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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 23-24, 2019
Atlanta, Georgia

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Final - October 17, 2019

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329
October 23-24, 2019

AGENDA ITEM		PRESIDER/PRESENTER(s)
Wednesday, October 23		
8:30	**Welcome & Introductions**	Dr. Jose Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
9:00	**Pertussis Vaccines**	
	Introduction	Dr. Henry Bernstein (ACIP, WG Chair)
	Safety of closely spaced Tdap vaccines in the catch-up immunization schedule	Dr. Pedro Moro (CDC/NCEZID)
	Tdap and Td: Summary of work group considerations and proposed policy options	Dr. Fiona Havers (CDC/NCIRD)
9:50	***Break***	
10:00	**Adult Immunization Schedule**	
	Introduction	Dr. Paul Hunter (ACIP, WG Chair)
	2020 Adult Immunization Schedule revisions	Dr. Mark Freedman (CDC/NCIRD)
10:40	**Childhood Immunization Schedule**	
	Introduction	Dr. Henry Bernstein (ACIP, WG Chair)
	2020 Child and Adolescent Schedule revisions	Dr. Candice Robinson (CDC/NCIRD)
11:20	***Break***	
11:30	**Public Comment**	
12:30	***Lunch***	
1:45	**VOTES & VFC VOTES**	
	Pertussis vaccines	Dr. Fiona Havers (CDC/NCIRD)
	Pertussis VFC	Dr. Jeanne Santoli (CDC/NCIRD)
	Immunization schedules	Dr. Mark Freedman (CDC/NCIRD), Dr. Candice Robinson (CDC/NCIRD)
2:15	**Influenza Vaccines**	
	Introduction	Dr. Robert Atmar (ACIP, WG Chair)
	Influenza surveillance update	Ms. Lynette Brammer (CDC/NCIRD)
	High-dose inactivated influenza vaccine update	Dr. Lee-Jah Chang (Sanofi Pasteur)
	Work group considerations	Dr. Lisa Grohskopf (CDC/NCIRD)
3:15	***Break***	
3:30	**Ebola Vaccine**	
	Introduction	Dr. Sharon Frey (ACIP, WG Chair)
	Ebola Virus disease	Dr. Mary Choi (CDC/NCEZID)
	Safety and immunogenicity of rVSVΔG-ZEBOV-GP	Dr. Beth-Ann Griswold Coller (Merck)
	Work group interpretation and next steps	Dr. Mary Choi (CDC/NCEZID)
4:30	**Vaccine Safety**	
	Vaccine safety monitoring systems and methods	Dr. Frank DeStefano (CDC/NCEZID)
5:00	**Adjourn**	

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Thursday, October 24

8:00	**Unfinished Business and Agency Updates**	
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, OIDP	
8:30	**Orthopoxvirus Vaccine**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
8:35	**Dengue Vaccine**	
	Introduction	Dr. Robert Atmar (ACIP, WG Chair)
	GRADE analysis for Dengvaxia	Dr. Gabriela Paz-Bailey (CDC/NCEZID)
	Dengvaxia cost effectiveness in Puerto Rico	Dr. Alex Perkins (University of Notre Dame)
	Summary of work group discussion and next steps	Dr. Steve Waterman (CDC/NCEZID)
9:40	**General Best Practices**	
	Introduction	Dr. Paul Hunter (ACIP, WG Chair)
	Update on recent postings	Dr. Andrew Kroger (CDC/NCIRD)
9:50	***Break***	
10:10	**Rabies Vaccine**	
	Introduction	Dr. Sharon Frey (ACIP, WG Chair)
	Background	Dr. Agam Rao (CDC/NCEZID)
	Rabies PrEP schedule and serological monitoring by risk category in healthy nonpregnant persons and special populations	Dr. Jesse Blanton (CDC/NCEZID)
11:10	**Measles**	
	National Measles overview	Dr. Paul Gastanaduy (CDC/NCIRD)
	Measles in New York State	Dr. Debra Blog (NY State Department of Health)
	Measles in New York City	Dr. Jane Zucker (NYC Department of Health & Mental Hygiene)
	Vaccinate with confidence	Dr. Sarah Mbaeyi (CDC/NCIRD)
11:55	**Vaccine Supply Update**	Dr. Jeanne Santoli (CDC, NCIRD)
12:00	**Adjourn**	

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
EtR	Evidence to Recommendations Framework
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]
OIPD	Office of Infectious Disease and HIV/AIDS Policy
PrEP	Pre-exposure Prophylaxis
Tdap	Tetanus, diphtheria and acellular pertussis
WG	Work Group
VE	Vaccine effectiveness
VFC	Vaccines for Children

