of the core transmission districts in Pakistan. There are clearly gaps that still exist in the country for population immunity as well as surveillance, which has led to a few viruses that have emerged and ongoing transmission that has been seen outside of the core transmission zones and a reduced transmission in the core transmission zones.

Afghanistan has shown similarly remarkable progress in program implementation. In 2016, the total number of Type 1 cases reported in Afghanistan was 13. More than half of those cases came essentially from one province in the Southeast part of the country, Paktia Province. Most of those cases came from one small district, Bannu District, with a total population of about 100,000 people. Essentially, that district had vaccine refusals and security issues. Two cases have been reported in 2017 in Kandahar, with another reported in Helmand, which is the adjoining province.

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Afghanistan and Pakistan are treated as one epidemiological block. The political borders between the countries is just an artificial line drawn on the land, but there is free movement of people from known and not so known points of crossing, which facilitates transmission. Three corridors of active transmission link reservoirs on both sides of the border:

- Nangarhar/Kunar: Khyber/Peshawar
- Paktika: FATA / Bannu
- Kandahar/Helmand: Balochistan (Quetta block)

Overall, these two countries have shown improvements in surveillance quality and supplementary immunization activities (SIAs) quality, and a decrease in the number of polio cases and environmental positive samples. There has been progress in the highest risk areas of Peshawar, FATA and Quetta, with a reduction in intensity of transmission and genetic diversity of circulating virus. There is strong coordination between the countries, with new National Emergency Action Plans (2016-2017) endorsed by TAGs. Emergency Operation Centers (EOCs) are now operational in Kabul and the 3 high-risk Afghanistan regions. However, there have been some concerning developments. There is continued viral transmission in South KP/FATA and adjoining South Eastern Afghanistan (Paktika Province), and recent positive environmental samples from Pishin (Quetta Block, Balochistan). The common themes that unite the countries are the issues of accessibility, conflict, and security. While these issues complicate program management, they do not rise to the same level that has been seen in other countries such as Nigeria.

Turning to Nigeria and Lake Chad, the last set of cases of Type 1 were seen in Nigeria in 2013. Since then, there has been no known transmission in Nigeria. The biggest setback to the program was the transmission in Nigeria in 2013. An environment sample of cVDPV2 was observed in March 2016, which was a long-term transmission different from Sabin type. This transmission had been missed for a long time. In July 2016, long-term transmission was noted for WPV1. This circulation was missed for at least 5 years. Each of the 4 cases that were picked up were genetically different from each other by long-term, and represent the “tip of the iceberg.” The key issue that defines this challenge is accessibility in Borno. There are numerous areas the program and Nigerian Army cannot access, because they are controlled by Boco Haram. Boco Haram does not negotiate for safe passage of vaccination teams, so even some small areas that have been cleared by the Nigerian Army are not accessible because of the necessity to access through Boco Haram-controlled areas. Therefore, they have to be accessed by helicopters or mechanisms from other countries to conduct surveillance and administer vaccines. The key linchpin here is changing access in Borno. Without improved access in this area, transmission cannot be properly controlled. This has been declared as a Level 3 health sector emergency by the United Nations (UN). There is also starvation, famine, and even a measles outbreak reported in that area.

Lake Chad coordination has been established in N’djamena with partner agencies and 5 governments. Lake Chad Countries have declared a regional public health emergency, and a regional Global Polio Eradication Initiative (GPEI) Coordinator was appointed by WHO/AFRO. This has led to a multi-country response in this entire area. The multi-country response plan includes 5 bOPV SIAs followed by mOPV2; surveillance enhancement, including active case search as well as enhanced laboratory capacity; strategies to reach children in inaccessible areas; advocacy, communications and social mobilization strategies; and strong linkages with humanitarian response.

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In summary, there has been unprecedented progress with the lowest global case count ever observed. Interruption of WPV1 remains challenging. At the same time, there are inaccessible areas in Borno, Nigeria.

At the same time, the Nigeria situation has been a lightning rod for the program and has led the program to look deeper into all of the areas associated with conflict and limited access, mapping them out, and assessing the risk based on the available data. There also is an understanding of the importance of looking beyond the indicators. The traditional polio indicators did not reveal the surveillance gaps noted in Borno, so it is important to look beyond these indicators to find ways to access these populations. Vaccination teams must be set up in coordination with the military, so the teams can move as rapidly as the military moves into an area.

Moving on to Objective 2, withdrawal of OPV and introduction of IPV is essential for achieving eradication. SAGE has recommended a phased approach, starting with OPV2. This was preceded by introduction of IPV to provide population immunity to Type 2 in 2015-2016, followed to a switch from trivalent (tOPV) to bivalent OPV (bOPV) in April-May 2016. Eventually, after achievement of certification, OPV use will stop. In April-May 2016, in a period of two weeks, all of the countries using tOPV stopped and switched to bOPV. This was a remarkable achievement for the program to manage an entire vaccine replacement worldwide. Independent monitoring of the switch began two weeks into the switch, with people visiting facilities to look for any potential vials of tOPV. Nearly 150,000 facilities were monitored all over the world to find tOPV vials. Did this go perfectly? Probably not. Some vials have been discovered outside of the areas that were monitored, and this has been published in an *MMWR* and also has recently been noted in Nigeria.

The key achievement for removal of tOPV has really been a dramatic decline in the number of cVDPVs. Of the total number of cVDPVs reported, cVDPV2 used to account for approximately 85% to 90% percent of the total. Now there has been a dramatic decline. As noted, the switch from tOPV was preceded by introduction of IPV. There was a clear set of criteria from Tier 1 to Tier 4 countries of introduction of IPV. A single dose of IPV was recommended by SAGE administered by 14 weeks of age. This has been delayed in several countries because of IPV supply issues. The supply situation remains bleak and continues to worsen. This led the program to rapidly evaluate how to prioritize use of IPV for eradication purposes or routine immunization. Introduction has been delayed in 21 Tier 3 and 4 countries. An additional approximately 22 Tier 3 and 4 countries will be forced into stock outs. The supply will remain constrained into 2018. Countries considered to be at highest risk for cVDPV2 outbreaks are currently all receiving IPV.

In terms of the policy response to this, SAGE developed a new recommendation that was published in a WHO Polio Position paper in March 2016 in which SAGE reaffirmed two fractional doses of intradermal IPV in lieu of one full-dose intramuscular. Uptake of this has been fairly slow. India has replaced two-thirds of its states with fractional IPV. The entire country is likely to be using fractional IPV by about the second quarter of 2017. Sri Lanka and Bangladesh have switched to fractional IPV. The remaining countries are still using intramuscular IPV when available.

In summary of the endgame, the OPV withdrawal and ability of GPEI to introduce IPV was a success in a short two-week window that has impacted risk. The supply situation clearly has an impact on the risk of cVDPV2, and impacts GPEI credibility. There has been slow uptake of the SAGE recommendation for 2 fractional IPV doses. Fractional IPV would ease the supply situation.

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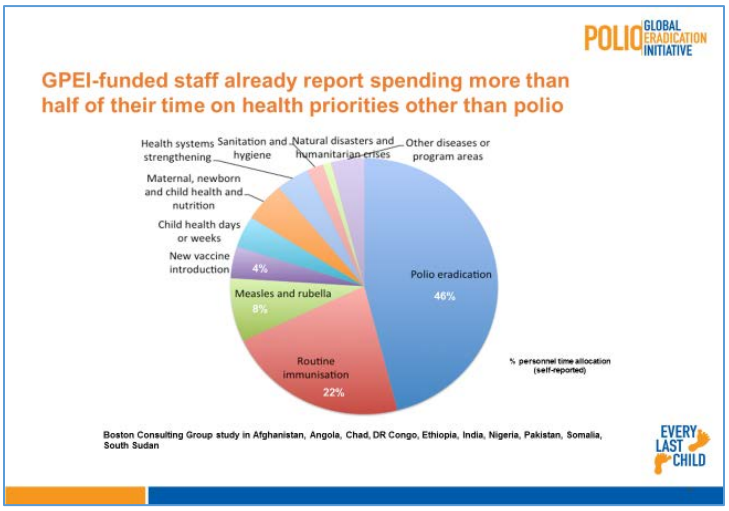
Moving on to containment and global certification, 23 countries reported hosting 58 designated Poliovirus-Essential Facilities (PEFs). These are all of the laboratories that have said they are hosting potentially infectious material to OPV2. There are other countries that probably will be hosting Sabin Type 2. That depends on the survey. There are countries that are running behind schedule on completing the survey to note whether they are holding Sabin 2.

Regarding transition planning, GPEI has learned many lessons on the road towards eradication, including the following:

- ❑ Accessing insecure and hard-to-reach areas
- ❑ Accountability
- ❑ Communications
- ❑ Social mobilization/community engagement
- ❑ Working in complex global partnership
- ❑ Achieving and maintaining political commitment
- ❑ Global disease surveillance networks

How can these lessons be used for greater benefit? GPEI-funded staff already report spending more than half of their time on health priorities other than polio, including natural disasters and humanitarian response as reflected in this pie chart:



The majority of GPEI staff are in Pakistan, Afghanistan, and Nigeria. Of the endemic countries, they have the largest footprint. There were 16 high priority countries that developed transition plans for using polio resources for other programs, as well as listing out the polio operations that need to continue beyond the presence of the GPEI. Another 14 countries and 5 regional offices will be expected to have transition plans prepared by the end of 2016, and 2 countries and 2 regional offices will be expected to have transition plans prepared within 12 months of interruption in the endemics. Specific timelines have been laid out for transition planning. The only country that actually has completed its transition plan as of now is India. Other countries are behind schedule and are expected to complete their transition planning some time in 2017. Obviously, there is a greater set of challenges in Afghanistan, Pakistan, and Nigeria which are the endemic countries and are focused more on the response at this time.

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In terms of program priorities for the next 6 months, the biggest priority clearly is the Nigeria outbreak in all 5 Lake Chad basin countries ensuring that high quality campaigns can be achieved. There were no high-quality campaigns for the Nigeria response, but the campaign quality has slowly improved. There is a need to continue to support Pakistan and Afghanistan. The program has turned around dramatically over the last few years to improve surveillance and response, but there now must be a focus on the final set of transmission zones and the weak spots in the country. It also is important to recognize transmission so that it is not missed as occurred in Borno. Is it possible that transmission has been missed elsewhere, what are the other conflict affected areas and how can surveillance quality be improved in those areas? There has clearly been a dramatic focus of the program on surveillance quality and establishment of new focus and new teams to look at surveillance. This is from the point of view of not just noting the existence of missed transmission, but also getting the programs ready for certification.

Discussion Questions

Dr. Hunter inquired as to why there is a shortage of IPV.

Dr. Anand replied that this has largely been due to production challenges that the manufacturers faced. Some batches of production went bad, which has led to shortages. There also has been a large increase in demand for IPV because of increased needs. Promises were made to increase the amount of infrastructure that the managers had to increase production, and those also have not lived up to the timelines.

Global Measles/Rubella Elimination Initiative

Gavin Grant, MD, MPH
Global Immunization Division
Center for Global Health
Centers for Disease Control and Prevention

Dr. Grant presented an update on the goals, strategies, and status of measles and rubella activities, many are coordinated by the Measles and Rubella Initiative (M&RI). The M&RI is a collaboration between the American Red Cross, United Nations Foundation, CDC, UNICEF and WHO. The Global Measles and Rubella Strategic Plan offers a context of the activities that are underway toward measles and rubella elimination.

Global elimination of measles and rubella elimination is important in the US; a great reminder is the 2014 Philippines measles outbreak. The graphic below illustrates how quickly measles can spread globally when measles is poorly controlled outside of the US:

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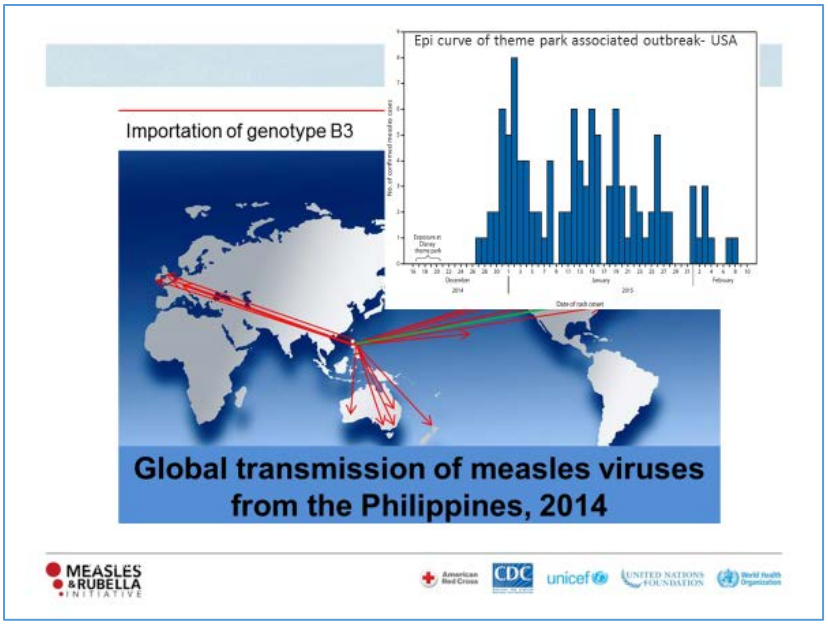

This large outbreak in the Philippines led to multiple importations in the US. Strains could be traced to the Philippines based on the sequence information. Most of the viruses that were exported were genotype B3, but genotype D9 was circulating in Southern Philippines and was imported to the US and is associated with a very large outbreak in Ohio. Another importation is very well-known because it was a theme park-associated outbreak after exposure at a Disney Land theme park. This outbreak led to multiple importations of measles virus throughout the world in addition to the US, including Europe, Australia, and Canada. The point is that trying to control measles and rubella on a global level has a direct impact on the US.

A framework to reach measles and rubella elimination was put forth in the *Global Measles and Rubella Strategic Plan 2012-2020*, which was developed by the M&RI partners. The vision for that plan is to achieve and maintain a world without measles, rubella, and congenital rubella syndrome (CRS). This plan establishes several targets and milestones, which are as follows:

Milestones by 2015

- ❑ Reduce annual measles incidence to < 5 cases per million and maintain that level
  - ➢ 90% coverage with routine MCV1 nationally and > 80% vaccination coverage in every district or equivalent administrative unit
  - ➢ 95% coverage with M, MR, or MMR during SIAs in every district or equivalent administrative unit
- ❑ Establish a rubella/CRS elimination goal in at least 1 more WHO Region
- ❑ Establish a target date for the global eradication of measles

By End of 2015

- ❑ Reduce global measles mortality by at least 95% compared with 2000 estimates
- ❑ Achieve regional measles and rubella/CRS elimination goals

By End of 2020

- ❑ Achieve measles and rubella elimination in at least five (of the six) WHO Regions

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Key Strategies to Reach Goals

- ❑ High population immunity through vaccination with two doses of M and R containing vaccines
- ❑ Effective surveillance, monitoring, and evaluation
- ❑ Outbreak preparedness and response and case management
- ❑ Communication to build public confidence and demand for immunization
- ❑ Research and development

In terms of achievement of the goals set forth, from 1980 to approximately 1990, coverage with the first dose of measles vaccine increased from 17% to about 70%, and continued to slowly increase until 2009, when coverage plateaued, at approximately 85%, and has remained at the same level today, globally. Data from 2016 is not presented because these data are the official WHO data, which are aggregated annually. The data for 2016 will not be available for several more months. The coverage milestone is a national milestone, which shows that 119 (61%) of countries have > 90% MCV1 coverage and are maintaining that milestone; however, the remaining countries failed to meet that milestone with 42 (22%) of countries having a very low measles coverage of < 80% MCV1 coverage.

In order to fill some of the immunity gaps, campaigns are conducted within countries. In 2015, 39 countries conducted 66 campaigns. These campaigns reached 180 million children. Of the 66 campaigns, 40 (61%) attained 95% coverage, which was the target. Because administrative coverage is not always accurate, coverage surveys are recommended to be used with many of these campaigns. Of the 66 campaigns, 18 (27%) had surveys. Of the 18 campaigns that had surveys, 4 surveys documented >95% coverage. These campaigns occurred in various countries, but not all countries, as measles campaigns occur intermittently according to the epidemiology and they are not expected to take place annually in any country.

The second milestone pertains to measles incidence. There has been a decrease in cases since 1980. Since 2000, there also has been a decrease of incidence. The current measles incidence is 36 / million, a decrease of 75% since 2000. This is great progress, though it did not achieve the milestone of < 5 cases / million population. This decrease has been concurrent with the increase in second dose measles campaigns, which have been occurring since the mid-1990s that has helped decrease the number of cases and measles transmission globally.

The third milestone is mortality reduction, with a target of a 95% decrease in mortality relative to 2000. From 2000 to 2015, a 79% decrease has been observed. This did not reach the target of 95%, but the decrease in mortality is quite significant. Approximately 20.3 million deaths have been averted in the past 15 years by measles vaccination, which is a remarkable achievement within itself.

Many measles elimination activities are taking place, and the rubella program has taken advantage of this opportunity to move rubella elimination forward. Over half the world's children are not vaccinated against rubella. Clearly, some progress needs to be made in order to increase global coverage of infants. Rubella vaccination coverage is not equal globally. Some regions of the world have very high rubella coverage of over 80%. In the Americas, Europe, and West Pacific Regions, there has been introduction of vaccine in all countries in each region. The Eastern Mediterranean Region tracks approximately with global coverage, just under 50% of the infants vaccinated, while the Southeast Asian and African Regions have coverage of < 20%, primarily because either most countries have not introduced vaccine or countries with very large populations have not introduced vaccine.

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Modeling data have provided an estimate of CRS incidence globally. Africa, Southeast Asia, and some countries in the West Pacific Region have relatively high incidence of CRS where the burden is great. Therefore, it is important to ensure that rubella vaccines are introduced at the global level. India delayed introduction of the vaccine until 2017. Overall, 148 (75%) of countries have introduced a rubella-containing vaccine, with 11 others expected to introduce one this year. It is good to note that also in the next 3 years, 17 countries are expected to introduce rubella vaccines. There has been rapid uptake of rubella vaccine. This introduction of rubella vaccine is in part supported by additional funds from the GAVI Alliance to support rubella introduction in the least developed countries.

Regarding regional progress in terms of the strategic plan, all regions have a measles elimination goal. Three regions (Americas, European, and Western Pacific) have rubella elimination goals. The Western Pacific Region has agreed on rubella elimination; however, the actual year they would like to reach that target has not been agreed upon in the region. Another area of note is the Southeast Region has declared a rubella control goal has been established, but an elimination goal has not been established.

One of the tools for elimination is establishment of Regional Verification Committees. Each of the 6 WHO regions is in the process of developing or utilizing their Regional Verification Committees. These committees review the data and evaluate whether elimination has been achieved, and also can provide guidance to countries to help with achieving that goal. Two regions are currently in the final stages of developing a verification committee for at least measles (African and Eastern Mediterranean Regions). However, a committee has not been convened in the South-East Asian Region, so they have not noted any elimination. The Americas Region has been the most successful in terms of measles and rubella elimination and have reached the elimination goal in all 36 countries for measles and rubella. In Europe, approximately 40 countries have been validated for measles and 45 countries for rubella. As of the last meeting, the Western Pacific Region has verified 7 countries for elimination. They have recently established guidelines for evaluating rubella verifications, which will be implemented at the coming meeting in 2017.

There also is a regional scorecard that evaluates the progress toward measles and rubella elimination. The African region is clearly off track to reach their 2020 goal, and they do not have a rubella target within that region. A lot of effort needs to be made to support Africa in reaching their targets and goals. The Americas Region has verified elimination of measles and rubella, which is a great success. Measles was verified in 2016 and rubella was verified prior to measles verification in May 2015. Europe and the Eastern Mediterranean Regions are off track to reach their targets as are the South-East Asia and Western Pacific Regions to reach their 2020 targets.

In terms of the regional situation, different regions have different challenges. Some challenges have been encountered in all regions. The Americas have eliminated rubella, but they have a risk of importation, so it is important to maintain a strong surveillance system. Rapid response to outbreaks of importations will be critical to sustaining their elimination status. In the African Region, there are weak immunization and health systems, which has resulted in a reliance on campaigns to achieve high population immunity. However, this has challenges for sustainability. Reliance on campaigns also increases the risk of mortality from other vaccine-preventable disease as campaigns tend to be much more vertical than the routine program. The European Regions have experienced problems with vaccine hesitancy, susceptible adults, and variable surveillance quality within the countries. The Eastern Mediterranean Region had some countries that were doing very well, but due to security issues that limited access,

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coverage in some of those countries decreased. Some countries in that region have persistently low coverage. In the South-East Asia Region, there are two large federalized countries, India and Indonesia, which constitute about 80% of the infants within that region. Those two countries have heterogeneous coverage, and they need to strengthen and expand their case-based surveillance. In the Western Pacific Region, there has been very high coverage for several years, but there has been a resurgence of measles in China and the Philippines, which the region is working to address. All regions have a need for increased visibility and political commitment to regional elimination goals. There also are susceptibility gaps, including among older children and adolescents who are not commonly targeted for measles vaccination, other challenges include a lack of human and financial resources and vaccine hesitancy in various populations.

The Measles and Rubella Initiative requested a mid-term review of the strategic plan to understand the status, the challenges, and what needs to be done to move forward towards elimination. This review found that while a tremendous amount of progress has been made since 2001, neither measles nor rubella elimination is on track to achieve the plan's ambitious goals. The basic strategies articulated are sound; however, full implementation has been limited by inadequate country ownership and global political will. This is reflected in inadequate human and financial resources. It is premature to set a timeframe for measles eradication at this point. A determination should be made, not later than 2020, whether a formal global goal for measles eradication should be set with timeframes for achievement. Disease incidence is the most important indicator of progress. There is an urgent need to strengthen the collection and use of surveillance data to better guide program strategy and implementation. Strengthening of immunization systems is critical to achieving regional elimination goals. Two doses of measles or measles-rubella vaccine delivered through ongoing services is the standard for national programs. Regular preventive campaigns should be conducted if coverage is insufficient for high population immunity.

In summary, the US is still at high risk of importation due to ongoing global transmission. Effective vaccination strategies exist, resulting in major achievements, but targets have not always been met. The mid-term review summary stated, "The basic strategies are sound, however, the main impediments to full implementation have been inadequate country ownership and global political will, reflected in inadequate resources." Global efforts to assist countries to introduce rubella-containing vaccine are needed. Mid-term review recommendations are being implemented to continue progress towards a world without measles, rubella and congenital rubella syndrome.

Discussion Points

Dr. Schaffner (NFID/IDSA) observed that according to the data presented, measles immunizations rates are very high in Europe. However, he was under the impression that that was not the case. It was not so long ago that there was a huge outbreak of measles in France. He wondered whether this had turned around so quickly.

Dr. Grant replied that there are some countries in Europe that do not have very high measles coverage. Like the US, countries have outbreaks in populations that are susceptible, but it does not necessarily extrapolate to the entire country. There are a lot of advocacy efforts to try to make sure these countries move forward, especially in Europe. The Regional Verification Committee has gone into Italy to try to advocate for the country to increase their resource control. His understanding is that France is working on it, but still has gaps in its program, but it may not be a national gap.

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Dr. Belongia emphasized what an accomplishment averting 15 million deaths in 15 years is. He asked what level of vaccine coverage is needed to prevent sustained transmission.

Dr. Grant replied that this is close to 95%, which supports the importance of two doses of measles vaccine in all of these countries.

Day 1: Public Comment

Lynn Bozof, President
National Meningitis Association (NMA)

Most of you know that I lost my college age son to meningococcal disease several years ago. While NMA applauds the Category B recommendation for serogroup B meningococcal disease, I would like to remind the committee of the personal toll of this disease. The average family is not having a discussion about serogroup B vaccination with their healthcare providers. Over the last several months, I have been getting emails and phones calls from families whose college age children have come down with serogroup B. Some have died. Others are facing limb amputations. The question I always get is, "How did this happen? My son (or daughter) was vaccinated." College campuses are rushing to vaccinate after the fact, after the whole campus is in a panic, after all the parents are in a panic. Although the number of cases isn't high, the individual loss and suffering is immeasurable. I hope that in the coming months, these Category B recommendations can be readdressed. Thank you.

Christina Hildebrand
A Voice for Choice

I wanted to speak to new research that was done and published in the *International Journal of Vaccination* looking at micro- and nano-contamination. The CDC hasn't come out with any comments that I know of, but it shows that all vaccinations, barring one which was a veterinarian vaccination, showed contamination with organic and inorganic particles, particulate matter, including tungsten and silver and a whole bunch of others. I can give you the journal article. The concern there is that the CDC hasn't said anything about that. These vaccines, every one of them on the CDC schedule, have been contaminated. Some of these particulate matters are known to cause cancer. Section 13.1 of every single vaccine package insert states that the vaccine has not been tested for carcinogenic, mutagenic, or infertility. It's really concerning that you aren't doing anything about this, or researching it more, or making it known that you're researching it more. So, I would ask you to look into that because we should not have vaccines that are dirty. And then the other piece of it—I guess that was my comment on that. I just ask you to do the research and to look into it, because our children should not have these vaccines that are dirty going into them. Thank you.

Claire Hannon
Association of Immunization Managers (AIM)

We are a membership association whose members direct immunization programs in the 50 states, 8 territories or federated states, and 6 large cities. I just wanted to share some information that we collected in the last week from some of our members about the impact of

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the live-attenuated influenza vaccine in this flu season. We had 26 of 64 awardees give us some input, 10 who tracked coverage rates in real-time using an IIS and one tracking according to vaccine ordering. Of those 11, one reported higher rates currently this season, 6 lower coverage rates, and 4 coverage rates were about the same. Twenty-two of those 26 replaced an entire LAIV order for an equal amount of QIV, 4 did not. We will follow up with those 22 later in the season to see if those replaced doses were all used. Eight reported that the loss of LAIV impacted their ability to vaccinate in the same capacity as previous years, 12 reported no impact, and 6 were not sure yet. Where we saw the greatest impact was in the school-located flu vaccination programs. Of the 18 awardees reporting that school-located programs are conducted in their area, 15 reported a reduction in the number of clinics conducted due to the lack of LAIV, 1 reported a 42% decrease in vaccine, several report schools and counties declining to participate, 3 report large counties or entire school districts declining to participate when they had previously participated using LAIV, 1 reported 40,000 less doses administered this year, 17 awardees reported that their providers are interested in having a non-invasive flu option available again, and 9 said they did not know, and none said that providers were not interested. And then we just asked, "Assuming if it was recommended, and it was added to the government contact, and it would be available for second round orders next year, would you order?" and 7 say yes they would order, 5 said no, 15 said it would depend on the demand. And that's an order that would come later in the season in October. Just to reiterate the key challenges that you all mentioned for a return of LAIV (which many of our programs really rely on the LAIV product for their school clinics): the timing of the availability would be very important, confidence in the vaccine, and the evidence supporting the vaccine effectiveness. Thank you for the opportunity to share the comments.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that CDC is gearing up for National Infant Immunization Week that will take place April 22-29, 2017. Each year, state and local immunization programs, coalitions, and partners plan and hold local events to celebrate the positive impact that infant immunizations have on babies, families, and communities. These events also offer opportunities for communities to focus time and attention on addressing local barriers and challenges to on-time immunization. She expressed her hope that everyone would engage locally to help support those efforts.

Another issue of importance is lot number differences, which affects the immunization community daily in terms of practical issues. Some vaccine manufacturers use different lot number patterns on the units of use (vials and syringes) than on the unit of sale (cartons) for specific vaccines. This has caused a lot of chaos in provider offices that are using bar codes to track use of vaccines, as well as to order vaccines. CDC is working with providers to try to resolve these issues, but this could take some time to resolve.

As a follow-up to the discussion on the first day of the meeting concerning polio containment, one of the major activities pertains to laboratories that potentially have polio-containing materials. A number of steps have been taken domestically. One effort has been to survey any laboratory in the US that might have either polio-containing material or potentially polio-containing material. This is defined broadly as gastrointestinal or respiratory specimens from a country that was using oral polio vaccine (OPV). A number of laboratories potentially have

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those materials, and containment is the process of making sure that laboratories that wish to continue to hold the specimens, do so under a variety of conditions that ensures no one will be exposed. In order to support this process, CDC is standing up a new unit under the Office of Public Health Preparedness and Response (OPHPR) to address containment. This work will begin in the laboratories that know they have polio-containing material.

In conclusion, Dr. Messonnier announced that NCIRD has a new Management Officer, Alexander Harrington.

Centers for Medicare and Medicaid Services (CMS)

Ms. Hahn reported that the voluntary course on quality measures in the Medicaid program has been revised to reflect the new adolescent quality measure that incorporates all of the adolescent quality measures into one. The individual HPV quality measure has been retired.

Department of Defense (DoD)

Dr. Deussing reminded everyone that influenza vaccination is mandatory for all uniformed personnel, including Active Duty, Coast Guard, Reserve, and National Guard with an immunization goal of 90% by mid-December. Influenza vaccination also is mandatory for HCP who provide direct patient care in military treatment facilities, and is recommended for all other HCP in these facilities. DoD achieved its 90% goal during the 2016-2017 influenza season by mid-December, despite using only injectable vaccine. The live intranasal vaccine, which usually accounts for 1 million or more doses of DoD's vaccine allocation each year, was unavailable following ACIP recommendations. DoD procured enough injectable vaccine at its military treatment facilities for all age groups be immunized against influenza. As of February 9, 2017, 1.9 million influenza vaccinations were given, with 96% compliance among DoD HCP. Regarding Yellow Fever (YF), the Defense Health Agency (DHA) Immunization Healthcare Branch (IHB) continues to work with Army, Navy, and Air Force services as well as the manufacturer on mitigating strategies to conserve available doses of YF vaccine and continues to monitor this situation very closely.

Department of Veterans Affairs (DVA)

Dr. Kim reported that a relationship between the VA and Walgreen's was established for the 2016-2017 influenza season to promote access to seasonal influenza vaccination for veterans receiving care at the VA. The intent of this relationship is to improve veteran access to influenza immunization. More than 77,000 immunizations were administered through this program through December 2016. In addition, the VA recently released an electronic decision support tool called a "Clinical Reminder" for HPV immunizations in February 2017. This Clinical Reminder can be used in the Veterans Information Systems and Technology Architecture (VistA), which is the VA EMR. In addition, development has begun on another electronic decision support tool for meningococcal immunization.

Food and Drug Administration (FDA)

Dr. Sun reported that the FDA's legacy is still in transition. They are still waiting on the nomination of their new Commissioner, as well as senior leadership guidance to implement the 21st Century Cure Act. The FDA had a busy year in 2016 in terms of vaccines, with one approval of a new original Biologics License Application (BLA) new vaccine, nine major approvals of supplements, seven of which involved influenza and two of which involved

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Trumenba® two-dose and HPV-9 two-dose. On the developmental side, the FDA has been very busy in working with other government agencies such as CDC, NIH, the Biomedical Advanced Research and Development Authority (BARDA), World Health Organization (WHO), and the European Medicines Agency (EMA) on developmental vaccines in areas such as Zika, Respiratory Syncytial Virus (RSV), Ebola, and healthcare-associated diseases, such as *Clostridium difficile* (*C. difficile*), *Staphylococcus aureus* (*S. aureus*), and multiply-resistant bacterial organisms.

Health Resources and Services Administration (HRSA)

Dr. Nair shared three updates for the Vaccine Injury Compensation Program (VICP). There continues to be an increase in the number of claims. In fiscal year 2016, there were 1120 claims filed. That is the highest number since the inception of the program in 1988. Of these claims, 856 were adjudicated. Of those, 677 were found to be compensable and 179 were dismissed. Compensation totaled $250 million for petitioners and their attorney fees. For this fiscal year, 219 claims have been filed and approximately $52 million in awards have been paid to petitioners and $7 million has been paid in attorney fees. More information about the numbers can be obtained from the website. As a result of the 21st Century Cures Act, the VICP will now cover vaccines that are recommended for routine use in pregnant women. Previously, VICP covered vaccines that were recommended for routine use in children only. Now those liability protections for manufacturers and vaccine-administrators are extended for vaccines that are recommended for use in pregnant women. The Final Rule that modifies the Vaccine Injury Table was published in January 2017. Those changes will go into effect in March 2017.

Indian Health Services (IHS)

Ms. Groom reminded everyone that IHS implemented a mandatory influenza vaccination policy for HCP, but had not successfully bargained it with the unions. They were able to only partially implement the policy. They now have successfully bargained the policy with the unions, so it did go into effect this year. Preliminary data suggest that healthcare vaccine influenza vaccine coverage was 89.9% in IHS facilities as of December 2016. IHS is very optimistic that they might achieve the Healthy People 2020 goals this year. In terms of clinical decision support, IHS included the two-dose HPV vaccine series into its clinical decision support in the IHS EHR. They also are working on an algorithm to identify individuals with chronic liver disease (CLD) and HepC for the purposes of HepA and HepB vaccine. That reminder should go into effect later this year. IHS recently began a collaboration within Johns Hopkins Center for American Indian Health to assess maternal immunization in some tribal communities. They have been working with communities on messaging and with provider intervention with the hope to create a reminder for maternal immunization in the IHS EHR in the future.

National Institutes of Health (NIH)

Dr. Gorman first shared a personnel update. Dr. Francis Collins has been asked to remain as NIH's Director by President Trump. It is unclear at this point from the announcements made whether this is a reappointment or, in fact, just an extension for transition. Major General James K. Gilman, MD has been named the new Director of NIH's Clinical Center (CC). He has 35 years of experience commanding virtually every large US Army hospital in the US. He is a Cardiologist and highly decorated leader, with rich expertise in commanding the operations of numerous hospital systems. "His medical expertise and military leadership will serve the NIH Clinical Center well," said Dr. Collins. Dr. John Gallin, the former Director of the CC, stays on as the Associate Director for Clinical Research and the Chief Scientific Officer of the CC. Inside

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NIAID, Dr. Emily Erbelding is the new Director of Microbiology and Infectious Diseases (DMID). She is an Infectious Disease Physician with broad research and clinical experience in both government and academic medicine. She has served as the Deputy Director of the Division of AIDS at NIAID since 2010. She has been involved in all aspects of scientific program management and support, helping to design and implement new initiatives involving basic, translational, and clinical research. She has administered complex extramural grant programs and complex research infrastructure. Prior to joining NIAID, she spent 14 years on the faculty of Johns Hopkins University. As an interesting link, General Gilman and Dr. Erbelding are both graduates of a medical school in Indiana. Dr. Catherine Laughlin of the Virology Branch (VB) is retiring in March 2017 after 29 years of government service. Dr. Cristina Cassetti has been announced as the Acting Branch Chief of the VB. Dr. Clare Schmitt was announced in late January 2017 as the Acting Branch Chief for the Enteric and Hepatic Diseases Branch (EHDB). Dr. Schmitt is acting in that capacity until a permanent replacement for Frederick Cassels can be named. Dr. Gorman also will be retiring in late April 2017 after nine years in government service.

Regarding some specific activities of interest, NIH funds additional medical centers to expand the Precision Medical Research Program. Four regional centers have been added to clinical care, hoping to engage more than 1 million US participants to enable research that will, over time, improve the ability to prevent and treat diseases based on individual differences in lifestyles, environments, and genetics. The new awardees are the California Precision Medicine Consortium, Geisinger Health System, the New England Precision Medicine Consortium, and the Trans-American Consortium for the Health Care Systems Research Network.
Dr. Collins and Dr. Kathy Hudson have published an article in the *New England Journal of Medicine* (*NEJM*) about the 21st Century Cures Act and the view from NIH. To summarize, they felt that the 21st Century Cures act would cut bureaucratic red tape related to paperwork and scientific conferences, enhance data sharing and privacy protection for volunteers, improve support for the next generation of researchers, and encourage NIH to extend its efforts to include diverse populations. Drs. Collins, Hudson, and Michael Lauer also published in the *Journal of the American Medical Association* (*JAMA*) in which they talked about a new era of trust and transparency in clinical trials and clinical trials reform. The authors described a multi-faceted approach to improve the quality and efficiency of clinical trials. This effort focuses on a variety of key points along the lifespan of a clinical trial, and the initiatives will reengineer the process by which clinical investigators develop ideas for new trials, how NIH reviews and selects clinical trials for support and oversees the process, and how results and aggregate data are shared both broadly and rapidly.

The first HIV vaccine efficacy study in seven years has begun. The experimental vaccine being tested is based on one investigated in the RV144 clinical trials in Thailand led by the US Military HIV Research Program and the Thailand Ministry of Health. The Thailand trial delivered landmark results in 2009 when it found for the first time that a vaccine could prevent HIV infection, although moderately. For the new HVTN 702 HIV Vaccine Study, the design, schedule, and components of the RV144 vaccine have been modified in an attempt to increase the magnitude and duration of the vaccine-elicited protective immune response. A new regimen has been adapted to the HIV subtype that predominates in South Africa.

In terms of antimicrobial resistance, there are two major efforts at NIH. The Antimicrobial Research Leadership Group and the Vaccine and Therapeutic Evaluation Units (VTEU) have been working on some projects. NIH recently launched a study that is hoping to enroll 400 children in a clinical trial to determine whether shorter courses of antibiotics, 5 days instead of 10, are effective in treating community-acquired pneumonia in children who show improvement

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after the first few days of antibiotics. That study is being conducted at Duke, Cincinnati, Children's Hospital of Philadelphia, and Children's Hospital at Pittsburgh. NIH recently published the results of a different clinical trial that examined shortening the treatment for middle ear infection, which showed that 5 days of therapy is less effective than 10 days of therapy. Of the 229 participants, 77 or 35% in the 5-day treatment experienced clinical failure or worsening of symptoms compared to only 39/238 or 16% in the 10-day treatment group.

Dr. Bennett thanked Dr. Gorman for his service to ACIP, emphasizing that he would be missed very much.

National Vaccine Program Office (NVPO) / NVAC

Dr. Gellin reported on both NVPO and NVAC. He reported that NVAC met earlier in the month. The highlights are that they completed and approved the mid-course review of the National Vaccine Plan (NVP). Essentially, this review constitutes the reprioritization of the aspects of the plan going forward. The 21st Century Cures Act came up at NVAC as well. This is a 1000-page bill, approximately 20 pages of which focus on vaccines. There is a piece that asks the Secretary to develop a report on the state of vaccine innovation. NVAC is in the process of assembling the approach to that report, but among them is to reach out to stakeholders broadly. NVAC will be the convener of that stakeholder session and is working on the timing, which probably will be in conjunction with the June NVAC meeting. This is a way to ensure that stakeholders are at the NVAC table, and for others to contribute their views on vaccine innovations.

Turning to NVPO, the *National Adult Immunization Plan: A Path to Implementation* is now available. This is a companion piece to the *National Adult Immunization Plan (NAIP)*. Along with partners in HHS, NVPO is now launching an awards program for people in non-federal organizations who are engaged in work to support the goals of the *NVP*. Nominations are due by April 26, 2017 and the non-monetary awards will be announced at the June 2017 NVAC meeting. Information regarding the criteria are on the website.

In terms of the transition, with Dr. Gellin's departure, Dr. Jewel Mullin, who has been the Assistant Secretary for Health, will be the Acting Director of NVPO going forward as the department is now assembling a national search. He said it had been a treat to be involved with ACIP for many years. Dr. Bennett thanked Dr. Gellin for everything, noting that there are not enough words to sum up the incredible contributions Dr. Gellin has made to keeping America safe. She thanked him for his service, and emphasized that he also would be missed very much.

Vaccination Errors

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro explained that the mission of the Immunization Safety Office (ISO) is to assess the safety of vaccines administered to children, adolescents, and adults. Post-licensure vaccine safety monitoring includes activities to rapidly identify new or rare AEs of clinical importance;

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monitor changes in patterns for known AEs; assess safety in special populations (e.g., pregnant women); and determine patient risk factors for particular AEs.

ISO's post-licensure vaccine safety monitoring infrastructures include: 1) Vaccine Adverse Event Reporting System (VAERS), a collaboration between CDC and FDA, which is a US frontline spontaneous (or passive) reporting system to detect potential vaccine safety problems; 2) Vaccine Safety Datalink (VSD), a collaboration between CDC and healthcare plans, which is a large linked database system used for active surveillance and research; and 3) Clinical Immunization Safety Assessment (CISA) Project, a collaboration between CDC and academic medical centers, which conduct individual clinical vaccine safety assessments and clinical research.

For the purpose of this review, a vaccination error is defined as a preventable event that might reflect incorrect use and/or potentially result in patient harm. It is important to understand that VAERS is a passive system. The reporting limitations of VAERS include reporting bias, inconsistent data quality and completeness, lack of an unvaccinated comparison group, and inconsistent pregnancy reporting. It is important to remember that it is generally not possible to assess whether a vaccine caused an AE from VAERS data alone.

The data Dr. Shimabukuro reported during this session were from a study published in 2015 by Hibbs et al in *Vaccine* titled *Vaccination Errors Reported to the Vaccine Adverse Event Reporting System* (*VAERS*). During this time period, there were just over 300,000 total reports to VAERS. Of these, just over 20,000 (7% of the total) were classified as vaccination error reports. Of the 20,000 just over 15,000 (75%) did not document an AE in the report and just over 5,000 (25%) did document an AE in the report. In the early 2000s, there were not many reports of errors in VAERS and the percentages were quite low. In the later years of this study period, there were increases in total reports, the number of error reports, and the percentage of error reports. This trend has persisted to the present, though there have been some slight differences in the actual types of errors reported to VAERS.

The vaccine error groups were created by investigators who assigned specific Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms to the error groups. Multiple MedDRA codes are assigned to error groups. The reports by error group in VAERS from 2000-2013 are shown in the following table:

~2/3 of error reports

Vaccine Error Group	N (%)
Inappropriate schedule	5,947 (27%)
Storage and dispensing	4,983 (23%)
Wrong vaccine	3,372 (15%)
General error	2,526 (12%)
Incorrect dose	2,002 (9%)
Administration error	1,951 (9%)
Accidental exposure	373 (2%)
Product quality	239 (1%)
Contraindication	215 (1%)
Equipment	205 (1%)
Product labeling/packaging	30 (<1%)
Total errors	21,843

Hibbs et al. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000-2013. Vaccine 2015;33:3171-8. 12

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Note that there are slightly more errors than there are reports. That is because reports may be assigned more than one MedDRA term (i.e., not mutually exclusive). Therefore, a report might be included in more than one vaccine error group. The top three rows are highlighted as they represent the top three error groups. Inappropriate scheduling accounts for 27% of the errors reported, storage and dispensing is 23%, and wrong vaccine is 15%. These comprise two-thirds of all errors reported to VAERS during the time period.

Inappropriate schedule errors include wrong age and wrong timing between doses. Of these errors, 57% occur in children 0 through 18 years of age. Within this age group, 53% of these errors were reported in children less than 1 year of age. This probably is not unexpected, given that a lot of vaccine is administered during the first year of life in a fairly complicated schedule. The most common vaccines associated with wrong timing were quadrivalent human papillomavirus (HPV) vaccine and rotavirus vaccine. Within these two vaccines, commonly reported for quadrivalent HPV vaccine were delays between dose 1 and dose 2, based on a 5% random sample review of these reports. Technically, a delay between dose 1 and dose 2 is not an error. The reason these are categorized as errors is because there was documentation in the report that there was some type of delay in receiving the second dose. The median delay was 577 days with a range from 179 to over 2067 days. Also commonly reported for this vaccine was dose 3 being given too soon, prior to the 12-week minimum interval. For rotavirus vaccine, the common timing errors were the first dose given after 15 weeks and the last dose given after 32 weeks. It is not recommended to give the first dose after 15 weeks or the last dose after 32 weeks according to the prescribing information.

The second most common error, storage and dispensing errors, was 23% of the total. These basically broke down into two groups: expired vaccine administered (55%) and incorrect storage (44%). Within expired vaccine administered, commonly reported vaccines were seasonal LAIV; herpes zoster; and measles, mumps and rubella (MMR). Within incorrect storage of vaccine based on a 5% random sample of reports, vaccines kept outside of proper storage temperatures were reported 88% of the time, so that appears to be the most common type of error for incorrect storage of vaccine. In 55% of these reports, the vaccine was exposed to temperatures below recommended storage temperatures, so they were stored too cold.