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Acronyms

9vHPV	9-valent HPV
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACHA	American College Health Association
ACHIV	African-Canadian Study of HIV-Infected Adults
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADM	Admiral
AE	Adverse Event
AFM	Acute Flaccid Myelitis
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
aIIV	Adjuvanted Inactivated Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APN	Advanced Practice Nurse
APRN	Advanced Practice Registered Nurse
AS	American Samoa
ASH	Assistant Secretary for Health
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
BSL-4	Biosafety Level 4
CBER	Center for Biologics Evaluation and Research
ccIIV	Cell Culture-Based Inactivated Influenza Vaccine
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CICP	Countermeasures Injury Compensation Program
CIR	Citywide Immunization Registry
CISA	Clinical Immunization Safety Assessment
CIVICs	Collaborative Influenza Vaccine Innovations Centers
CLD	Chronic Liver Disease
CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
CMV	Cytomegalovirus
CNS	Central Nervous System
COD	Cause of Death
COI	Conflict of Interest
CPI	Consumer Price Index
CRPS	Complex Regional Pain Syndrome
CFS	Chronic Fatigue Syndrome
CSTE	Council of State and Territorial Epidemiologists
CTD	Common Technical Document

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DC	District of Columbia
DENV	Dengue Virus
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
DSTDP	Division of STD Prevention
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
EB	Empirical Bayesian
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
ESRD	End Stage Renal Disease
EtR	Evidence to Recommendation
EU	European Union
EVD	Ebola Virus Disease
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
FSM	Federated States of Micronesia
FY	Fiscal Year
GAVI	Global Alliance for Vaccines and Immunisation
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
GI	Gastrointestinal
GISRS	Global Influenza Surveillance and Response System
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GP	Glycoprotein
GP-ELISA	Galactomannoprotein Enzyme-Linked Immunosorbent Assay
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immune Globulin
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HD-IIV	High-Dose Inactivated Influenza Vaccine
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration

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ICD	International Classification of Diseases
IDCRP	Infectious Disease Clinical Research Program
ICE	Immunization Calculation Engine
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ID	Intradermal
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHD	Immunization Healthcare Division
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
ILLC	Immunization Lifelong Learners Course
ILLSC	Immunization Lifelong Learners Short Course
IM	Intramuscular
IMPAc-TB	Immune Mechanisms of Protection Against Mycobacterium Tuberculosis Centers
ISD	Immunization Services Division
ISO	Immunization Safety Office
IVIG	Intravenous Immunoglobulin
LAIV	Live Attenuated Influenza Vaccine
LRN	Laboratory Response Network
MAA	Marketing Authorization Applications
MDH	Minnesota Department of Health
MedDRA	Medical Dictionary for Regulatory Activities
MHS	Military Health System
MMR	Measles, Mumps, and Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
MI	Multiple Imputation
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAIP	National Adult Immunization Plan
NAM	National Academy of Medicine
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
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 Primate
NIAID	National Institute of Allergy and Infectious Diseases

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NIC	National Immunization Conference
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIP	National Immunization Program
NIS	National Inpatient Sample
NIS-Child	National Immunization Survey-Child
NIS-Teen	National Immunization Survey-Teen
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NVSN	New Vaccine Surveillance Network
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NYC	New York City
NYC DOHMH	New York City Department of Health and Mental Hygiene
NYS	New York State
NYSDOH	New York State Department of Health
OASH	Office of the Assistant Secretary for Health
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OJNA	Orthodox Jewish Nurses Association
OPV	Oral Polio Vaccine
OSU	Ohio State University
PAIVED	Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEACH	Parents Teaching and Advocating for Children's Health
PEP	Post-Exposure Prophylaxis
PFU	Plaque-Forming Units
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PIE	Parents Informed and Educated
POTS	Postural Orthostatic Tachycardia Syndrome
PPV	Positive Predictive Value
PrEP	Pre-Exposure Prophylaxis
PR	Puerto Rico
PREVAC	Partnership for Research on Ebola VACcinations
PREVENT	Pregnancy Influenza Vaccine Effectiveness Network
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Terms (MedDRA)
PR	Puerto Rico
PREVAIL	Partnership for Research on Ebola Virus in Liberia
QALY	Quality-Adjusted Life-Year
QIV	Quadrivalent Influenza Vaccine