The third most common type of error reported was wrong vaccine administered at 15% of the total errors reported. This appears to occur commonly among vaccines with similar names, acronyms, and antigens. The following table shows common wrong vaccine mix-ups:

Common Wrong Vaccine Mix-Ups in Either Combination		
Varicella (VARIVAX®)	with	Herpes zoster (ZOSTAVAX®)
Diphtheria, tetanus and pertussis (DTaP)	with	Tetanus, diphtheria and pertussis (Tdap)
One type of trivalent inactivated influenza vaccine (IIV3)	with	Another type of IIV3 with a different age indication
Pneumococcal conjugate	with	Pneumococcal polysaccharide
Hepatitis A	with	Hepatitis B

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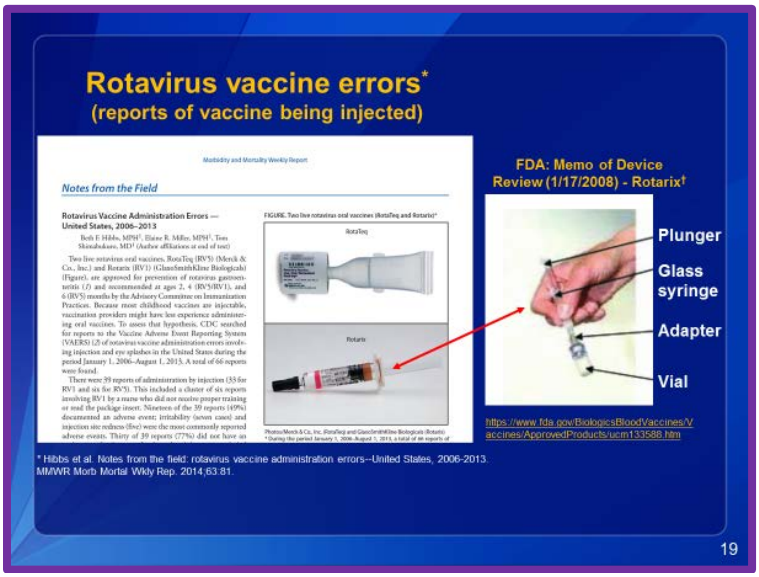
Adverse health events were reported in 25% of the errors. Of these, 92% were non-serious and 8% were serious. These percentages are similar to non-error reports to VAERS. The most common adverse health events were injection site erythema (13%), injection site pain (11%), and pyrexia (11%). This is similar to what is observed in non-error reports as well. The administration error group had the highest percentage of reports with a documented adverse health event (in 60% of administration error reports). The types of errors were wrong site, wrong technique, and incorrect route.

A number of reports of error clusters were detected. A cluster is defined as the same error in multiple individuals at the same location or clinic. There were 936 error clusters involving at least 6141 patients. The cluster size ranged from 2 to 501 patients, with a median of 5. Of the clusters, 110 involved 10 or more patients. In 586 clusters, the specific number of patients affected was stated as “unknown” or “several.” They basically submitted a report saying there was a cluster error, but did not specify the number. That is why the total estimate is said to be “at least” 6141, because it is likely to be an underestimate. Storage errors were the most common type of error clusters at 72% of all cluster reports. Incorrect storage (582 clusters, 1715 patients) and expired vaccine administered (96 clusters, 1340 patients) were the most commonly reported. LAIV was the most commonly reported expired vaccine administered (45 clusters, 990 patients).

Moving to case series reports of vaccination errors, the first case series involved a VAERS review of rotavirus vaccine error reports. For the purpose of this presentation, Dr. Shimabukuro focused on the vaccine injection errors. In the following graphic, the two types of rotavirus vaccines licensed in the US are shown, RotaTeq® and Rotarix®. In the VAERS review, there were 39 total reports of rotavirus vaccine being injected. Of these, 33 were with the Rotarix® product and 6 were with RotaTeq®. With the Rotarix®, there was one cluster of 6 that occurred on the same day with the same provider. Reasons documented in the report for this error included misinterpretation of instructions, inadequate training, not reading the package insert, confusing the oral applicator syringe with the syringe for injection, and confusing the vial with a vial for injectable vaccine. On the righthand side of the graphic, the Rotarix® vaccine is in the process of being reconstituted. The person is holding the syringe component, and then there is an adapter and a vial. The way this works is that the syringe is plunged to reconstitute the vaccine, withdraw, remove it from the adapter, and use the syringe the squirt into the infant’s mouth:



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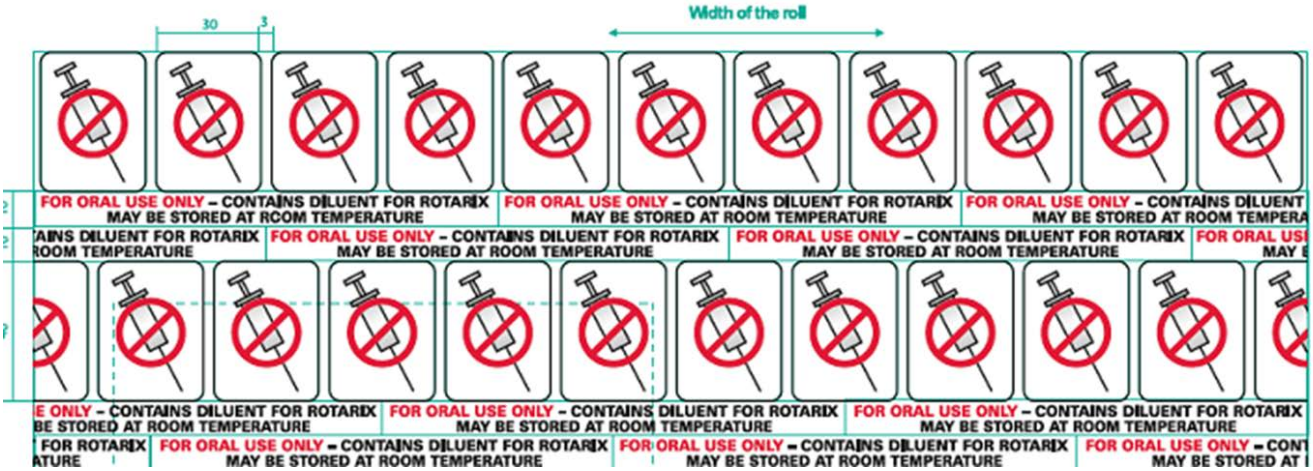
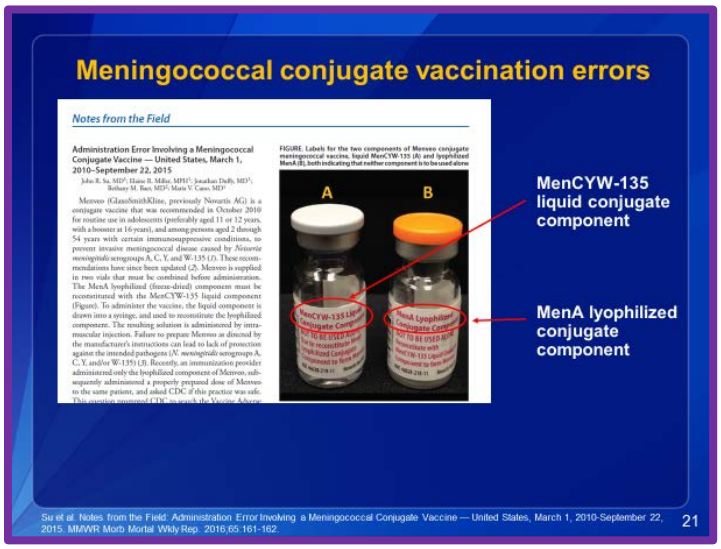
To test the theory that the syringe is being used to inject, Ms. Beth Hibbs, the lead for this project, went into the field and tested as many needles as she could find. The conclusion is that a needle simply cannot be attached onto this syringe. Therefore, it is highly unlikely that this is occurring because there is a freestanding needle syringe unit that is being injected. There is some other mechanism by which these errors are taking place. There was not sufficient information in the reports to draw conclusions. The following is an example of the current Rotarix® package, which shows the universal sign for do not inject and then prominently displayed in red is "FOR ORAL USE ONLY" to make the provider aware that this is not an injectable vaccine:



Graphic Courtesy of GSK

The next case series is a VAERS review of meningococcal conjugate vaccination error reports involving the Menveo® product, which is supplied in two vials that must be combined before administration. The liquid component shown in the left side of the following graphic is used to reconstitute the lyophilized component shown on the right side



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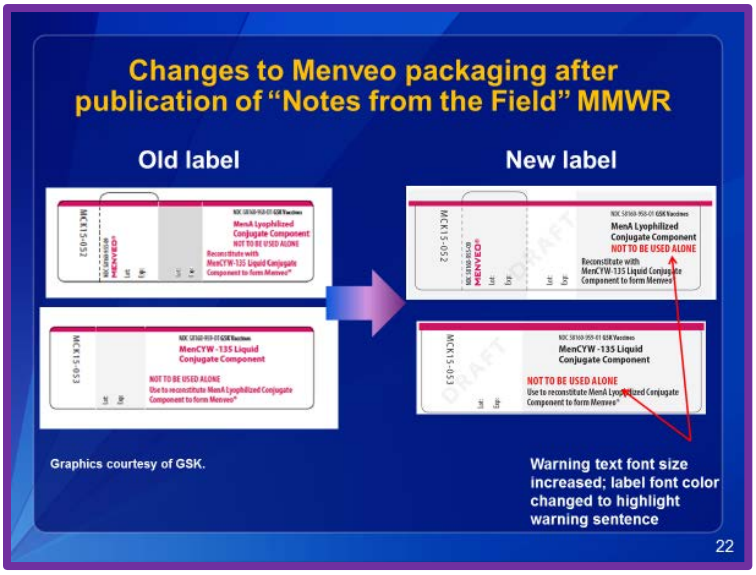
Administration errors involved only one component of Menveo® being given to patients. A total of 390 reports were detected from the period 2010-2015. Of these, 66% of recipients received only the liquid component and 34% received only the lyophilized component. When there was information about how that actually occurred, some common diluents used were sterile water, saline, HepB vaccine, and Diphtheria and Tetanus Toxoid and Pertussis (DTaP) vaccine. That is, other vaccines were used to reconstitute the lyophilized component. There also were reports of errors occurring with another two-component vaccine. There is a combination DTaP/IPV/Hib vaccine that needs to be reconstituted, and similar reports were detected for that vaccine as well. The following graphic shows changes made to the Menveo® label after publication of this paper:



On the left side, the old label has pink and smaller font. On the right side is the new label with changes in the font size and color so that "NOT TO BE USED ALONE" stands out more clearly to the provider reading the labels.

Another interesting investigation was of unintentional administration of insulin instead of influenza vaccine. This involved an apparent mix-up in which a cluster of 5 adult patients unintentionally received insulin instead of influenza vaccine. These patients were teachers who received their injections at a school clinic. All 5 experienced symptoms of hypoglycemia and two required treatment in the emergency department (ED) for severe hypoglycemia. This investigation was conducted by the St. Louis County Department of Public Health with assistance from the state health department, CDC, FDA, and the vaccine manufacturer. The conclusion was that improper storage, including inadequate segregation of insulin and influenza vaccine products in clearly labeled containers or bins, lack of standardized procedures for confirming the contents of vials, and decreased vigilance in preparation and administration likely contributed to the incident [Clogston et al. Unintentional administration of insulin instead of influenza vaccine: a case study and review of reports to US vaccine and drug safety monitoring systems. *Drugs & Therapy Perspectives*. 2016;32:439-446].

In summary, vaccination error reports comprised 6% to 15% of all reports to VAERS during the period 2007-2013. The number and percentage of total VAERS reports of vaccination error reports have increased substantially from 2000-2013. Of the vaccination error reports to VAERS, 75% did not document an adverse health event. Of the 25% of vaccination error

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reports to VAERS that did document an adverse health event, the adverse health events were generally similar to non-error reports. Based on reports to VAERS, vaccination errors usually do not appear to pose a substantial safety risk. However, errors do have an impact in terms of additional costs, possible effect on immunological protection, patient/parent inconvenience, and loss of confidence in the healthcare delivery system. Some errors do or have the potential to cause patient harm, such as the following:

- Unintentional administration of insulin instead of vaccine http://link.springer.com/article/10.1007/s40267-016-0333-2

- Reuse of syringes on multiple patients at a vaccination clinic https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6449a3.htm

- Incorrect reconstitution of measles-rubella vaccine using atracurium instead of the approved diluent in Syria, which resulted in 15 deaths http://www.who.int/mediacentre/news/statements/2014/interim-findings-idleb-syria/en/

Current strategies for reducing vaccination errors include: 1) Education and training on vaccine timing and spacing, especially for vaccines with complex schedules; 2) Training on proper administration technique, including general injection safety; 3) Improved monitoring of vaccine storage temperatures and expiration dates; 4) Improvements in differentiating vaccines and other products with similar sounding names and acronyms; and 5) Implementation and enforcement of procedures to properly screen for vaccine contraindications. A future strategy that has promise is passive engineered interventions that take human judgment and human behavior out of the process, which can prevent or substantially decrease the likelihood that an error will be made. One example that has been discussed is an indicator on the label of a vaccine that changes color when the vaccine has been out of temperature for too long; that is, a visual que to let the provider know that the vaccine needs to be discarded.

Following are some resources for reporting vaccination errors and strategies to prevent errors:

- VAERS guidance on reporting vaccination errors https://vaers.hhs.gov/esub/index**,** https://vaers.hhs.gov/esub/eSubpopup.htm

- Strategies to Prevent Administration Errors (in the Pink Book) https://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html

- CDC Vaccine Storage & Handling Tool Kit http://www.cdc.gov/vaccines/recs/storage/toolkit

- One & Only Campaign https://www.cdc.gov/injectionsafety/1anonly.html

- Technically Speaking: Vaccine Administration Errors (CHOP) http://www.chop.edu/news/technically-speaking-vaccine-administration-errors

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Discussion Points

Dr. Szilagy asked Dr. Shimabukuro to describe how some of the interventions are woven into AFIX (Assessment, Feedback, Incentives, and eXchange) visits.

Dr. Melinda Wharton (Director, ISD/NCIRD) replied that as part of quality assurance visits immunization programs make, generally to participating VFC providers, built into the visits are reviews of storage and handling procedures and vaccine management. That is the primary quality control the system schedules into the program.

Ms. Pellegrini asked whether there is a process for going to the settings where larger clusters are occurring to engage in some type of remedial action to ensure that it does not happen again.

Dr. Shimabukuro said he thought that was more of an institution and local health department issue. CDC primarily performs surveillance and investigations. He can report on the number and type of clusters and why they occur.

Dr. Melinda Wharton (Director, ISD/NCIRD) added that for single reports which come in routinely, there is not necessarily a high level of follow-up. Certainly, for some of the incidents where there are clusters, this is more concerning. For example, with syringe reuse or mishandling of vaccines in clinics, state or local public health would be involved in follow-up generally speaking. This is not something CDC would necessarily be involved in. In general, CDC learns about these incidents because a problem is identified and reported to state or local public health departments. They may be reported later to the VAERS system, but usually those types of incidents raise a sufficient level of concern that state or local health authorities are alerted.

Dr. Cohn observed that additional immunizations added specifically to the adolescent schedule seemed to comprise a number of the errors described. She asked whether Dr. Shimabukuro could say anything about the number of doses that were given over that period of time in relation to the number of reports received.

Dr. Shimabukuro replied that in 2007, there was a large increase in reports and also an increase in the number of error reports and the percentage of error reports as a total. The short answer is that it is not exactly clear why this happened, but several reasons are suspected. About that time, a number of new products appeared on the market. Zostavax®, Gardasil®, and RotaTeq® were licensed in 2006 and ACAM® started being used in 2007. It appears to be a combination of more new vaccines on the market, more vaccines being administered, and a period of getting used to the schedule. When a new vaccine comes on the market, there tends to be a spike in reports in VAERS which then decreases and levels off. Relatively speaking, a substantial number of reports in that spike are errors when the roll out is occurring and providers are getting used to the schedule. It also may be that there is just more awareness of errors and less reluctance to report errors, or a combination of all of those things.

Dr. Bennett observed that one of the problems with VAERS is the inability to calculate rates of AEs or errors. She wondered whether there was any potential going forward that EMRs would help to identify errors, or if errors do not make it into EMRs.

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Dr. Shimabukuro said he thought there were some ICD codes for medical errors. CDC could perhaps assess how frequently errors are reported. This work has not been done in VSD yet, but it is something they could look into.

Dr. Stephens asked whether there are any active, prospective studies that are examining error rates in settings.

Dr. Shimabukuro replied that he was not aware of any ongoing studies examining error rates for vaccines. There have been more studies assessing drug errors than vaccination errors. That may be because most vaccination errors do not cause patient harm.

Dr. Weinbaum (ISD/NCIRD) reported that there is a study looking at schedule errors, which is one of the top errors, using a centralized system of Immunization Information Systems (IIS) (microphone issues)

Dr. Bridges indicated that the National Adult Influenza Immunization Summit WG also recognized these problems with errors that may be more common in temporary or seasonal clinics, and developed a checklist that is available on the Summit website on which they would like feedback.

Dr. Moore commented that in the future, it would be helpful when discussing vaccine safety and VAERS reports to identify vaccines that are new to the market separated from those that have been on the market for a long time or errors that are reported based on multiple vaccines. This will make it easier to distinguish when an increase like this occurs that is associated with a number of vaccines coming onto the market how much of that is reports about these new vaccines that may be errors because of unfamiliarity with a new product as opposed to errors that are occurring with vaccines that have been on the schedule for a long time. She asked whether there was any change in the reporting, such as making it easier to report online, that also could have contributed to an increase in reports.

Dr. Shimabukuro replied that one possible reason was that in 2007, there was a switch from COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) coding to MedDRA coding. MedDRA coding evolves and the codes tend to get more specific from more general. With the switch to MedDRA coding, there were more options for errors with more specific codes. There were still error codes in COSTART, so it could be argued that an increase in errors should still be observed because there were COSTART options to select for an error. However, the wider variety of error codes available in MedDRA may have changed some of the coding behaviors of the coders because they have more options to choose from and are more aware of error codes.

Ms. Hayes (ACNM) indicated that her concern with the number of vaccines that were given when they had previously been stored at an improper temperature range and may lose their efficacy. In the clinics she has worked in, they are required to take a daily temperature of the refrigerator. There are extensive materials on vaccine handling procedures on CDC's website, but they have not been updated in a while, so she was curious as to whether there were any plans to work on improving the language around proper storage and handling.

Dr. Shimabukuro clarified that this is probably not administration of vaccine that was known to be out of temperature. These were realizations after the vaccine was administered.

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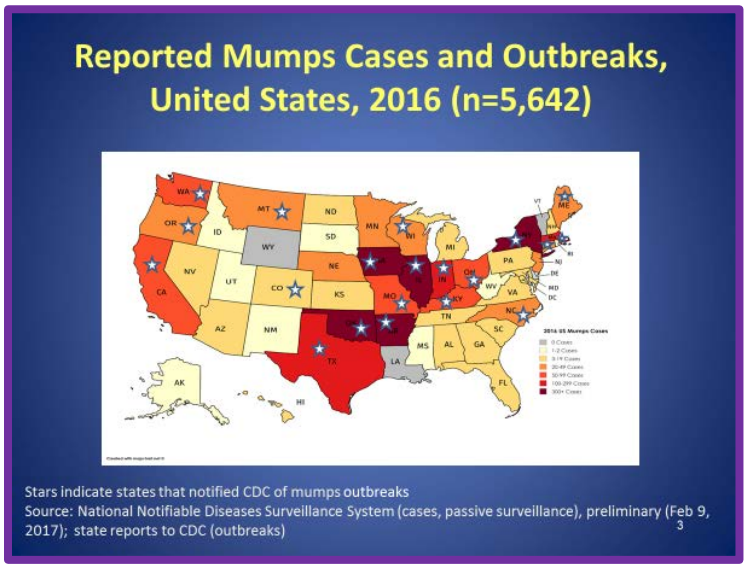
Dr. Melinda Wharton (Director, ISD, NCIRD) emphasized that issues pertaining to vaccine storage and handling have been a major focus of the ISD program state immunization programs and quality assurance visits for the past several years. An increase in the use of digital data loggers has made it easier to identify excursions and make appropriate interpretations of their significance. Often excursions might occur that are not of sufficient duration or magnitude that the vaccine potency is affected and, therefore, it is safe to use the vaccine. Assuring that offices have appropriate vaccine management practices in place, including recording and monitoring temperatures and taking appropriate actions when there are excursions is clearly an important priority for CDC. An extensive update was done over the summer of storage and handling materials, which are on the website.

Mumps

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

Dr. Moore introduced the Mumps WG that has recently been constituted. She reported that numerous mumps outbreaks have been reported in the US since 2006, particularly among highly vaccinated college populations. The second largest number of reported cases since 2006 occurred in 2016. Widespread distribution of these outbreaks across the US resulted in increased interest from state and local health departments and universities to implement third dose of MMR vaccination campaigns to control these outbreaks. However, data on the effect of a third MMR dose for outbreak control are limited. This map reflects the distribution of reported mumps cases and outbreaks across the US in 2016:



Mumps outbreaks are not required to be reported to CDC; however, state and local health departments and universities have voluntarily reported numerous outbreaks. In 2016, at least 19 university-based outbreaks were reported. The stars in the map represent states that reported outbreaks last year. When these outbreaks occur, the disease itself has not been serious for most individual patients. However, the disruption for the universities and disruption

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and expense for local and state public health, including public health laboratories, has been significant.

Dr. Moore shared the list of the Mumps WG members and expressed appreciation for everyone's expertise as they try to address new information available on this topic. Regarding the proposed terms of reference for the Mumps WG, the objective is strictly to evaluate and propose policy options to prevent or control mumps outbreaks in the US. The activities related to that in the coming months are to: 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 benefit provided by a third dose of MMR for mumps outbreak control; and 4) Evaluate programmatic implications and cost of various policy options for a third dose of MMR to prevent or control mumps outbreaks.

Regarding the timeline, the goal of the February 2017 meeting is to inform ACIP of the new WG, members, terms of reference, and kick off with a presentation focused on an overview of current mumps recommendations and epidemiology in the US. The first WG conference call is scheduled for March 2017. During the October 2017 ACIP meeting, an update will be provided on the WG's deliberations. During the February 2018 ACIP meeting, the WG anticipates presenting recommendations to ACIP.

Mona Marin, MD
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In anticipation of the WG deliberations and presentations to ACIP, Dr. Marin reviewed mumps vaccination recommendations and epidemiology in the US. For this presentation, she provided an overview of mumps disease and transmission, described mumps vaccine and vaccination recommendations in the US, presented mumps epidemiology in the US with a focus on recent years, and discussed the main topics that the WG will address based on the proposed terms of reference.

Mumps is an acute viral illness that classically presents with parotitis in approximately 60% to 70% of patients. Other presentations include other salivary gland swelling and non-specific respiratory symptoms or asymptomatic infection, which occur in approximately 30% of patients. In the pre-vaccine era, mumps complications were common with orchitis and mastitis being the most frequent. More serious complications such as aseptic meningitis leading to hospitalizations also occurred. In the vaccine era, complication rates and hospitalizations have been drastically reduced [McLean HQ et al. MMWR 2013; Data from US outbreak investigations 2006-2015].

Mumps is transmitted person-to-person by direct contact with infected droplets or saliva or by inhalation of infectious respiratory droplets. It requires close contact for spread. The infectiousness is less than for measles and varicella[1]. The infectious period is from 2 days before to 5 days after parotitis onset, although virus was isolated outside this period. Importantly, transmission can occur from patients with non-specific respiratory symptoms and asymptomatic infection. Mumps has a long incubation period of an average 16 to 18 days. Infectiousness before symptoms and transmission from persons with asymptomatic or non-specific presentation contribute to prolongation of transmission and outbreaks [[1]Hope Simpson RE. *The Lancet* 1952].

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Mumps is preventable by vaccination. In the US, mumps vaccine was licensed as a single antigen vaccine in 1967. Currently, the vaccine is available as combination vaccines either as MMR licensed in 1971 or MMR plus varicella (MMRV) licensed in 2005. These vaccines contain a live attenuated mumps strain, the Jeryl-Lynn strain, which belongs to genotype A. Effectiveness estimates for MMR for preventing clinical mumps are ~77% for one dose and ~88% for two doses [1,2] [[1] Schaffzin JK et al. *Pediatrics* 2007, Marin M et al. *Vaccine* 2008; and Cohen C et al. *Emerg Infect Dis* 2007, Deeks SL et al. *CMAJ*. 2011, Dominguez A et al. *Vaccine* 2010, Sartorius B et al. *Euro Surveill* 2005, Harling R et al. *Vaccine* 2005].

Recommendations for mumps vaccine use have evolved since the vaccine was licensed in 1967. It was not until 1977 that ACIP recommended 1 dose for all children at any age after 12 months[1]. In 1989, a second dose of measles vaccine was recommended for improved measles control, and it was indicated that both doses of measles vaccine should be given as combined MMR, stating that mumps revaccination is particularly important[2]. Effectively, the recommendation for a second dose of measles vaccine delivered a second dose of mumps vaccine. In 2006, a formal recommendation for 2 doses of a mumps-containing vaccine was issued to cover school-aged children in grades K-12 and adults in high risk groups, including healthcare facility personnel, international travelers, and students at post-high school educational institutions[3] [[1]ACIP. *MMWR* 1977; 26:393-4; [2]ACIP. *MMWR* 1989; 38(S-9):1-18; [3]ACIP. *MMWR* 2006; 55(22):629-30].

Reports of mumps cases declined dramatically following MMR vaccine licensure and the 1-dose recommendation. The second dose of MMR vaccine recommended in 1989 subsequently improved mumps control as well. From 1993 through 2005, only a few hundred cases were reported annually and vaccination coverage was high. However, several large mumps outbreaks have been reported from 2006 through February 2017. It is important to note that despite these recent outbreaks, there has still been a 99% decline in mumps cases compared with the pre-vaccine era [Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); National Immunization Survey (NIS) (1st dose coverage 19-35 year olds), National Health Interview Survey & NIS-Teen (2nd dose coverage); 2016 case data is preliminary (Feb 9, 2017) and subject to change].

The first large outbreak of the last decade occurred in 2006, with more than 6500 cases reported in 8 Midwestern states. This was the first multi-state outbreak attributable to 2-dose vaccine failure. Incidence was highest in young adults age 18 through 24 years, most of whom were college students. The 2-dose MMR coverage rate in affected colleges was 90% to 99%, with most students having received their second dose more than 10 years previously. Dormitory living, freshman class status, and time since the second dose were risk factors in college investigations. Standard control measures, including isolation and vaccine catch-up campaigns, were implemented to control this outbreak [Dayan GH et al. *N Engl J Med* 2008; Cortese MM et al. *Clin Infect Dis* 2008; Marin M et al. *Vaccine* 2008].

Then in 2009 -2010, two large outbreaks occurred among highly vaccinated populations and accounted for most of the mumps cases reported nationally during this period. In the Northeastern US outbreak, 97% of the cases were among members of the Orthodox Jewish community. In this outbreak, adolescent males were the most affected group and 89% of them had 2 doses of MMR vaccine. This community has unique schools with high densities and partner-style learning, as well as large households. These characteristics resulted in prolonged, intense exposures that likely overcame the protection afforded by the vaccine[1]. The second outbreak occurred in Guam. In this outbreak, the highest attack rate was in school-aged

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children 9 through 14 years of age, of whom 96% were vaccinated with 2 doses of MMR, as well as among ethnic minorities with higher household densities[2]. A third dose of MMR vaccine was used for outbreak control in these settings [[1]Barskey AE et al. *N Engl J Med* 2012; [2]Nelson GE et al. *Pediatr Infect Dis J* 2013].

Moving on to the most recent 6 years, an increase in the number of mumps cases and incidence and numerous outbreaks have been reported. In 2016 in particular, a high number of mumps cases and outbreaks were reported. For cases, even if the states with the 3 largest numbers of cases (Arkansas, Iowa, Oklahoma) are removed, the number of cases and incidence remain the highest of the past 6 years. Genotyping G virus has been the most commonly identified virus since 2006 when laboratory surveillance was established. Regarding outbreaks, during the second half of 2010 through 2015, 23 outbreaks with 20 or more cases have been reported in 18 states. Of these, 22 occurred in close contact settings, of which 18 were universities. In these outbreaks, the highest incidence was in those 18 through 25 years of age. In half of university outbreaks more than 85% of case-patients had documented 2 MMR doses. The spread outside the affected community was minimal, in only 3 outbreaks. Also, size of the outbreaks was limited. About 56% had less than 50 cases [Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); 2016 data is preliminary (Feb 9, 2017) and subject to change; Clemmons N, CDC, personal communication Feb 2017 (outbreaks)].

Several factors may contribute to the increasing number of mumps outbreaks. With a vaccine effectiveness of 77% for 1 dose and 88% for 2 doses, cases can still occur among vaccinated persons. Evidence also points to waning of vaccine-induced immunity, especially in the era of low disease incidence and absence of boosting from wild disease. Serologic studies have shown that seropositivity and neutralizing antibody titers decline over time[1-5]. However, there are no established correlates of protection[3]. Therefore, the implications of declining titer remain uncertain. Additionally, mumps vaccine also induces cell-mediated immunity. Although the contribution of the cell-mediated immunity to protection against mumps infection has not been clearly defined, evidence indicates that it declines over time less than seropositivity, if at all[6]. Epidemiologic studies also suggest waning of immunity with decreased vaccine effectiveness[7] and increased odds of contacting disease with time since vaccination[8-9], but evidence is still limited. However, waning of immunity itself does not explain the general geographical focal nature and that the oldest vaccinated cohorts are not always most affected [[1]Davidkin I et al. *J Infect Dis* 2008; [2]LeBaron CW et al. *J Infect Dis* 2009; [3]Rubin SA et al. *J Infect Dis* 2008;[4] Date AA et al. *J Infect Dis* 2008; [5]Kontio, *J Infect Dis* 2012; [6]Jokinen S et al. *J Infect Dis* 2007; [7]Cohen C et al. *Emerg Infect Dis* 2007; [8]Cortese MM et al. *Clin Infect Dis* 2008; [9]Vygen S et al. Euro Surveill 2016].

Intense exposure settings account for these features. Therefore, force of infection based on observations that outbreaks have occurred in settings with high population density and contact rates that facilitate transmission, such as college campuses or close-knit communities, is frequently postulated as a risk factor for current mumps outbreaks. Concern was raised that mumps vaccine-induced immunity may be less effective against other strains. There is no evidence to date. All sera collected from vaccinated children neutralized diverse mumps virus strains[1,2]. However, antigenic differences among strains led to lower antibody levels against non-vaccine strains[1-3]. These differences might become more important with increasing time since vaccination. Several examples that support these factors will be provided next. [[1]Rubin SA et al. *J Infect Dis* 2008; [2]Rubin SA et al. *J Virol* 2012; [3]Orvell C et al. *J Gen Virol* 2002].

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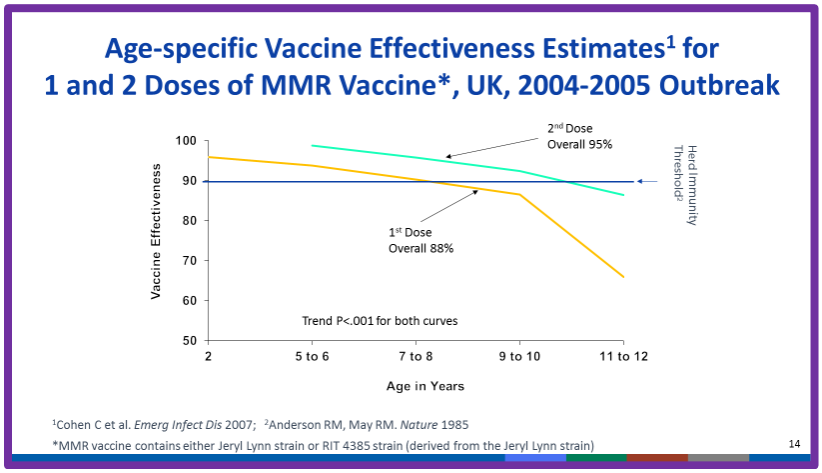
This graph shows the results of a study that documented decreasing vaccine effectiveness with time since vaccination:



Vaccine effectiveness was calculated during a mumps outbreak in UK in 2004-2005 with more than 56,000 cases primarily among under-vaccinated persons. The yellow line represents the first dose vaccine effectiveness which overall was 88%, while the aqua line represents the second dose vaccine effectiveness which overall was 95%. However, as seen from the graph, for the first dose, effectiveness declined from 96% in 2 year olds to 66% in 11 through 12 year olds. For the second dose, effectiveness declined from 99% in 5 through 6 year olds to 86% in 11 through 12 year olds. Assuming that age serves as a proxy for time since vaccination, these findings support waning immunity [[1]Cohen C et al. *Emerg Infect Dis* 2007; [2]Anderson RM, May RM. *Nature* 1985].

For serologic evidence of waning of vaccine-induced immunity, the following table presents data from a study that assessed mumps neutralizing antibodies against the Jeryl Lynn strain, which is the vaccine strain (shaded line), and a genotype G strain identified during the 2006 outbreak in IA (second row in the table):

Table 1. Geometric mean titers (GMTs) of serum neutralizing antibody against the Jeryl Lynn and USA06-Iowa-G viruses.

Virus	2–5 years after MMR1	1 month after MMR2	10 years after MMR2
Jeryl Lynn	107.9 (83.6–139.2)	280.5 (212.1–371.0)	94.8 (73.2–122.9)
USA06-Iowa-G	56.2 (46.8–67.6)	110.4 (90.3–135.0)	56.6 (47.3–67.5)

NOTE. Data are the GMT (95% confidence interval). Titers were measured before administration of 2 doses of the measles, mumps, and rubella (MMR) vaccine (MMR2) (given 2–5 years after administration of 1 dose of the MMR vaccine [MMR1]) and at 1 month and 10 years thereafter.

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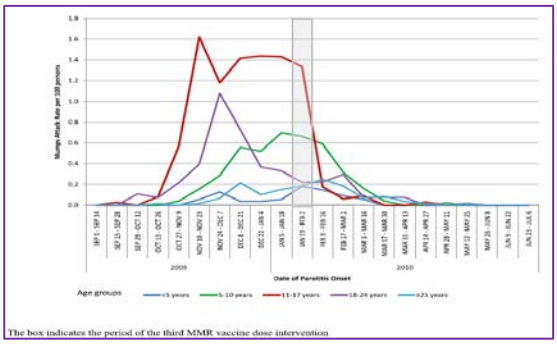
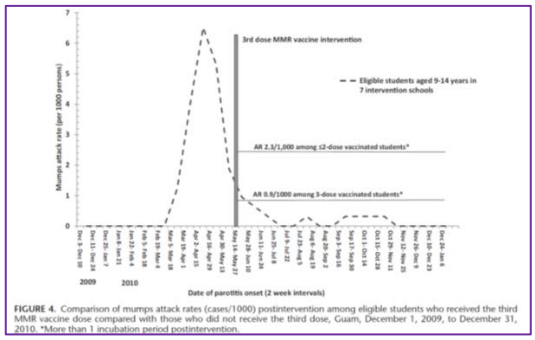
Neutralizing antibody is considered to contribute to protection, but the level required for protection has not been established. In this study, testing was performed on specimens collected days before receipt of the second dose of MMR (second column titled 2-5 years after MMR1), 1 month after the second dose MMR (third column) and 10 years after MMR2 (last column). This study found that antibody induced by vaccination effectively neutralized the genotype G virus for all study subjects at each time point tested, including 10 years after vaccination. However, the geometric mean titers (GMTs) against the genotype G strain were lower than the titers measured against the Jeryl Lynn strain, reflecting variability in antibody responses between strains. Titers to both viruses decreased over time since vaccination. As previously mentioned, in the absence of a correlate of protection, the clinical significance of these findings cannot be conclusively ascertained [Rubin SA et al. *J Infect Dis* 2008].

The hypothesis that waning immunity is a cause for mumps outbreaks led to interest in the use of a third dose of MMR vaccine for outbreak control. As mentioned earlier, third dose intervention campaigns were conducted in New York/Orange County where 81% of eligible students were vaccinated with a third dose[1] and in Guam where 33% of eligible students received a third dose[2]. As indicated by the two epicurves shown below, attack rates declined after a third MMR dose was administered in both school-based studies:



New York/Orange County



Guam

However, in Guam, statistical significance could not be established due to the small number of cases recorded and in both studies, because of the late timing of the third dose campaigns during the course of the outbreaks, 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].

These data were presented to ACIP in 2012. At that time, ACIP determined that the data were insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps outbreak control. Subsequently, CDC issued guidance for consideration for use of a third dose in specifically identified target populations along with criteria for public health departments to consider for decision-making. That includes settings with high 2-dose coverage, intense exposure, and ongoing transmission.

Data on laboratory evidence of the impact of a third MMR dose became available more recently. A study of neutralizing antibody titers in young adults 18 through 28 years of age found that very few subjects had titers that were negative (0.8%) or low (5.8%) before the third dose. Compared with pre-third dose considered baseline, GMTs were modestly but significantly higher at both 1 month and 1 year after the third MMR dose. However, as seen in the graph, the

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distribution curves show only minimal shifts in mumps titers from baseline (the continuous line) to 1 month (the dotted line) and 1 year (the dashed line in the middle)[1]:

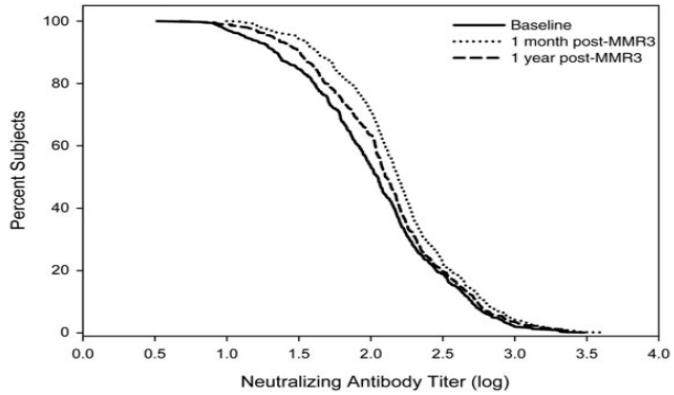

Figure 3. Reverse cumulative distribution curve using log-transformed titers by percent of subjects who had neutralizing mumps antibody titers at baseline and 1 month and 1 year following a third dose of measles-mumps-rubella (MMR3) vaccine.

These findings raise the question of short- versus long-term benefit of a third dose and implications for routine use versus outbreak policy recommendations. The qualitative aspects of the mumps immune response (e.g., antibody avidity, B-cell memory, or cell-mediated immune responses) have not been assessed [[1]Fiebelkorn AP et al. *Open Forum Infect Dis* 2014].

To conclude, use of the mumps vaccine reduced disease levels by approximately 99% since vaccine introduction in the US. Since 2006, mumps outbreaks have occurred in highly 2-dose vaccinated populations. The current 2-dose schedule is sufficient for mumps control in the general population, but outbreaks can occur in well-vaccinated populations in specific settings. Intense exposure settings and waning immunity appear to be risk factors for secondary vaccine failure. The benefit of a third MMR dose still needs to be assessed.

Dr. Marin ended with a summary of the main topics for WG discussion. The WG will review the available evidence for risk factors for mumps among 2-dose MMR vaccine recipients, including whether mumps vaccine protects against currently circulating mumps virus genotypes in the US. The WG also will review available evidence on benefit provided by the third MMR dose, whether there is an additional benefit and, if so, whether it is a short- or long-term benefit. More epidemiologic and laboratory evidence is forthcoming for the WG to review, including vaccine effectiveness in Iowa during the 2015 outbreak and Arkansas during the 2016-2017 outbreak, and antibody kinetics more than 5 years after the third MMR dose. Finally, the WG will examine the programmatic implications and conduct a cost analysis of various policy options for a potential third dose MMR recommendation to prevent or control mumps outbreaks.

Discussion Points

Dr. Reingold inquired as to whether more natural boosting at an earlier time period when the virus was circulating might explain why a reduction in vaccine effectiveness does not seem to be as true in older individuals.

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Dr. Marin clarified that when she referred to the older cohort, she meant within college investigations and the age span was narrow from 18 through 24 years of age. Higher rates of disease were seen in students 18 through 20 years of age, but not in those 21 and older. Given their year of birth, they were unlikely to be exposed to natural disease. The population over 30 to 40 years of age may have had exposure to natural disease.

Dr. Reingold noted that the pace seemed leisurely for the WG to report back to ACIP on forthcoming data. If these are important policy questions for health departments, he wondered whether the pace could be accelerated somewhat.

Dr. Marin replied that the Iowa investigation is almost complete. The analysis is largely finished, so those data will be available in a few months.

Dr. Messonnier agreed about the timeframe, but emphasized that the WG had not had their first meeting yet. One of the questions regards whether ACIP will be comfortable making a new recommendation based on the clinical efficacy data from existing investigations, or if they would like to see additional information, including some of the questions related to strain changes that will require more serological studies and will take longer. The WG certainly would welcome moving faster if they can.

Dr. Bennett noted that while Dr. Marin reported on the immunization rates overall at the institutions where there were outbreaks, but not on the rates comparatively between cases and non-cases. She wondered whether there has been any attempt to assess that and, if so, whether ACIP would see those data. In addition, she asked whether additional risk factor analyses could be performed. These seem like good opportunities potentially for case-control studies.

Dr. Marin indicated that the college investigations examined the coverage rate among cases versus non-cases in 2006, 2009, and 2010 but not so much in the past year. Most students in college now came from a time when 2-dose coverage was pretty high among children 4 through 6 years of age. There is a large portion of the population for which immunization status is not known. It is more difficult to get coverage information, but 2-dose coverage is high for college populations.

Dr. Moore assured Dr. Reingold that the WG would not be any more leisurely than absolutely necessary. Given that two universities reported cases to her in the previous three weeks, she personally feels the urgency to have the evidence to make an appropriate evidence-based decision. As soon as the WG feels that they have sufficient evidence presented to them to make an evidence-based recommendation, they will bring it to ACIP post-haste.

Dr. Schaffner (NFID/IDSA) asked whether there are epidemiologic or molecular data suggesting the source of these mumps virus outbreaks that are occurring, particularly in universities in terms of whether they are domestic or international mumps viruses.

Dr. Marin responded that the virus tested in 2006 was similar to the virus that cause the UK outbreak in 2005-2006. The index case in the outbreak in the Orthodox Jewish community was a 11-year old 2-dose vaccinated child who returned from the UK and two weeks later developed mumps. The genotype circulating is similar to the genotype circulating in Western Europe.

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Dr. Pallansch emphasized that unlike measles and rubella, mumps has not been eliminated from indigenous circulation in the US. It is just that currently genotype G is the most predominant, but is not exclusive. Importations are recognized, but genotype G being widely distributed globally makes it very difficult to say specifically in most situations. For some of the college outbreaks, it is not going to be possible to answer that question definitively.

Dr. Schaffner (NFID/IDSA) pointed out that while wild mumps is often an asymptomatic infection, not a lot of studies have been done about asymptomatic infections in the context of these outbreaks to his knowledge. He wondered whether this opportunity could be taken to study how frequently asymptomatic infection occurs among people who have been vaccinated, because they may be subtle transmitters.

Dr. Marin responded that this was an important point in 2006 when they went to Iowa. In the two colleges that were investigated, only 16% of students with mumps reported contact with a known mumps case. That suggested that there was a lot of asymptomatic disease that contributed to transmission.

Dr. Thompson (NVAC) pointed out that there is now an MMRV vaccine. She thinks that the timing of MMRV introduction and its increased use in 2006 is completely coincidental with the outbreaks. It is important for ACIP to examine this in its review and present the evidence. In the context of a third dose recommendation, she also thinks ACIP will need to say something about MMR versus MMRV, or if it is just MMR-containing vaccines.

Dr. Marin indicated that MMRV is licensed through 12 years of age. She agreed that it was coincidence, because MMRV was licensed in the US in 2005 and was not available during 2008-2009 due to a shortage. Also, after the ACIP MMRV Safety WG made recommendations for MMRV use, not many providers are using it for the first dose.

Dr. Even (ACHA) thought it was striking that none of the recent outbreaks have been reported in the military, which is comprised of the same age group and close quarters. She wondered whether DoD was doing something different.

Dr. Marin replied that the experience of the military has often been mentioned in support of a third dose. The military implemented vaccination of recruits regardless of their vaccination status in 1991, so those entering the military probably received a third dose. They made some changes based on serology, but the protocol is primarily giving a dose to everybody regardless of their status.

Margaret Yacovone (DoD) indicated that for all recruits entering the military, if there is no evidence of 2 doses of MMR, their antibodies are checked. If they are negative on any, they receive 2 doses of MMR. As a result, the military has very high immunity such that even if there is an isolated case, there is not transmission. Not all services in all recruit sites check for mumps. The DoD is trying to change this so that it will be unified across the services, especially with the outbreaks of mumps that have occurred throughout the US.

Dr. Romero indicated that in Arkansas, children under 10 years of age comprise most of the outbreak population.