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RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
RFFIT	Rabies Neutralizing Antibody
RIV	Recombinant Influenza Vaccine
RML	Rocky Mountain Laboratories
RN	Registered Nurse
RNA	Ribonucleic Acid
ROA	Route of Administration
RPMS	Resource and Patient Management System
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RVSH	Region Vaccine Safety Hub
rVSV	Recombinant Vesicular Stomatitis Virus
RVV	Rabies Virus Variants
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SHEA	Society for Healthcare Epidemiology of America
SIDS	Sudden Infant Death Syndrome
SIRVA	Shoulder Injury Related to Vaccine Administration
SME	Subject Matter Expert
SNS	Strategic National Stockpile
SSUAD	Serotype-Specific Urinary Antigen Detection
STI	Sexually Transmitted Infections
STI CRC	Sexually Transmitted Infections Cooperative Research Centers
STRIVE	Sierra Leone Trial to Introduce a Vaccine Against Ebola
TB	Tuberculosis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TECs	Tribal Epidemiology Centers
TCH Forecaster	Texas Children's Hospital Immunization Forecasting Software
TIV	Trivalent Influenza Vaccine
TMLE	Targeted Minimum loss-based estimator
tOPV	Trivalent Oral Polio Vaccine
UK	United Kingdom
US	United States
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
US Flu VE	US Influenza Vaccine Effectiveness Network
USPHS	US Public Health Service
USU	Uniformed Services University
USVI	United States Virgin Islands
UTD	Up-To-Date
UWSPH	University of Washington School of Public Health
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VCD	Virologically Confirmed Dengue

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VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever
ZEBOV	Zaïre Ebolavirus

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

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the October 2019 Advisory Committee on Immunization Practices (ACIP) and welcomed those present.

Dr. Cohn welcomed everyone to the October 2019 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 pointed out that multiple Centers for Disease Prevention and Control (CDC) staff were present at the entrance to the room and at the desk outside the room to assist members of the public with questions.

She noted that handouts of the presentations were distributed to the voting ACIP members and were made available for others on the tables outside of the auditorium. Additionally, slides were made available through a ShareFile link for liaison and *ex-officio* members. Slides presented during this meeting will be posted on the ACIP website approximately 3 to 4 weeks after the meeting. The live webcast also will be posted in about 4 weeks following the meeting, and the meeting minutes are posted to the ACIP website generally within about 120 days following the meeting. Minutes from the June 2019 meeting were scheduled to be posted shortly after the October 2019 meeting.

To ensure the health and safety of all individuals attending this meeting, Dr. Cohn reviewed a few safety regulations. She explained that in the event of an emergency resulting in an evacuation, the procedures would be as follows:

- ❑ Those sitting in the back of the room behind the ropes were instructed to exit out the rear doors and across the bridge the way they came in.
- ❑ Those sitting in the front of room were instructed to exit through the rear of the room, turn left, then proceed right down the stairs.
- ❑ Everyone should locate the blue building marker sign labeled “Conference and Meeting Space—GCC, 2nd floor” and group together to ensure all attendees are accounted for.
- ❑ Once the premises have been secured and an “all clear” has been issued, participants would be permitted to re-enter the building and the meeting would resume.

The next ACIP meeting will be convened at CDC on Wednesday and Thursday, February 26-27, 2020. Registration for all meeting attendees is required and will open on the ACIP website when the *Federal Register* notice is posted. Registration will be closed when the number of participants reaches the number of seats in the room. Registration is required for all meeting attendees. International visitors must register at least a month in advance. Registration is not required for webcast viewing.

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Dr. Cohn announced the following member substitutions for this meeting:

Ex Officio Representatives
- ❑ Sophie Califano, MD, MPH: Department of Veterans Affairs (DVA)
- ❑ Mary Rubin, MD: Health Resources and Services Administration (HRSA)
- ❑ Jillian Doss-Walker, MPH: Indian Health Service (IHS)

Liaison Representatives
- ❑ Paul Cieslak, MD: Council of State and Territorial Epidemiologists (CSTE)
- ❑ Yasmin Tyler-Hill, MD: National Medical Association (NMA)

Dr. Romero introduced the following new ACIP members:

Lynn Bahta, RN, BSN

Ms. Lynn Bahta is an Immunization Program Clinical Consultant at the Minnesota Department of Health (MDH) where she currently serves as a clinical expert for vaccines. She has 25 years of experience in the field of immunization, including adult and pediatric immunization. She brings with her extensive experience in adult and pediatric clinical nursing, state and local public health issues, vaccine development and clinical trials, and infectious disease.

Beth Bell, MD, MPH

Dr. Beth Bell is a Clinical Professor in the Department of Global Health at the University of Washington School of Public Health (UWSPH). Dr. Bell leads efforts to improve work in the areas of pandemic preparedness and global health security. She spent most of her career in government service at CDC, where she served as the Director of the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) until her retirement in January 2017.