Dr. Marin indicated that based on the age distribution of cases in Arkansas through the previous week, it was true that there have been a lot of cases in the younger age group. However, there are cases in the older age groups as well, 57% of case patients in Arkansas have been 5

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through 17 years of age. A potential explanation for the age distribution is case finding. Cases are reported primarily by schools. There is not good reporting from workplaces or other settings.

Dr. Riley asked whether there are good data to suggest for the college outbreaks that even for international students, the vaccination rates are just as high as for US-born students.

Dr. Marin said she did not think they specifically assessed international students, but national serologic surveys, examined mumps immunity by place of birth. People born outside the US have somewhat higher levels. One explanation might be that about 38% of the countries do not vaccinate against mumps. The mumps epidemiology is such that by 14 to 15 years of age, 90% of people have antibodies. College students coming from abroad from countries with no vaccination probably are immune.

Dr. Whitley Williams (NMA) asked whether Margaret Yacovone from DoD knew what percent of the recruits tested have negative mumps serology.

Margaret Yacovone (DoD) responded that she did not have that information, but they were finding higher antibody titers in some of their populations who were born abroad. They can share these data if it would help with ACIP's decision-making. The DoD has examined this a few times over the past several years.

Dr. Marin replied that this would be useful.

Dr. Maldonado said she understood that the patients from Arkansas may differ in other ways. For example, many of them are Marshallese students and tend to be younger and their symptoms are distinct as well. They have recurrent parotitis, which is generally not seen in a normal mumps outbreak situation.

Dr. Marin pointed out that it is difficult to confirm recurrent disease, especially in a situation like mumps where parotitis can be determined by other agents. Confirmation would be needed of both episodes, and she did not know how often that happened in Arkansas. There is evidence in the literature of symptomatic mumps after a previous infection occurred. Those were documented by laboratory confirmation and the profile of the immune response which supported reinfection.

Dr. Romero added that interesting about the Arkansas outbreak is that they are not seeing the secondary complications. For example, they would expect to see many more cases of aseptic meningitis, encephalitis, hearing loss, and orchitis. However, they are not seeing that. They do see some cases of orchitis, but not the central nervous system (CNS) disease that is anticipated with mumps. He would interpret that to mean that there is some protection from the vaccine.

Dr. Duchin (NACCHO) reported that Washington State is also experiencing an outbreak, primarily in King County. On an encouraging note, when they had to exclude students from a school district with about 15,000 total students who are unimmunized or did not have up-to-date MMR vaccination, over half were immunized and returned to school rather than staying out the entire exclusion period that would have been required. This is encouraging to see, and it suggests that there is not a true objection to vaccination and may just be other barriers. A certain percentage refuses to be vaccinated and are staying out of school for a prolonged period.

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Ms. Pellegrini noted the disproportionate share of Native Hawaiian and other Pacific Islanders with mumps in 2016. That is because about half of US cases in 2016 were reported from Arkansas that had a large outbreak affecting primarily the Marshallese community.

Dengue Virus Vaccine

Introduction

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

Dr. Walter reminded everyone that this WG was renamed the "Flavivirus Vaccines Work Group" to encompass work on Japanese encephalitis (JE), Yellow Fever (YF), dengue, and Zika vaccines. During the last few months, the WG began a review of dengue epidemiology, immunology, and diagnostics to prepare for submission of a dengue vaccine BLA. During the past few months, the WG also has monitored the YF vaccine supply and worked with the manufacturer on contingency plans to address shortages.

In terms of the dengue vaccine tentative timeline, Sanofi Pasteur is expected to submit a BLA during 2017. In June 2017, Sanofi Pasteur will present dengue vaccine data to ACIP. In October 2017, the WG will present modeling and cost-effectiveness data to ACIP. In February 2018, the WG will present the GRADE evaluation and proposed recommendations to ACIP.

Dengue Virus Vaccines

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

Dr. Waterman discussed the need for a dengue virus (DENV) vaccine in terms of the clinical disease burden and lack of primary prevention tools, vaccines constructs and candidates, epidemiologic challenges to vaccine evaluation, and results of the lead-candidate vaccine trial from Sanofi Pasteur. As a reminder, dengue viruses belong to Flavivirus genus of the *Flaviviridae* family. There are four antigenically distinct serotypes: DENV-1, DENV-2, DENV-2, DENV-4. These are enveloped single-stranded viruses with 3 structural proteins, the envelope, capsid, and membrane proteins. This phylogeny dendrogram based on the complete amino acid sequence of the polyproteins of important flaviviruses pathogens show that dengue, Zika, and YF viruses all share primate hosts and *Aedes* mosquito vectors. Dengue is relatively closely related to Zika virus:

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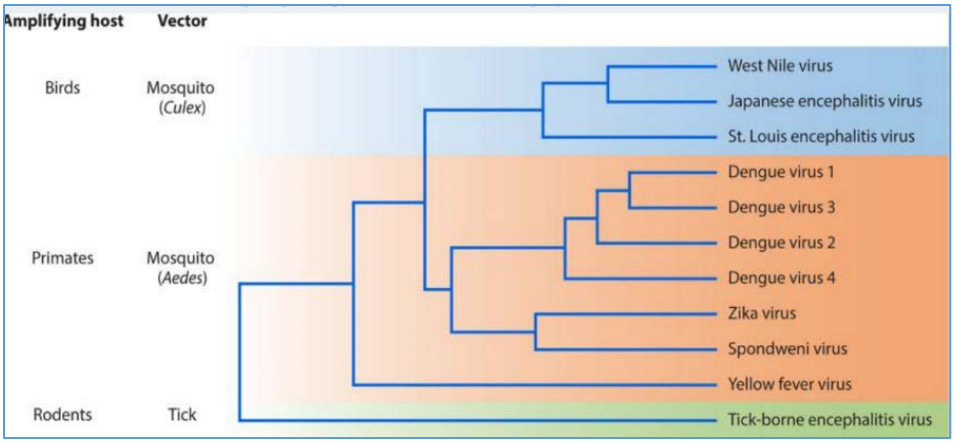

Lazear and Diamond 2016, Journal of Virology

DENV is primarily transmitted through a man-mosquito-man transmission cycle, with incubation periods in humans and mosquitos of roughly a week in each species. Dengue is arguably the most important arbovirus in terms of morbidity and mortality. It is an emerging disease, which is both epidemic and endemic in tropical and sub-tropical regions with an expanding distribution. The estimated global burden based on literature review and modeling is that there are an estimated 390 million infections annually with 96 million clinically apparent infections, 2 million severe dengue cases, and 20,000 deaths worldwide.

Severe illness has a distinct pathology involving shock, hemorrhage, and severe organ involvement. Shock involves systemic vascular permeability leading to vascular hypovolemia and Dengue Shock Syndrome (DSS). Hemorrhage involves bleeding manifestations, which are commonly due to the combined effects of thrombocytopenia and deranged hemostasis. Severe organ impairment such as encephalitis and hepatitis can occur. Risk factors for severe dengue have been studied extensively. One of the major risk factors is secondary infection with a second dengue serotype, although not all severe dengue is as a result of a secondary infection. Virus strain, host genetics, co-morbidities (especially in older adults), young age, and being female also have been identified as risk factors for severe disease.

The pathogenesis of severe disease seems to be related to viral burden, which often has been linked to heterologous non-neutralizing antibody enhancing infection. The immune response triggers inflammatory mediators, cytokines and chemokines which are thought to promote capillary permeability syndrome, although the exact mechanism is unclear. Coagulopathy is probably a result of the loss of essential coagulation proteins, but this is not completely understood in terms of the pathogenesis.

Regarding dengue vaccine status, one vaccine has been registered by Sanofi Pasteur in several countries including Mexico, Brazil, and the Philippines. There are multiple other vaccine candidates and many clinical trials underway. The vaccines would be indicated in pediatric and adult populations. The diagnostics necessary for clinical management and for assessing dengue vaccine trials are very good for acute disease, but antibody assays need to be improved. The recent co-circulation of Zika and DENV in many countries, which cannot be distinguished reliably by current available IgM tests, underscores this situation.

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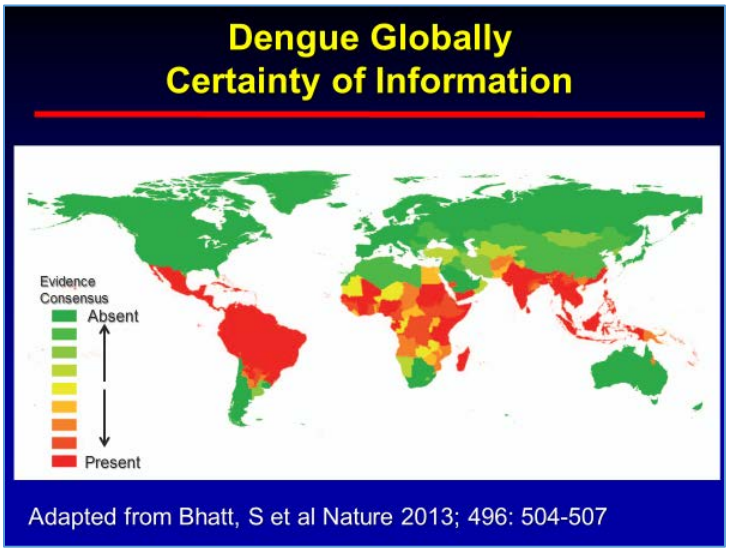
Large disease and economic burdens associated with hospitalizations and clinical care during outbreaks drive the rationale for a dengue vaccine. The primary prevention of vector control, has not been effective in the last 50 years as evidenced by the expanding number of cases and distribution of the disease. An effective primary prevention tool is needed for dengue. Secondary prevention currently involves medical management of severe dengue, which can be quite effective in reducing mortality with severe dengue to less than 1%, but again the healthcare burden could be ameliorated significantly by having a primary prevention tool such as a vaccine.

A publication by Bhatt et al in *Nature* recently reviewed the evidence and modeled the likely burden of disease. As shown on the following map, DENVs circulate throughout the tropics and subtropics in the major continents:



The largest burden of disease is in Asia, followed by the Americas in terms of documented disease, with Africa likely having a similar disease burden, but not very well-documented. Puerto Rico, the most affected US territory, experiences two or three large epidemics each decade with thousands of hospitalizations and dozens of deaths. Roughly 80% of the population of Puerto Rico is infected with dengue by the second decade of life.

This WHO Dengue Prevention Framework highlights the potential importance of vaccines for primary prevention, with key roles for surveillance and diagnostics in assessing vaccine efficacy [Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. New Edition. WHO, 2009; Global Strategy for Dengue Prevention and Control 2012-2020. WHO, 2012].

The conventional correlate of protection for dengue is neutralizing antibodies by the plaque reduction neutralization titer ($PRNT_{50-70}$) test and cell culture using cells that are not actually the primary targets of infection *in vivo*, which are Fc receptors (FcR)-bearing cells. Homotypic antibodies against the infecting serotype are protective for many years, if not for life. Heterotypic antibodies develop after infection to non-infecting serotypes and provide cross-protection against dengue infection for a limited time interval of 6 months (Sabin, 1952) or perhaps longer.

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As mentioned, secondary dengue infections have been shown to be a risk factor for severe dengue. *In vitro* studies demonstrate enhanced infection in cell culture in the presence of heterotypic (non-neutralizing) antibodies, a phenomenon known as antibody dependent enhancement (ADE). Animal and mouse models have demonstrated similar results. The most convincing evidence for heterotypic antibody playing a role in pathogenesis for dengue is in infants where primary dengue infection in the presence of passively acquired maternal antibody has been shown to lead to dengue hemorrhagic fever (DHF). Cohort studies of school children also have documented secondary infection being a risk factor. As a result of such studies, the ideal product profile has been viewed for some time as a tetravalent vaccine for all four serotypes. The ideal characteristic, as for other vaccines, would be logistically easy to deliver vaccines with high efficacy and without the need for booster doses.

A number of dengue vaccines are in development. The commercial vaccines furthest along are live-attenuated cell culture-adapted infectious cloned chimeric virus vaccines as well as a vaccine combining chimera with attenuated by site directed mutagenesis, recombinant subunits of DENV envelope proteins, and inactivated dengue viruses. Next generation in development include viral vectored subunits, virus-like particles (VLPs), peptide chimeras, and DNA. The specific dengue vaccine candidates are shown in the table below:

Dengue Vaccine Candidates

Producer (Developer)	Vaccine Type	Clinical Trial		
		Phase I	Phase II	Phase III
Sanofi Pasteur (Acambis)	Live attenuated - chimera 17D yellow fever + DENV	→	→	→
Takeda (CDC, Invirogen)	Live attenuated - chimera DENV-2 + DENV 1,3, 4	→	→	
Butantan (NIAID)	DENV attenuated - mutations + DENV/DENV chimera	→	→	
GSK (WRAIR)	Cell culture derived, inactivated	→		
MERCK (Hawaii Biotech)	Envelop subunits of DENVs	→		

Chimeric flavivirus vaccine technology involves using either YF 17D backbone or dengue genome cloned as complementary DNA (cDNA). The prM and E protein genes are then inserted into the structural backbone, chimeric cDNA is transcribed to RNA, transfected into cell culture and grown, which results in the chimeric vaccines with the envelope proteins having heterologous viruses as illustrated below:

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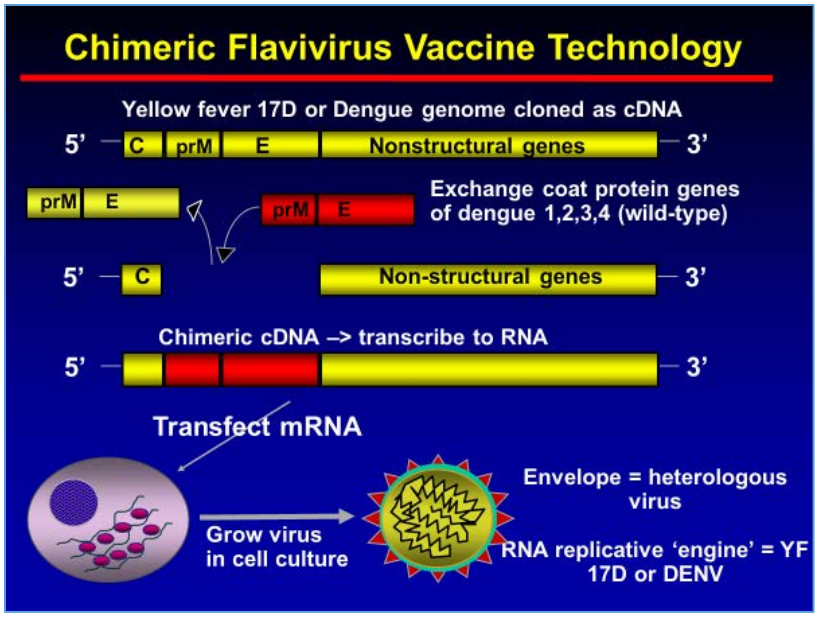

Good animal models are lacking for vaccine evaluation. A Macaque model does not produce disease and does not predict immunogenicity in humans. An AG 129 interferon deficient mouse model does produce DHF. A human challenge model is rarely used, although such human challenge is under consideration by NIH. Human clinical trials are the gold standard that are going to be required to determine the performance of dengue vaccine candidates.

Dengue epidemiology is a challenge to vaccine evaluation. Dengue is an acute febrile illness (AFI) syndrome, which can only be defined by diagnostic testing. Many look-alike AFIs in dengue endemic areas include: malaria, influenza, leptospirosis, meliodosis, hepatitis A, et cetera. Other challenges are the cyclical and seasonal transmission in endemic areas with multiple serotypes, varying age-specific incidence in various parts of the world, and a spectrum of illness with a large percentage of asymptomatic infections and a small proportion of severe disease. These epidemiologic characteristics dictate a large population base for phase III trials because of the focal nature of dengue. Febrile illness surveillance needs to be set up to identify dengue fever (DF) syndromes, gather data on age-specific disease incidence, determine variation in incidence over several seasons, and have molecular and immuno–diagnostic testing capability. Molecular testing is good for the first few days, and then after that serologic capability is needed [Guidelines for Clinical Evaluation of Dengue Vaccine in Dengue Endemic Areas. Vaccine 2008;26:4113-4119].

This graphic illustrates the period of viremia during which an rRT-PCR or NS1 antigen detection can be diagnosed in the first few days of illness and post-fever onset. After about 5 days, IgM is present for a couple of months:

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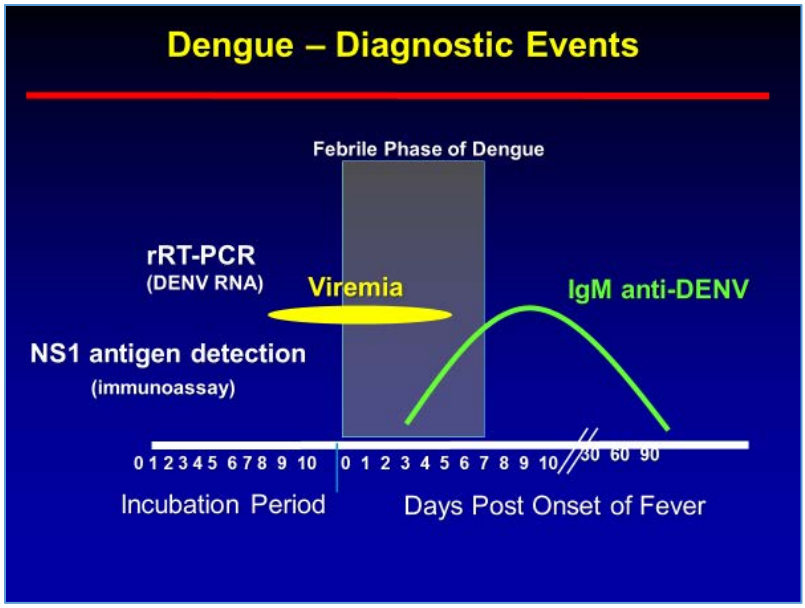

In terms of some of the preparatory studies that have been conducted, a prospective cohort study was conducted in Ratchaburi, Thailand during 2006-2009. This study illustrates some of the complexities. This study included approximately 3000 children 3 through 13 years of age. Active surveillance was conducted for absences and febrile episodes in schools and home visits. Fever was defined as 37.5°C oral irrespective of duration. In this study, 0.53 febrile episodes were found per child per year. In terms of clinic visits by day post-fever onset, the investigators were able to examine 53% of the children within 1 to 2 days after fever onset, 30% after 3 to 4 days, and 14% after 5 to 6 days. Clinic evaluation included an initial and follow-up blood draw, with diagnostic testing by PCR and IgM anti-DENV. In this study, dengue incidence varied considerably year-by-year, ranging from 1.7% to 5.7%. The serotype incidence also varied markedly by year, ranging from 43% overall for DENV-1 to 8% overall DENV-4 over this 3-year time period. The majority of the infections were mild illness or undifferentiated fever (UF). All of the DHF cases, 84% of classic DF cases, and 15% of the UF cases were hospitalized. Of the infections, 86% were secondary in these children in this highly endemic area [From Sabchareon, A et al. PLoS NTD 2012; 6: e1732].

The Sanofi Dengue Vaccine Efficacy Trials (CYD) were randomized, blinded, placebo-controlled trials among children 2 through 16 years of age. The children were given 3 doses of tetravalent, live, attenuated vaccine at 0, 6, and 12 months. The control groups were given a normal saline vaccine diluent placebo. The endpoint was symptomatic, confirmed DF requiring clinical acute febrile illness and PCR-detected viremia. The follow-up period was 25 months total, including 13 months after the last dose. Longer-term follow-up of 48 months is being conducted.

This table shows the characteristics of three published trials with large sample sizes in which pre-existing DENV antibody was present in approximately 70% to 80% of the children:

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Site(s)	Design	N	Ages (yrs)	Pre-Existing DENV Antibody (%)
Ratchaburi, Thailand	Phase 2B	4002	4-11	69.5
Asia – Indonesia, Malaysia, Philippines, Thailand, Vietnam	Phase 3	10,275	2-14	67.5
Latin America Colombia, Brazil, Mexico, Puerto Rico, Honduras	Phase 3	20,869	9-16	79.4

In terms of the results of these trials, overall VE was about 61%. However, VE varied considerably by serotype. The lowest efficacy with this vaccine was for DENV-2 at 42% with higher VE for DENV-1 at 50%, DENV-3 at 74% and DENV-4 at 78%. In terms of clinical outcomes of dengue, there were no differences between the vaccine and placebo groups in clinical features or severity of dengue, including: duration of clinical syndrome, fever, hospitalization, bleeding, plasma leakage, thrombocytopenia, shock, or organ impairment. Regarding other outcomes, no safety signals were observed in the short-term. Long-term, blinded follow-up is ongoing. Immunogenicity and protection in children without previous DENV infection is poor.

In conclusion, tetravalent, DENV – chimeric yellow fever-dengue vaccine (CYD) has been shown, and is reflected in some recent recommendations from WHO's Strategic Advisory Group of Experts on Immunization (SAGE), to be safe when administered to children living in a dengue endemic area and with a high background of previous DENV infection. A caveat is that in the Asian study, a higher rate of DHF was seen in the vaccine group in Year 3. Only partial protection has been shown against dengue, with lowest protection against DENV-2, followed by DENV-1, and highest protection against DENV-3 and 4 [From: Sabchareon, A et al. Lancet 2012; 380:1559-1567; Capeding MR, et al Lancet 2014; 834: 1358-1365; Villar L, et al. NEJM 2015: 372 113-123].

Sanofi Pasteur will be invited to present to the Flavivirus WG in the coming months, and would like to invite them to present during the next ACIP meeting to provide more details and answer questions.

Discussion Points

Dr. Belongia asked whether the type with which children were previously infected was known and if that was associated with the lower efficacy for DENV-1 and DENV-2.

Dr. Waterman indicated that there were pre-antibody samples in a limited number of children, and it is difficult to tell what the prior infecting serotypes were. There are additional studies, some of which are just coming out. A study was published recently in *JID* about the antibody response. This remains a complicated question with no definitive answers.

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Dr. Stephens asked whether there were estimates of efficacy for the individuals with poor immunogenicity who had a prior dengue infection.

Dr. Waterman replied that it was approximately 40%, and that more detailed data will be presented from the studies.

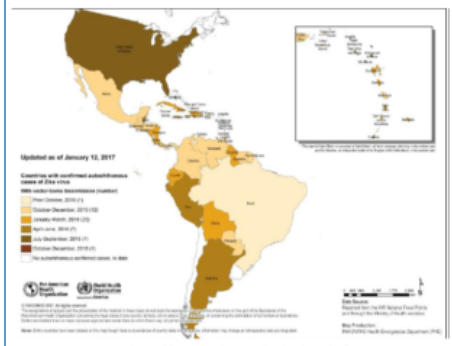
Zika Virus Update

Marc Fischer, MD, MPH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Fischer reminded everyone that Zika virus was first isolated from a sentinel rhesus macaque monkey in Uganda in 1947. Prior to 2007, only sporadic human disease cases were reported from Africa and Southeast Asia. In 2007, the first Zika outbreak was reported on Yap Island, Federated States of Micronesia. In 2013–2015, more than 30,000 suspected cases were reported from outbreaks in French Polynesia and other Pacific islands. Prior to 2014, less than 10 countries reported any type of mosquito-borne Zika virus activity. In 2015, with the spread to the Americas, there was a substantial increase over 2015 and 2016. The greatest increase was in the Pan American Health Organization (PAHO) regions of the Americas, but there were increases in other countries as well. As of mid-January 2017, 76 countries or territories around the world had reported Zika virus transmission at some point. In May 2015, the first locally acquired cases in the Americas were reported in Brazil. There likely had been transmission for a number of months prior to that. As of January 2017, local transmission has been reported in 50 countries or territories in the Americas. The only countries in the Americas without reported local transmission are Bermuda, Canada, Chile, and Uruguay.

The map below on the left shows the time of first reported cases, with lighter countries being earlier. The move into darker colors shows the spread and increase in transmission. The table on the right below reflects the number of locally transmitted Zika virus disease cases reported to PAHO by countries and territories in the Americas:

Locally transmitted Zika virus disease cases reported by country/territory in the Americas, 2015–2017 (as of Jan 12, 2017)



Country (N=50)	(N=738,783)*	
Brazil	342,459	(46%)
Colombia	106,697	(14%)
Venezuela	61,825	(8%)
Puerto Rico	37,488	(5%)
Martinique	36,692	(5%)
Honduras	32,234	(4%)
Guadeloupe	31,224	(4%)

***27% of cases are lab-confirmed**

http://www.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&lang=en

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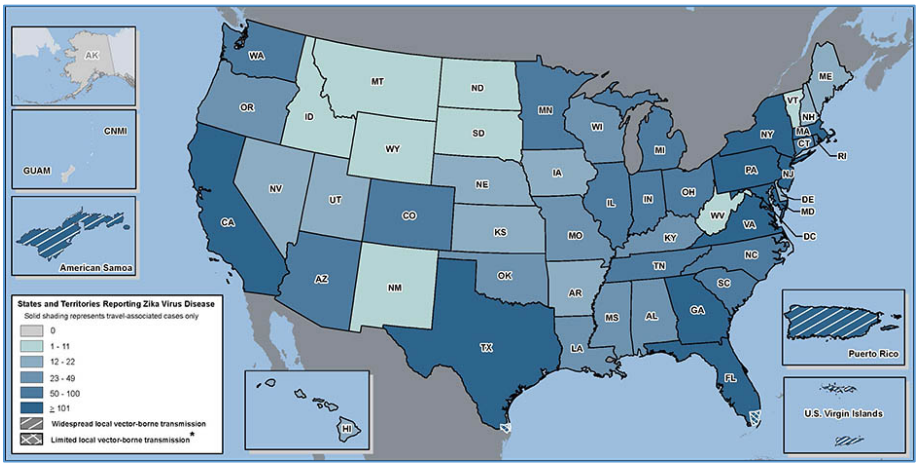
As of mid-January 2017, almost 740,000 total suspect or confirmed cases had been reported. Brazil and Colombia accounted for approximately 60% of the total reported. About a quarter of the cases were laboratory-confirmed, while the remaining three-quarters of the cases were clinical cases that met the suspected case definition and could have included some other diseases or viruses, such as dengue. Most suspected and confirmed locally transmitted cases reported to PAHO, as of January 2017, were reported from South America (70%), followed by the Caribbean (20%), Central America (8%), and North America (2%).

From 2007–2014, only 14 Zika virus disease cases were identified in US travelers who traveled to the Pacific Islands or Asia. With recent outbreaks in the Americas, recent cases among US travelers increased substantially. Limited local mosquito-borne transmission has been identified in two states: Southern Florida and Southern Texas. There have been widespread outbreaks in three US territories: Puerto Rico, US Virgin Islands, and American Samoa.

A total of 4710 travel-associated cases were reported to ArboNET from US states from January 1, 2015 through January 25, 2017. It is important to note that travel-associated cases include cases in travelers and their contacts with presumed sexual or in-utero transmission, and one case with unknown route of person-to-person transmission. One laboratory-acquired case was reported in a researcher. A total of 35,644 locally acquired cases were reported in the territories. In the states, 219 locally-acquired cases were reported.

The following map shows these cases broken down by state, with darker shading having more cases. The cross-hatching shows Puerto Rico, American Samoa, the US Virgin Islands, and small regions in Southern Florida and Texas having local transmission. These numbers are updated weekly on the CDC webpage. In terms of the state of residence for these laboratory-confirmed Zika virus disease cases, the highest reporting travel-associated cases were in New York (1001; 21%) and Florida (840; 18%), followed by California (411; 9%) and Texas (294, 6%). The majority of locally-acquired cases were reported from Florida (213; 91%), followed by Texas (6; 3%):



Beginning in July 2016, sporadic locally-acquired cases were identified in multiple counties in South Florida. Active ongoing transmission was identified in three small areas of Miami-Dade County. That prompted recommendations for pregnant women to avoid travel to those areas, and for pregnant residents to be tested and followed for their pregnancy outcomes. There was an intensive public health response, including unprecedented aerial adulticide and larvicide

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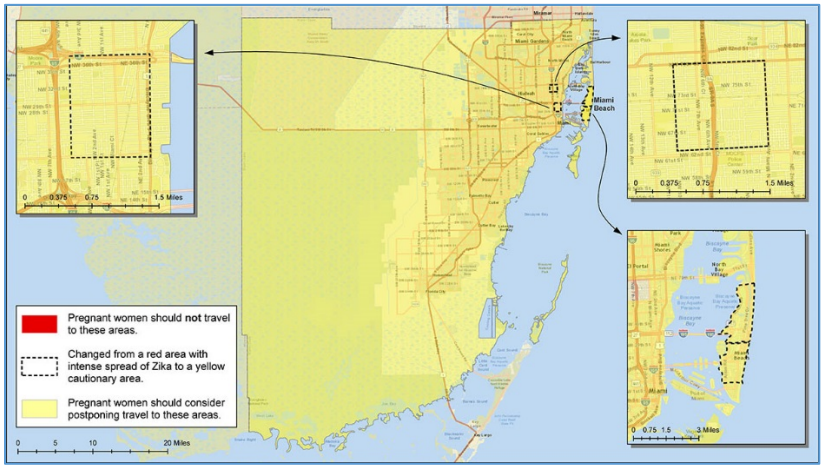
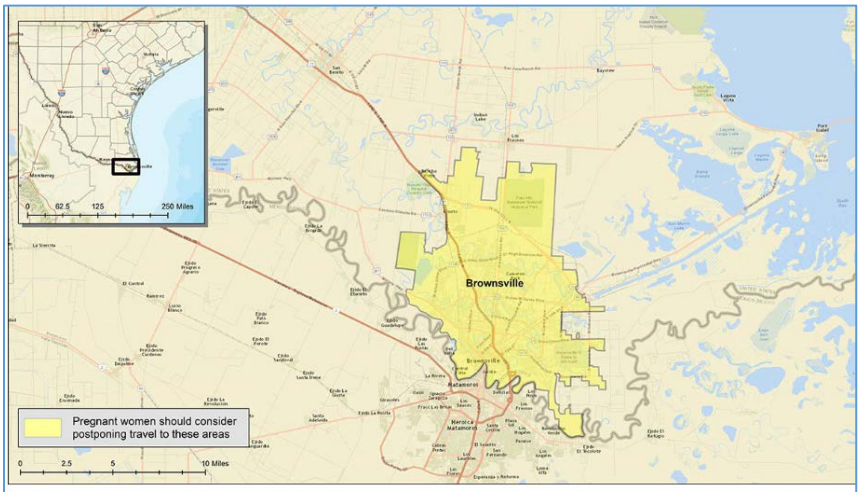
applications, which appeared to help control the outbreaks. At this time, there is no evidence of ongoing, sustained local transmission [Florida Health Newsroom].

This map shows where that transmission occurred. The main map is Miami-Dade County and then there are three insets that show how small the areas are where active, local transmission occurred. These areas are generally about 1- to 2-miles square, with the area in Miami Beach in the lower right being slightly larger:



In November 2016, the first case of local mosquito-borne Zika virus infection was reported in Brownsville, Texas. This area borders Mexico and there are frequent border crossings in both directions, including people who go across the border daily. Active Zika virus transmission was reported in Mexico near the US-Mexico border. That continues to this day. In December, CDC designated Brownsville a Zika cautionary area, shown in yellow on the map. This means that there are recommendations for pregnant women to avoid travel to those areas and pregnant residents to be tested and followed. As of January 25, six cases of local mosquito-borne transmission had been identified and reported from the Brownsville area. This map tries to put into context the size of the area. The inset shows the county and area at the very tip of the bottom of Texas bordering the Gulf of Mexico and Mexico:



Brownsville, TX. Yellow shows areas where pregnant women should consider postponing travel.

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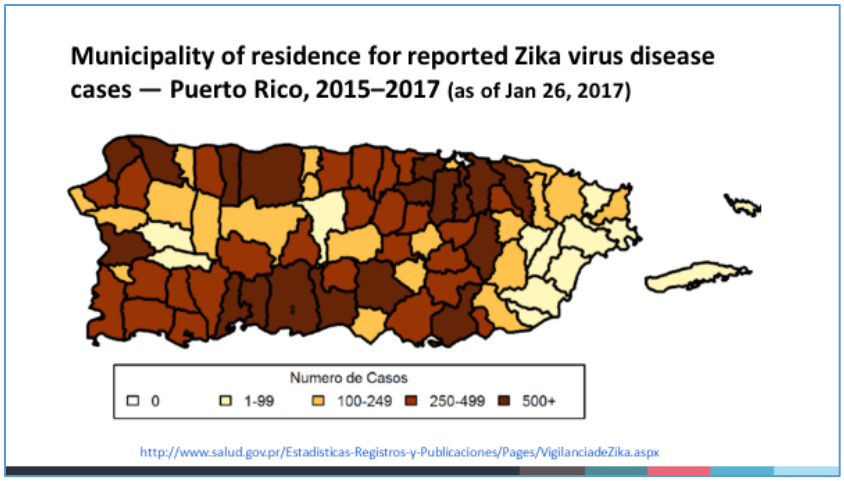
The vast majority of reported Zika virus disease cases in the US territories for the time period 2015 through January 2017 were locally-acquired (N=33,712), with 97% (N=32,848) being reported from Puerto Rico, 2% (N=807) from the US Virgin Islands, and 1% (N=5) from American Samoa. This is a map of Puerto Rico showing cases by municipalities, with the darker shades being larger numbers of cases. The primary point is that all municipalities in Puerto Rico have reported local Zika virus transmission, so the outbreak on the island was widespread. The darker shadings are around the major metropolitan areas where the most cases were seen in the Northeast in the San Juan metropolitan area and Southwest in the Ponce metropolitan area:



This figure shows the age group distribution for reported Zika virus disease cases in the US states and territories as of January 25, 2017. The age distribution was similar for laboratory-confirmed reported cases of Zika virus disease cases in the states, with a slightly higher proportion of cases among children and young adults in the territories. The higher numbers of cases in the 20-39 year age group and the 40-59 year age group may reflect, in part, the additional testing occurring in pregnant women as well as exposure among travelers in these age groups.

This is the epi curve showing month of illness onset for Zika virus disease cases reported in US states and territories, with the peak of the outbreak occurring in late summer, with a steep decline occurring in the fall and winter.

Returning to Zika virus transmission and clinical manifestations, Zika virus is an RNA flavivirus related to dengue, YF, JE, and West Nile viruses. Transmission to humans is primarily by *Aedes (Stegomyia)* species mosquitoes. In the Americas, that includes *Aedes aegypti* and *Aedes albopictus*. Infection is typically asymptomatic or causes mild dengue-like illness. However, recent outbreaks in the Americas and Pacific Islands have identified new modes of transmission and clinical manifestations.

In terms of clinical course, most infections are asymptomatic. The clinical illness is usually mild and is characterized by fever, rash, arthralgia, or conjunctivitis. These symptoms usually last for several days to a week. Severe disease requiring hospitalization is uncommon and fatalities have been rare.

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Clinical manifestations newly identified in the last couple of years include fetal loss, microcephaly and other congenital anomalies, Guillain-Barré Syndrome (GBS) and other neurologic syndromes, and thrombocytopenia.

Non-mosquito-borne modes of transmission that have been documented include intrauterine transmission resulting in congenital infection, intrapartum from a viremic mother to a newborn, sexual transmission, laboratory exposure, and blood transfusion. Possible modes of transmission include organ or tissue transplantation, breast milk, and other body fluids.

Regarding the risk of adverse outcomes of pregnancy, the incidence and clinical spectrum of congenital Zika virus infection remains unknown. The risk of fetal loss and congenital anomalies appear to be greater with infections early in pregnancy. The risk of congenital microcephaly following Zika virus infection during the first trimester of pregnancy is estimated to be 1% to 13%. It is probably on the lower end of that for microcephaly, but possibly in that range for all other anomalies as reported.

This table shows microcephaly or other CNS malformations possibly associated with Zika virus infection reported to WHO by country or territory as of January 20, 2017. This includes cases that may not have laboratory confirmation, and can include cases that were acquired in residents in one country who then traveled to another country to deliver:

Country/Territory (N=29)	(N=2,635)		
Brazil	2,366		(90%)
Colombia	78		(3%)
United States	41		(2%)
Dominican Republic	22		(1%)
Martinique	18		(1%)
French Guiana	16		(1%)
Guatemala	15		(1%)
22 other countries/territories	79		(3%)
*Includes cases acquired in other countries			

As mentioned, the clinical findings in infants with congenital Zika virus infection clearly extend beyond microcephaly, although that is one of the most severe manifestations and the first to be recognized. It now includes other brain anomalies including subcortical calcifications that appear to be a particular distribution, ventriculomegaly, abnormal gyral patterns, corpus callosum agenesis, and cerebellar hypoplasia. There also have been a number of ocular anomalies including microphthalmia, cataracts, chorioretinal atrophy, and optic nerve hypoplasia. Other neurologic sequelae related primarily to the brain anomalies include hypertonia or hypotonia, irritability, tremors, swallowing dysfunction, hearing loss, and visual impairment. Congenital contractures due to lack of movement of the fetus can include clubfoot and arthrogryposis.

Two cases of Zika virus perinatal transmission have been reported in the literature from French Polynesia from the 2015 outbreak. Both women developed mild rash illness within 3 days of delivery. One infant developed a transient rash and mild thrombocytopenia at 3 days of life. The second infant remained asymptomatic. Both mothers and infants had evidence of Zika virus RNA in serum. The newborns otherwise had unremarkable clinical courses.

Sexual transmission was first identified in sexual partners with discordant travel histories. The first report in 2011 was in a returning traveler from Colorado who went to Senegal. Little attention was given to this until 2016 when sexually transmitted cases were reported from 12 countries, including 38 cases in the US all among travelers with discordant travel histories.

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Most reported cases have been from men with symptomatic illness transmitting to their female or male partner. One report of transmission was from a woman to a man, and two reports of transmission were from asymptomatic men to their partners.

Zika viral RNA has been detected in semen up to 6 months after illness onset and in vaginal fluid up to 2 weeks after illness onset. Zika virus has been cultured from semen up to 70 days after illness onset. However, most of the sexual transmission that has been reported has occurred within the first month to 40 days after illness onset in the transmitting partner. The data thus far are primarily from case reports, which may not reflect true incidence or risk of transmission. The full length of duration of RNA or live virus in semen or vaginal fluids and the level of risk remains unknown. There are ongoing studies to better determine that.

The incidence, duration, and risk factors for sexual transmission are unknown. One modeling study from Brazil suggested that the apparent increased incidence of disease in women compared to men could possibly be due to sexual transmission. Obviously, there are many other factors like increased awareness and testing because of the concerns about congenital infection. Another model determined that sexual transmission is likely not a significant factor in driving an outbreak, that it really is mosquito-borne transmission that drives the outbreak, although sexual transmission certainly contributes to cases. Two prospective cohort studies in the US are ongoing to better evaluate the frequency and duration of Zika virus RNA and live virus in semen. One of these is being performed in Puerto Rico, and preliminary data have been published on that. The second is among men in the Continental US (CONUS).

Pertaining to transfusion-transmitted Zika virus infections, Zika virus RNA was identified in 42 (3%) of 1505 blood donors in French Polynesia in 2013–2014. None of those products were transfused, so there were no transfusion-related events. In 2016, at least 3 cases of transfusion-transmitted Zika virus infections were reported from Brazil. In February 2016, the FDA issued recommendations to reduce the risk of transfusion-transmitted Zika virus in the US. From April through December 2016, routine screening identified Zika virus RNA in 360 (0.6%) of 54,588 blood donations screened in Puerto Rico. In August 2016, the FDA recommended routine Zika virus screening of all blood donations in the US, which is currently ongoing under an IND process.

From 1964 through 1980, there were 4 to 6 reports of probable Zika virus infections due to laboratory exposure. Based on the range and probability from some of the publications, it is unclear if they overlap with other publications because there are not enough details. In addition, there was at least one case in which a person worked in the laboratory and was conducting field work in the Zika forest. It was unclear whether that person was actually infected and whether it was due to mosquitos or work in the laboratory. In 2016, there was one report of confirmed Zika virus infection following a needle stick injury in a US researcher. That person developed a mild symptomatic illness without further complications.

Zika virus transmission through breast milk has not been documented thus far. However, Zika virus RNA was detected in breast milk collected several days after onset of illness in the two women who had perinatal transmission documented in French Polynesia. In those cases, culture of the breast milk was negative for live virus. However, since that time both RT-PCR for RNA and culture have identified Zika virus in breast milk in one case that was collected 4 days after onset of illness in a woman in New Caledonia. There has since been a subsequent report of positive breast milk for both RNA and culture. The infant in the New Caledonia case remained asymptomatic and had no laboratory evidence of infection, and there has otherwise not been evidence of transmission thus far. Therefore, to date WHO and CDC believe that the

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benefits of breastfeeding outweigh the theoretical risk of transmission to an infant through breast feeding.

As far as other body fluids, Zika virus RNA has been detected in saliva and tears. One case of possible person-to-person transmission was reported from Utah. The index patient developed fatal septic shock and had a level of viremia approximately 100,000 times higher than average. It is unclear why the patient had that high a level of viremia. Zika virus infection was diagnosed in a family member who had close contact (i.e., kissing and touching) with the index case outside and inside the hospital in the days leading up to his death. An extensive investigation was performed by the Utah Department of Health with CDC. No specific source or mode of transmission was identified. In addition, there was an extensive investigation of other family members who had contact with the patients, hospital and morgue workers, and the community. Among those hundreds of people, no additional infections were identified among people who had contact with the patient.

GBS following Zika virus infection was first described in French Polynesia during the 2013–2014 outbreak. An additional 19 countries have now reported at least one GBS case with laboratory evidence of Zika virus infection. There have been 13 GBS cases reported from US states and 50 from Puerto Rico. Overall, there are an estimated 1.6 cases of GBS per 10,000 Zika virus infections. Outcomes and increased risk in older adults appear to be similar to GBS due to other causes.

In terms of neurologic disease with non-congenital Zika virus infections, there have been rare published reports of encephalopathy, meningoencephalitis, myelitis, and uveitis. In addition, there have been reports of peripheral paresthesias, with or without GBS. The frequency is still to be defined.

An estimated 1% of symptomatic Zika virus disease cases may have mild thrombocytopenia defined as a platelet count <100,000. That is based on work done in Puerto Rico. But, there have been rare reports of severe thrombocytopenia with hemorrhage or septic shock, including at least two fatal cases. One of these was the case described in Utah and one in Puerto Rico, and similar cases have been reported from other countries.

With respect to Zika virus treatment and prevention, the primary prevention mode is to reduce mosquito exposure through vector control and personal protective measures (e.g., insect repellent, door screens, window screens, and air conditioning). As recommended by CDC and many other countries, pregnant women are advised not to travel to areas with local transmission and to take steps to protect themselves against possible sexual transmission. Currently, there is no vaccine or medication to prevent or treat infection or disease. Numerous candidate vaccines are being evaluated. There is a coordinated US government effort to facilitate development that includes Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), NIH, CDC, and Department of Defense (DoD). As far as how these vaccines will be used, the targeted use likely will depend on the ongoing incidence and locations of disease, further information on the complications related to the disease, and the vaccine characteristics (e.g., safety, efficacy, and duration of protection).

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Zika Vaccines in Development

Gerald R. Kovacs, PhD
Biomedical Advanced Research and Development Authority
Office of the Assistant Secretary for Preparedness and Response
US Department of Health and Human Services

Dr. Kovacs presented a brief update on what BARDA has done so far on the development of Zika vaccines. This is one of the most challenging, dangerous, and potentially insidious viruses the government is working on currently. While currently there is no licensed Zika vaccine available, vaccines for other flaviviruses have been developed and used for over 70 years. Active development programs for dengue and West Nile vaccines have been ongoing for over 30 years; however, knowledge of Zika virus was limited at the outset of the epidemic. Past experience is being leveraged for Zika vaccine development. Zika research and development (R&D) efforts have been accelerated greatly by NIAID, Walter Reed Army Institute of Research (WRAIR), and BARDA. A coordinated, interagency portfolio management team was established to oversee and accelerate vaccine development. A multidisciplinary approach is taken to accelerate the types of countermeasures needed at any given time.

Regarding the product development pipeline and how the government works together, each agency has particular roles and responsibilities. In the case of Zika, NIH and DoD took on a very important role early in developing and testing candidates. ASPR/BARDA takes the handoff from NIH in this respect and is involved in advanced product development, which in essence means taking products through clinical development to manufacturing and scale-up. This is done primarily by partnering primarily with manufacturers. Suffice it to say that some manufacturers come to ASPR/BARDA for funding and some do not. A number of companies are currently developing Zika vaccines, diagnostics, other countermeasures, and therapeutics that do not have government funding. Importantly, the FDA works with all companies. In the traditional sense, the FDA usually works with companies after a certain amount of information is gathered pre-clinically, clinically, and toxicologically. In the case in which countermeasures are being developed in response to an epidemic such as Zika, the FDA takes on a different role and works with ASPR/BARDA daily to help develop vaccines in such a way that as much important information as possible can be gained in the shortest amount of time.