Katherine Poehling, MD, MPH

Dr. Katherine Poehling is a Professor of Pediatrics at the Wake Forest School of Medicine. She is board certified in pediatrics and an expert on the community impact of vaccines, specifically pneumococcal and influenza vaccines. She is the Wake Forest representative on the North Carolina Immunization Advisory Committee, and has collaborated with CDC on the New Vaccine Surveillance Network (NVSN) and with the CDC Active Bacterial Core Surveillance (ABCs) group.

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Pablo Sanchez, MD

Dr. Pablo Sanchez is a Professor of Pediatrics in the Division of Pediatric Infectious Diseases at Ohio State University (OSU). He is triple board certified in pediatrics, neonatology, and pediatric infectious diseases. He has had a distinguished career as a clinical and scientific investigator in neonatal and perinatal infections with major contributions in areas such as congenital syphilis, congenital cytomegalovirus (CMV) infection, respiratory syncytial virus (RSV) infections, neonatal sepsis, antimicrobial stewardship in the Neonatal Intensive Care Unit (NICU), and immunizations in premature infants.

Dr. Romero then took a moment to recognize Cynthia Pelligrini, who was an integral member of ACIP and an active contributor to its work from July 1, 2013 through December 31, 2018. Cindy passed away on July 26, 2019 following a courageous and unyielding battle with ovarian cancer:

Cindy served as ACIP's Consumer Representative and as a member of multiple ACIP work groups (WGs). Her work while on the ACIP impacted the lives of millions of United States (US) children and adults by helping craft immunization policy. Those who served alongside Cindy during her 5-year tenure on the ACIP were fortunate enough to witness her intelligence, empathy, kindness, quick wit, grace, poise, and most of all humility as she executed her role and participated in the activities of the ACIP.

Dr. Romero noted that on the flight to this meeting, he happened to read an article in the *New York Times* about the growing recognition of humility as an important personality trait. The research now shows that this has become a trait that is strongly linked with curiosity, reflection, and open-mindedness. These were characteristics clearly exhibited by Cindy. She listened to everyone, challenged scientists and thought leaders at the appropriate times, and pushed the ACIP to become a stronger committee serving the public. Cindy transformed the role of Consumer Representative. She conferred a truly personal and unique touch to that role by personally writing letters to each individual who offered public comment during every ACIP meeting. She continuously reminded the members of ACIP of the children, adults, parents, and

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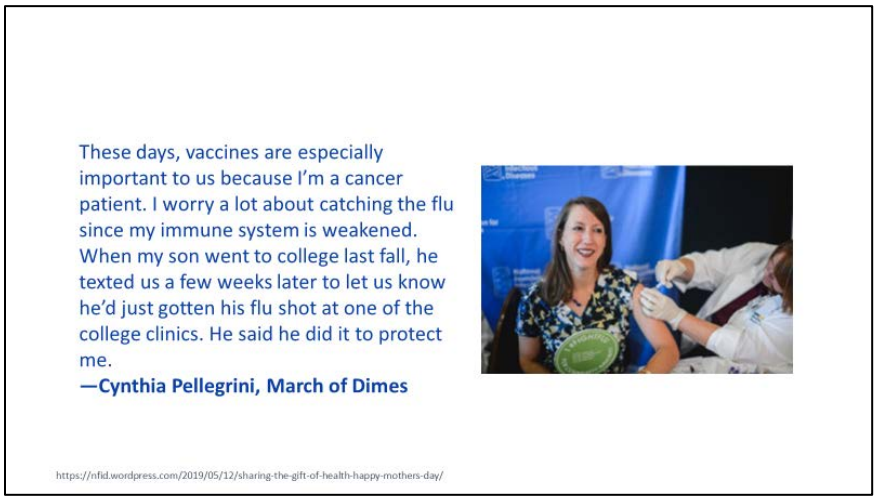
grandparents who are the reason the ACIP members put so much of their hearts into each decision they make.

John Temte, ACIP Chair from 2011-2015, said of Cindy, “We were truly blessed by her presence at the ACIP. Cindy was a wonderful and kind person who acted with dedication and compassion and purpose.” Nancy Bennett, ACIP’s Chair from 2015-2018, expressed it so well by saying, “Cindy brought a different sort of wisdom to the ACIP. She was not steeped in the medical and research paradigm that encompassed and sometimes blinded us. Rather, she brought with her a fresh and thoughtful perspective grounded in common sense and deep commitment to the public—all of the public. Amanda Cohn, ACIP’s current Executive Secretariat, said of Cindy, “She is one of my mentors. She balanced life so beautifully and was so proud of and full of love for her family and children. The world is left a little emptier with Cindy’s passing. Let us always remind ourselves that we should attempt to fill that void in her honor.”

Here is a quote from Cindy who, while she was sick, did a blog for the National Foundation for Infectious Diseases (NFID):



Dr. Cohn emphasized that this quote from Cindy personifies everything about her and the way that she humanized the importance of vaccines to individual people. CDC is developing an award that will be given out during the National Immunization Conference (NIC) that will be called the “Cindy Pelligrini Immunization Award for Outstanding Public Engagement.” More details about this award will be announced soon.

In terms of public comment, an apropos segue to the tribute to Ms. Pelligrini, Dr. Cohn stressed that ACIP is, at its heart, a public body. Engagement with the public and transparency in ACIP’s processes is vital to the Committee’s work. As part of ACIP’s commitment to continuous improvement, ACIP recently strengthened its oral and written public comment process to accommodate increased public interest in ACIP’s work, maximize opportunities for comment, and make public comment more transparent and efficient. Dr. Cohn indicated that for this meeting, there would be an oral public comment period on the first day of the meeting at 11:30 AM prior to the scheduled votes.

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To create a fairer and more efficient process for requesting to make an oral comment, people interested in making an oral comment were asked to submit a request online in advance of the meeting. Priority is given to these advance requests, and if more people request to speak than can be accommodated, a blind lottery is conducted to determine who will be the speakers. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Dr. Cohn requested that the public comment speakers identified for this meeting sign in at the information table outside the main auditorium to confirm their presence.

For written public comments, ACIP is using a docket on regulations.gov where any member of the public can submit a written comment. This process allows for the ability to submit longer comments and the ability to include attachments, comments to be visible to the public, and a longer window for comment submission. Comments may now be submitted up to 48 hours following the end of the meeting, and all comments submitted by 72 hours of the meeting will be made available to the ACIP members prior to the meeting. At the time of this meeting, the written comment docket was still open. Using docket ID CDC-2019-0073, those interested were invited to submit a comment at regulations.gov. This information also can be found in the *Federal Register* notice announcing ACIP meetings and on the ACIP meeting website. She encouraged everyone to access and read the public comments posted.

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 conflict of interest (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 these vaccines, but 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 provision that he/she abstains on all votes related to the vaccines of that company. At the beginning of each meeting and prior to each vote, ACIP members will state any COIs.

Dr. Romero conducted a roll call to determine whether any ACIP members had COIs. No members declared any COIs. He then requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes from the October 2019 ACIP meeting.

Pertussis Vaccines

Introduction

Henry Bernstein, DO, MHCM, FAAP
Chair, Child and Adolescent Immunization WG
Professor of Pediatrics, Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center New Hyde Park, New York

Dr. Bernstein reminded everyone that ACIP currently recommends that all non-pregnant adolescents and adults aged 11 years and older receive a single dose of Tdap, preferably at ages 11-12 years. To ensure continued protection against tetanus and diphtheria, booster doses of Td are recommended every 10 years. The single Tdap dose can replace a decennial

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Td booster dose, but the dose of Tdap, when indicated, should be administered regardless of the interval since the last tetanus or diphtheria toxoid-containing vaccine. Td may also be recommended for tetanus prophylaxis in the setting of wound management if a tetanus-toxoid containing vaccine has not been administered in the previous 5 years. The catch-up immunization series for persons not fully vaccinated against pertussis and tetanus is a 3-dose series with one Tdap, preferably the first, followed by 2 doses of Td. In order to prevent infant pertussis, pregnant woman are recommended to receive a dose of Tdap during every pregnancy, irrespective of the patient's prior history of receiving the vaccine and regardless of the interval since prior vaccination with Td or Tdap. Note that this is an off-label recommendation, and the WG did not evaluate any changes to the routine pregnancy recommendation.

The ACIP Pertussis Vaccines WG's terms of reference are to consider the evidence for a potential policy change to allow either Td or Tdap vaccine to be used in situations where only Td vaccine is currently recommended for: 1) decennial Td booster in adults; 2) tetanus prophylaxis as needed for wound management; and 3) the catch-up immunization schedule. During the June ACIP meeting, the Evidence to Recommendation (EtR) framework was presented. The WG is in favor of the policy questions under consideration regarding whether either Tdap or Td should be allowed to be used for the decennial Td booster, for tetanus prophylaxis in the setting of wound prophylaxis, or for additional doses of the catch-up immunization schedule for persons aged 7 years or older, including in pregnant women.

This session included presentations on: 1) safety of closely spaced Tdap vaccines in the catch-up immunization schedule; and 2) Tdap and Td: Summary of work group considerations and policy options.