As of February 2016, there were only two US government-funded Zika vaccine projects ongoing, one with the NIH and the Institute Butantan and the other at the DNA-Vaccine Research Center (DNA-VRC) with a DNA plasmid approach. Little was being done in terms of preclinical development. These products were in the early phases of discovery, and there was nothing in Phase 1 yet. An interagency consortium of experts on vaccine development was formed and developed three aims towards the goal of developing a safe and efficacious Zika vaccine to prevent congenital Zika syndrome: 1) 2016-2018, evaluate available vaccine candidates to assess safety, efficacy, and immunogenicity and identify protective immune correlates during the time of highest disease incidence; 2) By 2018, deploy an available vaccine under an appropriate regulatory mechanism to US populations at high risk of exposure; and 3) By 2020, work with industry partners to commercialize vaccine(s) for broad distribution.

Aim #1 involves evaluating as many vaccine candidates as possible, assessing a myriad of platforms, developing animal models, developing reagents, and developing enough data to perhaps apply a correlate of protection that would be useful for clinical developers. Aim #1 is currently being fulfilled with a vast number of candidates. Aim #2 is relatively aggressive. This involves vaccines at the pre-licensure stage that would be made available under an EUA or

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Expanded Access IND. These vaccines would be used in CONUS, or Puerto Rico and other territories when there are outbreaks. The government is engaged in partnerships with a number of large and medium pharmaceutical companies, with the hope that by 2020 one or more of those manufacturers will have submitted a BLA to the FDA.

Before launching into supporting any type of vaccine candidate platform, all platforms available at the time were assessed. Some of these platforms, such as whole virus inactivated and live attenuated vaccine platform had been used in the past and placed in the market such as Japanese encephalitis, tickborne encephalitis (TBE), and yellow fever vaccines. The only issue with those platforms is that they take a significant amount of time to develop using Good Manufacturing Practices (GMP). Also available were a couple of nucleic acid platforms, DNA and mRNA. These platforms are more easily manufactured using GMP and can be quickly placed in the clinic setting as long as the correct antigen needed to vaccinate with is known. This was done with DNA and mRNA backbones. In earlier stages of development were viral-vectored and recombinant/subunit candidates. The pros and cons for each candidate are compared in the table below:

General Considerations on Vaccine Technologies

Technology	Pros	Cons	Licensed Human Flavivirus Vaccines
Nucleic Acid (DNA, mRNA)	Simple process development/mfg. Potential for rapid response capability.	No DNA or mRNA vaccines licensed for human use. Limited experience at commercial scale.	No
Whole Virus Inactivated	Commercial platforms exist. Inactivated vaccines approved for other indications.	May need several doses and adjuvant. Need large production requirement.	Japanese Encephalitis, Tick Borne Encephalitis
Live Attenuated (including flavi-chimeras)	Commercial platforms exist.	Generally contraindicated in pregnant women and very young children.	Yellow fever, Dengue, Japanese Encephalitis
Viral Vectors	Viral-vectored vaccines in advanced trials for other diseases. Commercial platforms exist.	Safety concerns in pregnant women, depending on replication competency.	No
Recombinant/ Subunit	Low risk. Several commercial platforms exist.	Some difficulty depending on the platform, *e.g.* protein folding. Use of adjuvants may increase concerns.	No

Relative to the three aims, a number of candidates are in development. The NIH Vaccine Research Center (VRC) is developing a candidate DNA vaccine. In addition, an mRNA candidate vaccine was developed by Moderna, a commercial company based in Bostin, in coordination with NIH and BARDA. These vaccines are currently in phase 1 clinical trials. Inovio, another commercial company, is developing another DNA vaccine without US government support and started their Phase 1 trial about a month before the VRC. The hope is that some of these vaccines make it to Aim #2, the deployment stage for one or more of these candidates. Based on safety and efficacy data that will accrue over the next year or two, potentially the DNA and/or mRNA platforms may fulfill that goal.

The candidates envisioned to fulfill Aim #3 include products such as the two inactivated candidates being developed by Sanofi Pasteur and Takeda, and potentially the mRNA candidate being developed by BARDA and Moderna. That would be the first marketed mRNA vaccine. A fourth vaccine, which is being developed by the Laboratory of Infectious Diseases, is a live attenuated Zika-chimera. In addition to all of these, a number of earlier products are in

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R&D including a VSV vectored vaccine (NIAID, Harvard), chimera and VLP (CDC), mRNA (VRC, GSK), and PIV (BARDA, Butantan).

The VRC has conducted a Phase 1 trial on the initial construct and is currently conducting another Phase 1 trial on a modified construct. These constructs primarily encode the prM and E genes in Zika virus and use the PharmaJet® injector. The initial results from the first trial are being analyzed currently. The second trial is ongoing and should be completed in a couple of months in anticipation of conducting the Phase 2/2b clinical trial. This trial will be conducted in the US in areas where Zika is observed, as well as in Central and South America. In this trial, 2 doses of DNA plasmid vaccine will be administered using the needless PharmaJet® injector in either 4 mg or 8 mg 3 times in the phase 2a study. Those data will be analyzed and the best regimen and dose will be taken into a phase 2b trial, which is basically a 1:1 randomization of placebo to test vaccine in approximately 2400 people in 30+ sites in the US, Caribbean, Central and South America. These data may provide sufficient efficacy information to allow its access to be expanded in an IND and/or through an EUA. That would fulfil Aim #2 of the strategy.

The second nucleic acid candidate is being developed by BARDA in partnership with Moderna Therapeutics. This is a novel technology whereby synthetic mRNAs are used to deliver virtually any gene. It is very useful for the US government to have a platform such as this, because it is basically a “plug and play” technology. There is relatively little difference between different vaccines that are made using this platform. The key to developing this platform for vaccine purposes was an ingenious discovery made that nucleotides that are incorporated into the mRNA synthetically not only have to be native, but also they have to include pseudouridine. Doing so evades a lot of the innate immune responses intracellularly like toll-like receptor responses. Once inside the cell, it acts like a native mRNA to express a foreign gene. This has produced a robust, protective immunological responses in animal models. Delivery is relatively simple with a needle and syringe. This technology is currently in a clinical Phase 1 trial in the US.

There are a number of purified whole virus inactivated vaccine candidates in development by two major pharmaceutical companies that have in the past or are currently developing flavivirus vaccines, Sanofi Pasteur and Takeda. They are using a formalin-inactivated Zika virus that is alum-adjuvanted. The proof-of-concept for this technology was done by WRAIR and NIAID last year. The vaccine is currently in Phase 1 clinical trials across the US. It has been published this vaccine is fully protective in non-human primates (NHP) and rodent models. NIAID and WRAIR are conducting Phase 1 clinical trials to evaluate safety, immunogenicity, regimen, dose-sparing, and prior flavivirus immunity in subjects who have received yellow fever vaccine. WRAIR is transferring the technology to one of its major pharmaceutical partners, Sanofi Pasteur, for accelerating development. Takeda is developing their technology on a different platform on their own.

Another candidate is the live attenuated dengue/recombinant Zika vaccine, which is being developed by NIAID’s Laboratory of Infectious Diseases (LID). The dengue quadrivalent vaccine described by Dr. Waterman earlier is basically a recombinant dengue 2 with the Zika prM and E genes inserted in place of the dengue 2 prM and E genes. This vaccine is being developed in combination with Butantan. The dengue component is currently in Phase 3 trials. The Zika component is currently in development, with a plan to begin Phase 1 with a monovalent Zika component probably in the end of 2017. This could be envisioned as not only a monovalent, but also a pentavalent Zika/dengue vaccine.

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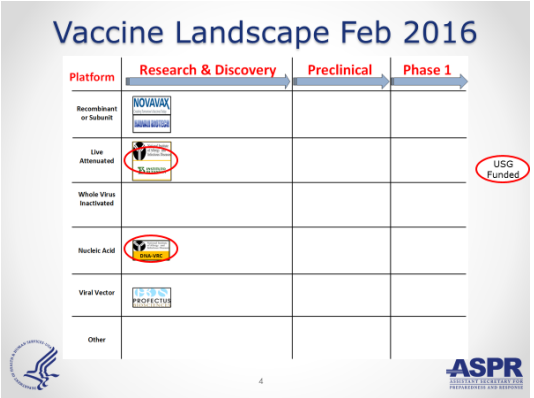
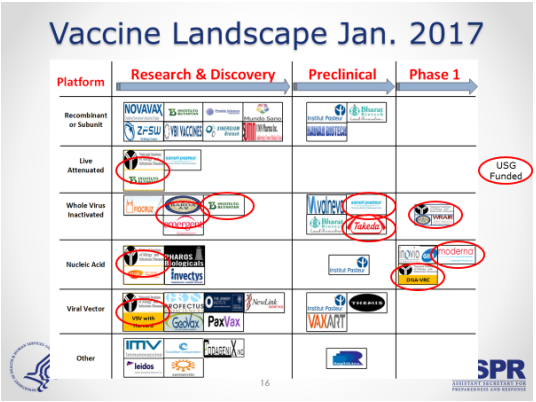
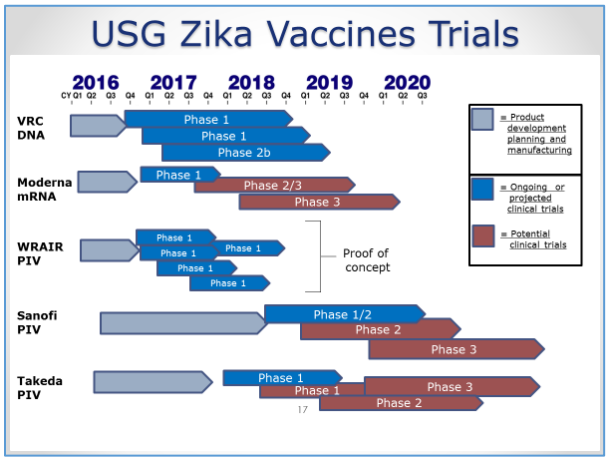
These tables compare the vaccine landscape in February 2016 to January 2017:





There has been a significant amount of activity, with an influx of funding from the US government that helped to build this pipeline. Currently, there are 7 ongoing Phase 1 clinical trials with 4 different candidates. Of those, 3 are being fully supported by the US government. A number of candidates are in R&D and pre-clinical phases. The landscape looks much better than this year than it did last year at this time.

The following graphic was provided to show ACIP where hypothetically clinical trials might be in the future:



In dark blue are the ongoing, ready to begin Phase 1 trials with Zika vaccines. In red are the putative clinical trials that would be conducted based on the clinical development plans of the different manufacturers and the US government for the individual vaccine candidates. By 2019-2020, at least one of those candidates will have completed Phase 3 studies.

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In conclusion, a number of key regulatory/clinical and manufacturing challenges and questions remain:

Regulatory/Clinical

- ❑ Will future disease incidence support evaluation of vaccine efficacy? In order to develop a vaccine based on prevention of clinical symptomatic disease, studies must be conducted in areas where there is a significant attack rate. Based on modeling exercises, this will become more difficult as time passes. Efforts are being made to develop animal models that will allow for the development of correlates of protection that potentially could be used as surrogates for different regulatory mechanisms.

- ❑ Which regulatory path will be most feasible? The regulatory paths include the traditional path currently being taken assessing clinical endpoints in field trials. There also is an accelerated approval pathway that potentially could be used if a surrogate becomes available. The last one used in the past for biodefense purposes was the Animal Rule, which is presently being put on the "back burner."

- ❑ Will human challenge and/or accelerated approval (correlate of protection) facilitate/accelerate evaluation? This was discussed in an NIH consultation a couple of months ago. The findings of that committee are now published and show that there is not sufficient information on Zika relative to its pathology and how it is transmitted from humans to humans to support a human clinical study at this time. As more information is accrued about the disease, the potential for this type of study will be revisited.

- ❑ Will an animal model(s) provide sufficient data to support efficacy determinations in humans?

- ❑ Will pre-immunity to other flaviviruses affect Zika vaccine take, and/or vice versa? This is a concern primarily based on antibody-dependent enhancement that has been observed with another flavivirus, dengue in particular. It is important to ensure that Zika vaccines "do no harm." It also is important to determine, by virtue of so much cross-immunity being observed with different flaviviruses, if there is any effect on the actual take of a Zika vaccine in individuals who are flavi-positive already.

Manufacturing

- ❑ Will manufacturers be able to develop a vaccine fast enough to impact the epidemic?
- ❑ Will previous flavivirus vaccine platforms work well enough to prevent congenital infections?
- ❑ Will the market sustain more than one vaccine?

While as many vaccines as possible can be developed, it will be necessary for manufactures to stay in for the long-haul. With cuts in funding and decreasing enthusiasm about Zika, it becomes challenging for the US government to continue to engage with manufacturers on these types of products. The hope is that all of the partners will continue their endeavors with the US government, but this cannot be guaranteed.

One thing that is incredibly challenging about developing Zika vaccines versus other vaccines is that it may be necessary to develop a vaccine that is extremely potent—one that not only prevents symptomatic disease in the primary infection, but also one that prevents the

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transmission of virus from mothers to children. Animal models are being developed in conjunction with the NIAID that will help to elucidate those pathways.

Discussion Points

Dr. Reingold inquired about safety, particularly with respect to GBS. He also wondered whether there are any trials for younger ages, noting that the trial mentioned was conducted in those 15 to 35 years of age, which seems like an unusual age in any country.

Dr. Kovacs replied that the trial in 15 to 35 year olds is being conducted to support use in men and women of childbearing age, though there are exceptions to that range. The incidence rate of GBS is very low and it will not be possible to see any events in these clinical trials. The greatest concern with GBS is with Zika vaccination with the live attenuated vaccines.

Dr. Messonnier clarified that in thinking through vaccine development, consideration also must be given to delivery methodology in terms of other routine vaccinations. The 15-25 year old group is not an age range for which there is a platform for vaccination.

Dr. Hunter asked for clarification regarding whether the mRNA is being placed inside the vaccinee and the vaccinees themselves are making the antigen, and how long the mRNA persists in the person's body.

Dr. Kovacs replied that the mRNA delivers only the gene and the body makes the vaccines. The active pharmaceutical ingredient is the mRNA nanoparticle. Studies conducted in small animals shows that the vaccine is disseminated throughout the body and expression can be seen for weeks. This technology is being developed not only for vaccine purposes, but also for the delivery of therapeutics such as monoclonal antibodies.

Dr. Romero requested further information about mRNA and 5-prime and 3-prime untranslated region (UTR).

Dr. Kovacs explained that there is a robust expression level *in vivo* that can be taken advantage of for both purposes. The mRNA is transcribed *in vitro* off of a plasmid vector using T7 RNA polymerase. It does not have any fancy 5-prime or 3-prime UTRs. It looks just like a native mRNA. The insert in this case is prM and E. The polyadenosine (poly-A) tail is encoded on the plasmid, so it is transcribed with a poly-A tail.

Dr. Bennett wondered whether it is possible that what is being observed with the recent decline in Zika actually is the end of the epidemic, or if it is more likely due to seasonality.

Dr. Fischer replied that it is likely a combination of both. It is early in the Americas to determine the seasonality. From other locations where Zika virus is seen, there is likely seasonality that is similar to dengue. This means that in some areas, there is seasonal progression that is related either to temperature, rainfall, and humidity. In other areas, there may be low levels of endemic transmission that continues. With chikungunya, another arbovirus introduced into the Americas in 2014, the first season was quite large, the second season was smaller, and there were decreases in subsequent years. That probably offers a better idea with what might be observed with Zika virus.

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Dr. Gorman (NIH) requested further information on present or future plans to assess infants through 2 years of age, a period of time during which the brain continues to grow fairly rapidly.

Dr. Fischer reported that there are follow-up studies of the infants who were congenitally infected. In addition, there are plans for either case-control or a cohort study to follow-up young children who are infected postnatally through mosquito-borne infection. Based on surveillance data, thus far there has been no evidence of severe disease in young children or evidence of post-effects. There are other congenital infections for which that pattern would seem to be similar, where there are severe effects when transmission occurs in utero but not when it is seen postnatally. Those questions remain to be answered.

Adult Immunization

Introduction

Laura Riley, MD
Work Group Chair

Dr. Riley provided an overview of the Adult Immunization WG activities over the last year. The 2017 Adult Immunization Schedule was published in the *Annals of Internal Medicine* on February 7th and in an *MMWR* announcement on February 9th. There was an error pertaining to meningococcal vaccination, so an erratum is due to be published in the *MMWR* on March 3rd. There has been wide promotion of the 2017 Adult Immunization Schedule by partner organizations, and the schedule has been evaluated for usefulness and usability.

Implementation of Standards for Adult Immunization Practice

David Kim, MD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Kim emphasized that low adult immunization coverage has been an ongoing challenge for CDC and its partners for a number of years. It is known that recommendations by HCPs is a key predictor for adult vaccination. Standards for adult immunization practice were published to improve awareness among HCPs and uptake of ACIP-recommended vaccines for adults.

Regarding the most recent adult vaccination coverage rates based on the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS), a brief update was published on the CDC website on the same day that the 2017 schedule went live on February 7, 2017. The full article containing the adult vaccination coverage rates for 2015 is pending publication in the *MMWR*. The key findings include:

- A 3% increase in pneumococcal vaccination for adults 19 through 64 years of age who are at high risk from 20% in 2014 to 23% in 2015
- A 3% increase in Tdap vaccination to 23% for those 19 years of age and older, and a 10% increase to 42% for adults living with infants less than 1 year of age who are too young to receive pertussis vaccination

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- A 2.7% increase in shingles vaccination to 30.6% for adults 60 years of age and older.
- Influenza vaccination of 41.7% for adults 18 years of age and older, similar to 2014 estimates
- Pneumococcal vaccination of 63.6% for adult 65 years of age and older, similar to 2014 estimates
- Hepatitis B vaccination of 24.4% for adults 19 through 59 years of age with diabetes, similar to 2014 estimates
- Persistent racial and ethnic disparities with lower coverage among Blacks and Hispanics, similar to 2014 estimates

Standards for Adult Immunization Practice were developed originally in 1990 by the National Coalition for Adult Immunization (NCAI) to improve vaccine delivery to adults, and were updated in 2014 by the National Vaccine Advisory Committee (NVAC). The standards state that all HCPs, including those who do not provide vaccine services, have a role in ensuring that their patients are current on vaccines.

The standards include a call to action for HCP for adults to:

- ASSESS the vaccination status of all patients at every clinical encounter
- Strongly RECOMMEND vaccines that patients need
- ADMINISTER needed vaccines or REFER patients to a vaccine service provider
- DOCUMENT vaccines received by patients in state vaccine registries

The Standards are promoted widely through the National Adult and Influenza Immunization Summit (NAIIS) among other venues. The summit is a large collaborative of public and private organizations dedicated to improving the use of ACIP-recommended vaccines by working to improve access to immunization, educate providers, identify gaps, develop performance measures, and engage in other activities.

To assess the status of the implementation of the Standards, CDC conducted two surveys. One was administered to the general adult population to evaluate the extent to which they received care that reflects the Standards during their most recent visit to their HCP or pharmacist in the previous 12 months. The other survey was administered to HCPs and pharmacists to evaluate the extent to which they implemented the Standards during patient visits. These Internet panel surveys were conducted on outpatient visits from February through March 2016. The surveys were probability-based and were weighted to be nationally representative using established references, such as the US Bureau of Labor Statistics (BLS). The general adult survey included a sample of adults 19 years of age or older and asked about their visits to their HCP or pharmacist. The HCP survey included a sample of physicians, nurse practitioners, physician assistants, pharmacists, internal medicine, family medicine, OB/GYN, and specialty care. Black and Hispanic HCPs and pharmacists were over-sampled to have sufficient data for analyses.

In terms of the results for the general adult population, of the 3473 panelists invited to participate, 2004 (57.7%) accessed the survey and 1905 (95.1%) completed the survey. Based on the data analyzed for the 1905 completed surveys, 1476 (77.5%) had outpatient visits with HCP providers or pharmacists in the past 12 months, 459 (68.3%) self-reported as non-Hispanic white, 50% were female, the median age was 55 years (range 19–92 years), 1399 (94.7%) were insured, and 1203 (59.7%) had at least a college education.

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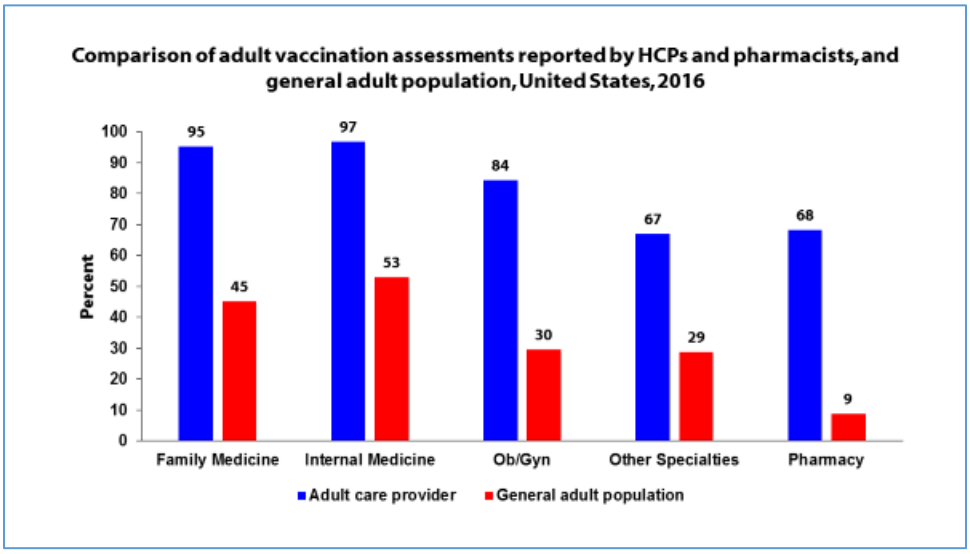
Email invitations were sent to 74,067 HCPs. Of these, 1907 started the survey, 1684 (88.3%) completed the survey, and data analysis was performed on 1641 eligible participants. Among the responding practices, there were 32.3% family medicine, 27.5% internal medicine, 21.3% OB/GYN, and 18.8% other specialties. Among these, 45.8% were private practices and 37.5% were healthcare system-owned practices. There were 65.9% non-Hispanic white participants. Email invitations were sent to 9310 pharmacists of whom 320 started the survey and 277 (86.6%) completed the survey. Data analysis was performed on 277 eligible participants. Of the respondents, 44.2% were chain drug store pharmacists, 31.9% were retail or grocery store pharmacists, 17.7% were independent, 87.2% were employees, 7.2% contractors, 5.6% were owners, and 70% were non-Hispanic white.