In terms of next steps, the WG has been asked by the National Center for Immunization and Respiratory Diseases (NCIRD) leadership to evaluate the spacing between booster doses of vaccines for tetanus and diphtheria, which is currently recommended every 10 years. Note that this question is separate than those in this WG's terms of reference, which focused on whether it is appropriate for providers to be able to substitute Tdap in situations where Td is currently recommended. The question of the spacing of booster doses has arisen given information about the duration of protection against tetanus and diphtheria. Some countries do not give Td boosters and others give Td booster doses less frequently than every 10 years. The WG will evaluate evidence regarding whether the current 10-year interval between Td booster doses should be changed. This question was not addressed during this session, but the WG will be addressing it in the future.

Safety of Closely Spaced Tdap Vaccines in the Catch-Up Immunization Schedule

Pedro L. Moro, MD, MPH
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Moro reminded everyone that the current adolescent and adult catch-up schedule series for those with incomplete or unknown vaccine history are an initial Tdap dose followed by a Td dose at 1 month and a second Td at 6 to 12 months. The proposed policy option under consideration is for an initial Tdap dose followed by Td or Tdap at 1 month and Td or Tdap at 6 to 12 months. However, limited data exist on the safety of the current versus the proposed catch-up schedule for adolescents and adults. An approach to address this issue is to look at

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published and unpublished data on the safety of immunization regimens similar to the proposed schedule and administering closely spaced (≤12 months) Tdap doses.

The objectives of this presentation were to: 1) review published literature on studies that have assessed the safety of closely spaced Tdap compared to closely spaced Td doses and a non-comparative, descriptive study; and 2) review unpublished safety data on closely spaced Tdap from CDC's vaccine safety monitoring systems, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

In terms of Tdap versus Td, one study was a double-blind, randomized, controlled clinical trial. The study enrolled 460 adults ≥ 40 years from 3 European countries with no Td vaccine for 20 years or unknown vaccination history. The study arms received the following in a 0-1-6 month schedule: 3 doses of Tdap, 1 dose of Tdap-IPV followed by 2 doses of Td, or 3 doses of Td vaccine (control). The study outcomes were immunogenicity and reactogenicity. There were no statistically significant differences in local or general symptoms between groups [Theeten H, et al. Current Medical Research and Opinion. 2007;23:11,2729-2739].

A second study was a cohort study of maternal Tdap reactogenicity. This study enrolled 374 pregnant women and 225 non-pregnant women. A sub-population of interest was comprised of 8 pregnant women who had more than one Tdap within the past 12 months. There was no comparison group in this study. The study outcomes were injection site and systemic reactions. No severe local or systemic reactions were observed; however, there was a small number of subjects [Fortner K, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and non-pregnant women. Vaccine. 2018 Oct 8;36(42):6354-6360].

As a reminder, VAERS is a national passive surveillance system that is co-managed by CDC and the Food and Drug Administration (FDA) that can rapidly detect safety signals and can detect rare adverse events (AEs). However, this system also includes a number of limitations such as the lack of an unvaccinated comparison group and the fact that it generally cannot assess causality. There are no denominators, so it is not possible to calculate the incidence or prevalence of an AE or calculate measures of risk. In order to look for closely spaced Tdap reports, the VAERS database was searched for US reports of all persons who received more than one dose of Tdap between January 1, 1990 and June 30, 2019. VAERS reports and any medical records were reviewed to assess for the length of interval between doses and the AE, if any. Reports with an interval of two Tdap doses ≤12 months were included in the final analysis. Among 34,804 reports of Tdap submitted to VAERS during the search period, 342 involved multiple doses of Tdap. In 88 reports, an interval of two Tdap doses ≤12 months was reported. Of these, 67 (76.1%) did not describe an AE (vaccination errors) and 21 (23.9%) described an AE. The most common AEs were injection site reactions in 8 reports.

In terms of the unpublished analyses from the VSD, the first is a retrospective cohort study that evaluated repeated Tdap doses in a supplementary analysis on an existing dataset[1]. The study sub-population of interest was comprised of 13,599 non-pregnant adolescents and adults 11-64 years of age who received Tdap or Td within 12 months of prior Tdap. The comparison groups were 11,687 Tdap versus 1912 Td vaccines given within 12 months of prior Tdap. The outcomes were pre-specified local reactions and neurologic adverse events[2]. Repeated Tdap was not associated with an increase in any adverse event compared to Td within 12 months of prior Tdap [[1]Jackson M, et al. Pharmacoepidemiol Drug Saf. 2018;27:921-925
[2] Cellulitis, Limb swelling, Pain in limb, Encephalopathy, encephalitis and/or meningitis, Paralytic syndromes, Seizure, Cranial nerve disorders, Guillain-Barre Syndrome].

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The second source of unpublished information is a study of maternal Tdap safety in the VSD based on unpublished data from a VSD retrospective cohort study evaluating maternal Tdap safety. The study sub-population of interest is 187 women with multiple Tdap vaccines during the same pregnancy who were excluded from the larger published study. There was no comparison group. The outcomes were acute AEs (fever, allergy, and local reactions) and adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight). Only 1 of the 187 women had an acute event following multiple Tdap vaccines in the same pregnancy, with an International Classification of Diseases (ICD)-9 code of limb pain and limb swelling 7 days after vaccination. This occurred on the day of delivery, but the affected limb was unspecified. The baby was born at 39 weeks. Birth outcome rates were similar to pregnant women exposed to a single Tdap dose during the same pregnancy [Sukumaran L et al. JAMA. 2015;314(15):1581-7].

In summary, the published studies used a number of regimens that had some resemblance to the regimens in the current and proposed catch-up schedules. In the Theeten study, there were no differences in reactogenicity between Tdap and Td. In the Fortner study, there were no severe local or systemic reactions. In terms of the unpublished VAERS reports, most reports (76%) of excess doses of Tdap in VAERS did not describe an AE. Among reports with AEs (n=21), local reactions were most commonly reported (n=8). Regarding unpublished VSD reports, among subjects who received a Tdap dose ≤12 months compared to Td, no increased rates of AEs were observed. Among 187 women in the VSD who received multiple Tdap doses in the same pregnancy, one presented with limb pain and limb swelling 7 days after vaccination. It is unclear whether this was vaccine-related.

In conclusion, published data on closely spaced Tdap doses shows no increase in AEs when Tdap or Td was administered as a second or third dose. Regimens similar to the current and proposed catch-up schedule did not show differences in reactogenicity. Unpublished data of closely spaced Tdap doses shows no unusual or increased reporting of any AE. While data on multiple Tdap doses is limited, the review of published and unpublished safety data is reassuring.

Tdap and Td: Summary of WG Considerations and Proposed Policy Options

Fiona Havers, MD, MHS
Lead, Pertussis Vaccines Work Group
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Havers indicated that for the remainder of this session, she would summarize the WG's assessment of the safety data, talk about a clarification of the current CDC guidance, briefly summarize the WG considerations, and present the proposed text for the policy options.

The WG reviewed data for the safety of using Tdap in place of Td for catch-up immunization and concluded that although data were limited, the randomized controlled trial (RCT) that compared Tdap and Td for the 3-dose series was reassuring, as were other published and unpublished data as presented by Dr. Moro. The WG also noted that there was no concerning safety signals in multiple sources of data, including in pregnant women, although data are sparse on multiple doses of Tdap during a single pregnancy and that there is need for continued safety monitoring. Given this, and as presented at the ACIP meeting in June, the WG was in favor of allowing either Td or Tdap to be used for additional doses of the catch-up immunization

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schedule for persons 7 years of age and older, both in the general population and for pregnant women.

There is a clarification of CDC guidance that Dr. Havers shared for awareness before moving to the discussion of the language for the proposed policy options. This is not something that needed to be voted on by ACIP, but she wanted to mention it as this is in the policy note and also on the childhood immunization schedule. Current guidance states that children 7 through 10 years of age who receive Tdap inadvertently or for catch-up immunization should receive Tdap again at age 11 through 12 years. CDC has received many questions from state health departments, immunization programs, providers, and other stakeholders asking about 10 year-olds who are vaccinated for school entry requirements and whether they need to receive another Tdap at age 11 or 12. Of note, both Tdap vaccines are licensed down to 10 years of age. The plan is to simplify these recommendations for providers to say that 7 through 9 year-olds who receive Tdap for any reason should receive the adolescent Tdap booster at 11-12 years of age. On the other hand, a Tdap given to a child 10 years or older can count as the adolescent Tdap dose and it does not need to be repeated. Similar changes are made to clarify guidance on inadvertent DTaP in this age range. This clarification will be included in the upcoming Policy Note and potentially in the childhood immunization schedule.

Dr. Havers returned to the terms of reference which asked the WG to evaluate whether either Td or Tdap should be allowed for use in settings where only Td is currently recommended for the decennial booster, tetanus prophylaxis for wound management, and the catch-up immunization schedule. As a reminder, the WG presented its EtR framework during the last ACIP meeting, a summary slide of which is shown here. The WG's interpretation was that allowing this change would give increased flexibility to providers and that while there may be some additional benefit for pertussis control, there was not enough evidence to preferentially recommend Tdap over Td. They concluded that there were no substantive safety concerns and given this, the benefits of the recommendation change outweigh potential harms. The WG also concluded that providers value flexibility and that there is evidence that Tdap has largely replaced Td regardless of current recommendations, which indicates that the change would be valued by stakeholders and that it is likely acceptable and feasible. Although Tdap is more expensive than Td, economic analyses had limited utility. Given that the change has been widely implemented already, regardless of the higher cost and the uncertainty of key parameters in the various economic models, economic impact was not a major consideration for the WG for these questions. As presented during the last meeting, the WG was in favor of the policy option to allow either Td or Tdap to be used in settings where only Td is currently recommended for the decennial booster, tetanus prophylaxis in the setting of wound management, and the catch-up immunization schedule.