Of the 1476 adult respondents; 46% were assessed for vaccination; 23% received recommendations for vaccination; 19% received a recommendation for influenza; 9% received a recommendation for a non-influenza vaccination; and 18% received an offer for vaccination; 4% received referrals. Overall; 11% reporting having received an assessment, recommendation, offer, and referral primarily related to influenza vaccination; and 8% received vaccination. By provider specialty, adult patients reported having received the highest percentage for vaccination assessment, recommendation, and offers during their internal medicine and family medicine visits, followed by visits to OB/GYN and other specialty practices. Reported vaccination assessments by pharmacists lagged compared to clinical providers.

In terms of the responses by HCPs and pharmacists, each specialty reported a much higher percentage of vaccination assessment, recommendation, and administration compared to what the adult patients reported. Within each specialty, reported use of an IIS was low at 47% for family medicine and internal medicine, 39% for OB/GYN, 22% for other specialties, and 42% for pharmacies. High levels of assessment, recommendation, and administration or referral were reported by physicians, nurse practitioners, physician assistants, and pharmacists. Again, the reported use of IIS was low. Although the two surveys were administered in different populations, the results of what the adult patients and HCPs/pharmacists reported were compared. The following table shows the results of a comparison of the first component of the standards; that is, vaccination assessment by practice specialty:



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Clearly, there is a major difference between what HCPs/pharmacists and the general adult population report.

In summary, adult patients reported low levels of receipt of care that reflected the standards. In contrast, HCPs and pharmacists reported high levels of implementation of the standards, except for the use of vaccine registries.

Limitations to these surveys might explain some of the differences. For the adult patient survey, adult patients may not have been aware that some vaccination assessments done "behind the scene," such as the staff checking patient records in the vaccine registry or reviewing patient medical records without necessarily talking with the patients. For the HCP survey, healthcare respondents may have generalized their immunization practices for some patients to all patients or some vaccines to other vaccines. There are also study design limitation that include sampling and recall bias. There is a potential for sampling bias, given that these were self-selected internet panels of respondents and there could be differences between respondents and non-respondents. Recall bias is also of concern on self-report surveys and is not verified. The survey response rate cannot be calculated because opt-in recruitment sampling does not permit enumeration of the denominator.

Dr. Kim stressed that this presentation should not have been a surprise to anyone. CDC simply quantified what most had suspected. The key messages are that the standards should be incorporated into routine clinical practice for every patient and at every visit. Adult patients need to hear from their HCPs and pharmacists about vaccines. The large discrepancy between what HCPs and pharmacists believe they are doing and what adult patients perceive regarding vaccination assessment could be improved this way. As mentioned earlier, an HCP recommendation is a key predictor for adults to get vaccination. Although the data were not presented during this session, the adult patient survey found a statistically significant association between providers giving a strong recommendation and patients actually getting vaccinated. Consistent implementation of the standards is needed to improve adult immunization coverage in the US. The NAIIS and state and local immunization program partners are hard at work to get the word out.

Discussion Points

Dr. Bennett asked whether providers were asked about standing orders and/or engagement of other members of their teams to implement immunizations.

Dr. Kim replied that the survey asked about standing orders; documentation; types of recordkeeping systems; and knowledge, attitudes, and issues that might play into implementing the standards. There are some analyses on this, for which the information will be coming out soon.

Dr. Kempe acknowledged the need to have more effective provider recommendations, et cetera. However, she thought it was somewhat of a false dichotomy to compare patients presenting for a visit who have been seen in the last 12 months who may or may not be eligible for anything other than influenza vaccine and who generally are not aware that people are looking at their immunization records. She emphasized that while provider recommendation is extremely important, all of the systems that support provider recommendations are what really gets this done. Incorporation into adult practice of the systems that have been shown to be effective in pediatrics, where all of the action is in immunization, would be highly beneficial.

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Dr. Szilagyi pointed out that in the survey of patients, the percentage of patients who said they received an influenza vaccination was unbelievably low; whereas, it is known that 40% of adults receive an influenza vaccination. Something is off with the data. In the interest of not always flogging adult providers who are just inundated with chronic disease and managing patients with very serious adult problems, it would be great to hear presentations parallel to some pediatric presentations about what types of interventions have been found to work and how those could be implemented in healthcare systems and practices.

Dr. Belongia encouraged Dr. Kim not to compare the physician survey to the patient survey when publishing, because the limitations are great. That does not discount the message, which is important. However, that direct comparison is not really valid. He asked whether consideration had been given to systematically assessing the system and institutional barriers to doing a better job that providers face in their practices.

Dr. Kim replied that some questions have been asked related to barriers, such as questions about the obstacles providers face in terms of delivering vaccines to their patients. Some of this information is already known based on other surveys, information contained in the *Community Guide*, and elsewhere. The barriers can be combined into three major categories: 1) Financing (payments, billing coding, et cetera), which is perhaps the most important barrier from the provider perspective; 2) Systems (standing orders, EMR) to promote notification for the provider to begin the vaccination discussion and for patients to receive notification, perhaps before their appointment, so that the patient arrives prepared; and 3) Education and training for patients and providers. Of course, there are many competing priorities for providers. Vaccination may not be at the top or even near the top of their daily activities. Making it easier and perhaps taking it out of the hands of the busy HCP who has many things to address during a 10-minute visit by automating the process would be beneficial.

Dr. Foster (APhA) thought the data would be beneficial to share with the APhA members to illustrate the realistic perspective. He pointed out that pharmacists do consider themselves to be HCPs, so separating them out is going to result in a lot of feedback.

Regarding standing orders, Dr. Tan (IAC, NAIIS) reported that there is an IAC project called Take a Stand!™. This initiative began in 2016 to help healthcare practices and provider systems implement standing orders to boost adult immunization rates. He expressed gratitude to the ACIP for all of their comments about implementation. Thanks to CDC's leadership and support from the NVPO, the summit has been trying to address the implementation question. The summit website has a nice collection of a lot of the resources NAIIS has been assembling to address the various comments regarding provider implementation of adult vaccines. During the NAIIS in-person meeting scheduled for May 9-11, 2017 at the Hyatt Regency Atlanta in Atlanta, NAIIS will organize a meeting of healthcare systems to work with them to understand best practices to improve adult immunization rates. He acknowledged Dr. Kempe for her phenomenal success with her adolescent standing orders immunization project at Denver Health.

Dr. Bridges (SME) added that quality measures are known to drive a lot of action in healthcare systems, but there is a paucity of measures for adult immunization. A lot of work is being done at NVPO and through the NAIIS on developing additional quality measures for adult immunization. The VA and IHS have participated.

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Dr. Hayes (ACNM) applauded the study, recognizing that it created a new level for conversation on this topic. She inquired as to how the public was recruited for the survey, and if Dr. Kim had a breakdown of the types of nurse practitioners (adult, women's health, nurse midwives, geriatric, et cetera) who answered the survey.

Dr. Kim replied that the public was recruited through an established internet panel through a list of commercially available names and demographic information, and it is an opt-in process. In terms of the breakdown of nurse practitioners, nurse midwives were not specifically identified as a recruitment variable. Recruitment was through a list of providers for physicians, nurse practitioners, and physician assistants. But, they could be practicing in a particular medical specialty. He does have this information and it will be included in any publications that may be forthcoming.

Dr. Moore pointed out that it was not clear just how much could be said about a survey with just over a 2% response rate among HCPs, which means that there could be a tremendous amount of self-selection bias among optimistic practitioners. It is important to remember that the immunization registries represent a very important tool that is very under-utilized for adult immunization. That is where all information about vaccines should be entered in these registries. Clinical decision support is available in registries that can help prompt HCPs so that they do not have to remember what an adult is supposed to have.

Dr. Savoy (AAFP) has found that as they expand to use a patient care team in her practice, patients may say they were not offered something if she did not specifically offer it herself, even if her MA or behavioral health nurse did offer. This suggests that the questions may need to be asked differently. For example, "When you were in the office, did anyone ask you X?"

Dr. Kim indicated that this was done on the survey. Respondents were asked who asked the question, during what time of the visit, and where (front desk, nurse triage, examination room, check-out).

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 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, the WG briefed ACIP about YF-VAX® production and contingency plans to address any supply shortages. During this meeting, Dr. David Greenberg of Sanofi Pasteur will provide an update on yellow fever vaccine supply.

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Update on YF Vaccine Supply

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

Dr. David Greenberg reported that in the past several years, intermittent production issues have resulted in temporary supply shortages. To improve supply, Sanofi Pasteur invested in and is transitioning manufacturing to a new state-of-the-art facility planned for mid-2018. This transition was intended to be seamless and without impact on supply. In the first quarter of 2016, a manufacturing issue resulted in the loss of a large number of doses being produced to bridge supply until the new facility was online. Sanofi Pasteur immediately instituted ordering restrictions to extend supply to HCPs.

Given yellow fever outbreaks in other countries and global supply issues, stakeholder discussions were initiated in the Spring of 2016. Key participants have included CDC, FDA, and DoD. Sanofi Pasteur's focus has been to assure a continuous YF vaccine supply for travelers, US government employees, military, and other response groups. Sanofi Pasteur has pursued multiple paths to ensure continuous supply of yellow fever vaccine, including product ordering restrictions; additional production of YF-VAX® vaccine in the existing facility; and importation of Stamaril® via an Expanded Access Investigational New Drug (IND) Program Expedited Access Pathway (EAP).

In terms of product ordering restrictions, HCPs are required to verify that vaccine recipients are travelling within 30 days to a YF-endemic country or a country that requires proof of vaccination for entry. Account order limits have been activated to avoid account over-ordering. Regarding production of YF-VAX® vaccine, additional product was produced in the existing facility. Further manufacturing issues limited new production; thus, not enough product could be made to fully bridge to the new facility. Restrictions will enable continued use of YF-VAX® vaccine through mid-2017. With respect to importation of Stamaril® vaccine, Sanofi Pasteur worked closely with the FDA to rapidly develop and submit an EAP. The FDA rapidly reviewed the application and granted approval in October 2016. The EAP protocol allows the product to be used at authorized facilities in a restricted format. By mid-2017, Sanofi Pasteur will supply Stamaril® vaccine under an EAP to fulfill US YF immunization demand.

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 as in YF-VAX® vaccine. Stamaril® vaccine is used globally in more than 100 countries. It has been licensed for more than 30 years, and more than 430 million doses have been distributed. The safety and efficacy for Stamaril® vaccine are comparable to YF-VAX® vaccine. Stamaril® vaccine is supplied as a vial of lyophilized powder and a syringe prefilled with diluent.

As an investigational product, there are protocol and tracking requirements for the sites that administer Stamaril® vaccine. Sanofi Pasteur plans to enroll approximately 150 to 170 high-volume centers that can dedicate resources and train personnel to counsel, administer, and monitor safety. Outreach will begin in March 2017 in order for sites to review and accept the protocol and obtain approval from local Institutional Review Boards (IRBs) as needed. Sites are anticipated to be ready by the end of May 2017, including completion of training. YF providers and travelers will be notified in the May to June timeframe of Stamaril® vaccine sites.

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Sanofi Pasteur is working closely with CDC programs, including the Division of Global Migration and Quarantine (DGMQ) and the Division of Vector-Borne Diseases (DVBD). In addition, they will share information and are developing support for communications materials and plans, product and logistics information, the Stamaril® vaccine site selection process, Stamaril® vaccine site location information, and access to state health departments.

In summary, Sanofi Pasteur will provide Stamaril® vaccine under an EAP by mid-2017. Site enrollment and training will begin in March to ensure readiness. Patients will be directed to designated clinics to receive Stamaril® vaccine. HCPs will be notified to send their patients to these sites. Stamaril® vaccine will be supplied to sites until the new production facility is online mid-2018. Sanofi Pasteur will continue to work diligently to make YF vaccine continuously available throughout this transition.

Discussion Points

Dr. Hunter asked whether supplies are being diverted to the US that would otherwise go to Africa or South America.

Dr. Greenberg replied that the supply of Stamaril® vaccine in the Sanofi Pasteur manufacturing facility in France is very robust. The millions of doses that will be going to other international sites are not affected in any way by the relatively small number of doses that will be coming to the US.

Dr. Reingold pointed out that there seemed to be lingering misinformation that people need a YF vaccine every 10 years, and he wondered whether travel physicians will be counseled to determine whether their patients have ever had YF vaccine.

Dr. Greenberg responded that they leave that to the HCP. It is not Sanofi Pasteur's place to comment on ACIP and WHO recommendations. The company is bound by the product information that is provided with the vaccine. At the end of the day, they will have to trust that providers will act in good faith based on good information. Sanofi Pasteur has done their best to supply the information.

Dr. Gershman (SME) added that the information about the booster dose is well-publicized, and that it is going to providers who should be aware of that and a smaller subset who will be receiving and administering the Stamaril® vaccine. That was passed by an ACIP vote in 2015 and published in the *MMWR*, and the CDC Yellow Book in hard print and on-line, and CDC's Traveler's Heath website. There is fairly wide awareness about the change in the 10-year booster policy.

Dr. Fryhofer (ACP) noted that many doctors keep records only for 10 years. She has experienced some instances recently in which a person has lost the yellow book with the stamp, and the travel clinic has destroyed the records. Because she keeps her records for more than 10 years, she has been having to retrieve records and send them to the travel clinics so they can give patients another YF stamp. She asked whether there is a special registry for YF vaccination that could incorporate a lifelong record, or if any thought has been given to this. She also wondered if a YF is documented in a state IIS it would be accepted as proof of vaccination.

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Dr. Gershman (SME) replied that there is no registry for individual patients; however, there is a registry of clinics that CDC maintains with the help of state health departments. It is up to individual practices to maintain good records. Every state has its own practices.

Dr. Moore added that registries do exist in all states except New Hampshire, which is working on theirs. A state immunization registry can accept YF vaccine documentation. If an immunizing provider reported administration of that to the state immunization registry along with other vaccines, that could be used as evidence that the person has had a YF vaccine in order to reissue a yellow card. However, she was not certain about International Health Regulations (IHR).

Even though she does not administer YF vaccine herself, Dr. Fryhofer wondered if she could enter a YF vaccine into the state system even though she does not have the stamp.

Dr. Moore responded that ideally, the person who administers the vaccine should enter it. That is the best possible record. However, to her knowledge, if Dr. Fryhofer had a patient's yellow card and was reviewing, she could report in the registry that an immunization was given.

Day 2: Public Comment

No public comments were offered in-person during this session. However, Dr. Bennett noted that the following three letters were submitted for inclusion in the record:

Gilberto F. Chavez, M.D., M.P.H.
State Epidemiologist
California Department of Public Health

January 27, 2017

Nancy Bennett, M.D., M.S., Chair
Amanda Cohn MD, Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30329

Dear Dr. Bennett,

The California Department of Public Health (CDPH) commends the Advisory Committee on Immunization Practices' (ACIP) ongoing work to protect the nation's health by setting and adjusting national immunization policies based on available evidence.

Despite high coverage rates of immunization with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap), pertussis disease in adolescents continues to be reported frequently in California. CDPH respectfully requests that ACIP reappraise its routine recommendation since 2006 for a single dose of Tdap vaccine for adolescents and adults in light of subsequent data (including references 1-16) on the limited duration of protection from acellular pertussis vaccines:

- Are the current recommendations still appropriate, or are any changes warranted?
- What are the estimated benefits from the Tdap recommendations to individuals and communities in:

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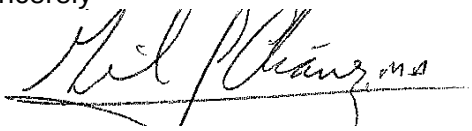
- Preventing or reducing the severity of pertussis, tetanus and diphtheria?
- Increasing coverage rates of other immunizations recommended for preteens?

Systematic review of the current data, and any adjustments in the recommendations that might follow, will help to sustain confidence in immunization, ACIP, and the policies, such as state school immunization requirements, that typically are based upon its recommendations.

Thank you for your consideration of this request.

Sincerely



Gilberto F. Chavez, M.D., M.P.H.
State Epidemiologist
California Department of Public Health

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Richard Hoffmann
Parkinson's Disease Foundation Research Advocate Consumer Representative for the FDA Advisory Committee on PCNS Drugs

February 07, 2017 6:09 PM
To: Advisory Committee on Immunization Practices (CDC) <acip@cdc.gov>
Subject: Upcoming February ACIP Meeting

Hello:

Would you please add to your agenda for the February meeting consideration of adding Parkinson's disease (PD) to the chronic medical conditions listing for pneumococcal vaccines. Aspiration pneumonia is the number one cause of death in this chronic progressive disease and many people under the age of 65 are being denied these vaccines, yet 15% of PD patients are less than 50 years of age. If there are medical or scientific reasons for this exclusion, please let the PD community know.

Thank You Very Much,

Richard P. Hoffmann, PharmD
Parkinson's Disease Foundation Research Advocate Consumer Representative for the FDA Advisory Committee on PCNS Drugs

Pam Rockwell
Concord Massachusetts
No Affiliations

Written Comments for February 22, 2017 ACIP Meeting -Pam Rockwell, 1810 Main St., Concord MA, 01742, no affiliation, pam@tiac.net The ACIP should change the recommendation for flu vaccine so that women who are in their first trimester of pregnancy or are trying to get pregnant should not receive flu vaccine.

In 2015 I wrote to the ACIP:

> ***Pregnant women should not receive influenza vaccine in their first trimester.*** *Fever and/or influenza infection during pregnancy has been linked to miscarriage and autism. There is growing evidence that autism is an autoimmune disorder caused by maternal antibodies that attack the fetal brain. In animal models of maternal antibody induced autism, female fetuses are reabsorbed, so that only males are born. ACIP discussed data in June that influenza vaccine in the first trimester increases the likelihood of miscarriage, but no data has ever been published about whether children exposed to prenatal vaccines develop normally, since studies are limited to one year. ACIP should stop recommending vaccination of women during their first trimester of pregnancy until follow-up studies on maternal vaccination can be done to determine if prenatal exposure to vaccines cause autism. Women naturally have reduced immune response during pregnancy. Such an evolutionary disadvantage must have an explanation. Perhaps making antibodies during pregnancy is bad for the future development or immuno-competence of the offspring.*

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In November 2016, the very first study published that evaluated whether there was a link between autism and maternal vaccination did indeed show a link between influenza vaccination in the first trimester and an increased autism risk of 4 cases in 1000 live births (a 20% increased risk):

> Zerbo O, et al Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder. JAMA Pediatr. Published online November 28, 2016. doi:10.1001/jamapediatrics.2016.3609
> https://www.ncbi.nlm.nih.gov/pubmed/27893896
>
> *"We found that influenza vaccination in the first trimester was associated, in an initial analysis unadjusted for multiple comparisons, with a slightly increased ASD risk after controlling for maternal allergy, asthma, autoimmune conditions, gestational diabetes, hypertension, age, education, race/ethnicity, child conception year, conception season, sex, and gestational age. However, adjusting for the multiplicity of hypotheses tested suggests that the results could be due to chance.* ***If influenza vaccination during the first trimester of pregnancy causes ASD, our results suggest that it would amount to 4 additional ASD cases for every 1000 women vaccinated. Our finding of a possible association between maternal influenza vaccination in the first trimester and increased ASD risk parallels previous studies reporting an association between maternal viral infection or fever and increased ASD risk in the first trimester."***

The maternal autoantibody theory of autism explains the gender bias in autism by supposing that female fetuses are more susceptible to these antibodies and are more likely to be reabsorbed (in mice) or spontaneously abort (in primates), and this is supported by animal data. The Zerbo study only evaluated full term pregnancies, so it would not have noticed if female fetuses were at increased risk of spontaneous abortion. But at your June 2015 meeting, ACIP discussed a Vaccine Safety Datalink study led by Dr. Jim Donahue, et al. at the Marshfield Clinic titled, "Evaluating the risk of spontaneous abortion following administration of influenza vaccines containing H1N1pdm09 and H3N2 viral antigens," which did show correlation between first trimester flu vaccine and miscarriages. (You discounted this data because you felt that women who do not receive flu shots are less likely to seek medical attention for a miscarriage, even though there is no evidence to support this excuse to ignore the data.) The combination of increased numbers of males with autism in the Zerbo study and the increased miscarriages in the VSD study mirrors the animal models of the maternal autoantibody theory of autism.

One of the confounding factors that is discussed in the Zerbo paper is autoimmunity. Autoimmune disorders are much more common in relatives, particularly female relatives, of children with autism. Because it is a known link, Dr. Zerbo checked for prior autoimmune diagnoses in the women in the study. But the study did not check to see if autoimmune disorders were diagnosed in the women after their influenza illness and/or vaccination. If flu infection or vaccination triggers a previously undetected autoimmune disorder, then perhaps that affects the fetus, either triggering a miscarriage or developmental disorder, as might be expected during a flare of an autoimmune disorder during pregnancy.

My 17-year-old son is autistic, although I was not vaccinated or obviously sick during my pregnancy. One of the medical interventions that has made a big difference in my son's progress is the drug amantadine, which was prescribed to him by a neurologist because it is a glutamate receptor antagonist, like the Alzheimer's drug memantine, which is also used to treat autism. But amantadine also neutralizes influenza M2 proton pumps. I think this is not a

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coincidence – that influenza M2 proton pumps mimic human glutamate receptors to avoid a strong immune response. That could mean that the autism and miscarriages described by Zerbo and Donahue are due to a specific antigen in the vaccine, and not necessarily a general response to any vaccine.

But whatever the mechanism, right now you have evidence in front of you that flu vaccinations in the first trimester of pregnancy could trigger autism or miscarriage, and there are some animal models of autism and miscarriage that show that antibodies could be the cause. The ACIP should change their recommendation to advise women who are trying to get pregnant or are in their first trimester not to get vaccinated until you can collect some data that actually shows that the vaccines are safe.

Thank you,
Pam Rockwell

Some papers about maternal autoantibodies or infection and autism:

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Certification

Upon reviewing the foregoing version of the February 22-23, 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.

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September 26, 2016
Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2016 through June 30, 2017

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Professor of Medicine and Public Health Sciences
Director, Center for Community Health
Co-director, Clinical and Translational Science Institute
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Term: 07/01/2015-06/30/2018

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Chief, Infectious Diseases Service
Ben Taub General Hospital, Harris Health System
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Term: 7/1/2016 – 6/30/2020

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