Before presenting the proposed text for the potential policy changes, Dr. Havers reminded everyone that if ACIP did vote to change the recommendations for the use of Tdap, there would be several situations in which recommendations would be for off-label uses. This table, which was shown at the last meeting in June, shows the two licensed Tdap products with a summary of their FDA approved indications for usage and administration in the second column. The last three columns indicate where use of these two products would be off-label if recommendations are changed. Off-label indications based on age have not changed. New off-label indications for Adacel® would include any additional routine or catch-up Td dose beyond a second dose administered ≥8 years from a first Tdap dose, if not given for wound prophylaxis within the specified guidance. For Boostrix®, any additional doses beyond the single licensed dose would be off label:

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Potential off-label recommendations

Licensed Tdap product	FDA approved indications for usage and administration	Potential off-label recommendations		
		Decennial Td booster (adults only)	Tetanus prophylaxis for wound management	Catch-up immunization series[1,2]
Adacel (Sanofi Pasteur)	• Age: 10 – 64 years • Routine booster[3] with a 2nd dose ≥8 years after first (any) Tdap dose • Tetanus prophylaxis if ≥5 years since last tetanus containing vaccine[4]	• Age ≥65 years • Any dose beyond 2nd Adacel dose administered ≥8 years from first Tdap	• Age <10 or ≥65 years	• Age 7 – 9 years or ≥65 years • >1 Tdap dose
Boostrix (GSK)	• Age: ≥10 years • Single dose[3] • Tetanus prophylaxis if no previous Tdap[4]	• Any dose if previously received Tdap	• Age <10 years • Any dose if previously received Tdap	• Age 7 – 9 years • >1 Tdap dose

[1] Current catch-up immunization recommendations: persons with incomplete or unknown vaccine history should receive a single dose of Tdap as one dose (preferably the first) of the three-dose catch-up series. If additional doses are needed, Td is recommended. [2] Note on pregnancy: Both Tdap vaccines may be administered during pregnancy with the same intervals and restrictions (vaccine specific) as would apply to a non-pregnant individual. [3] **Five or more years after a dose of DTaP or Td vaccine.** [4] Please see Td package insert for indications and intervals for wound management

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Moving on to the proposed language for the policy issues under consideration, note that if changes are made, recommendations for persons 7 through 18 years and those 19 years and older will be listed in separate sections, but the proposed language for both groups is identical in most instances and, where noted, have been combined in this presentation. Note that important words that are changed will be highlighted. In most instances, the highlighted text was changed from "td" to "either Td or Tdap."

For the decennial booster in persons with documentation of previous Tdap, the sentence will be changed to read:

> *"To ensure continued protection against tetanus and diphtheria, booster doses of **either Td or Tdap** should be administered every 10 years throughout life."*

For Tetanus prophylaxis for wound management in persons with previous documentation of Tdap the sentence will be changed to read:

> *"For nonpregnant persons with documentation of previous vaccination with Tdap, **either Td or Tdap** should be used if a tetanus toxoid–containing vaccine is indicated."*

For the catch-up immunization series, the proposed text reads:

> ***"Persons aged (7–18 years and ≥19 years)** who have never been vaccinated against pertussis, tetanus, or diphtheria should receive a series of three tetanus and diphtheria toxoid-containing vaccines, which includes **at least 1 dose of Tdap**. The preferred schedule is a dose of Tdap, followed by a dose of **either Td or Tdap** at least 4 weeks afterward and another dose of **either Td or Tdap** 6 to 12 months later.*
>
> ***Persons aged (7–18 years and ≥19 years)** who are not fully immunized against tetanus and diphtheria should receive 1 dose of Tdap (preferably the first) in the catch-up series; if additional tetanus toxoid–containing doses are required, **either Td or Tdap** vaccine can be used."*

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Note that the catch-up immunization schedule for pregnant women and the general population is the same, but there is an additional paragraph on the prevention of obstetric and neonatal tetanus. The text of that paragraph has not been changed, but for clarity propose the highlighted sentence was added:

> "The risk of neonatal tetanus is minimal if a previously unimmunized woman has received at least 2 properly spaced doses of tetanus toxoid–containing vaccine during pregnancy; one of the doses administered during pregnancy should be Tdap, administered according to the current guidance. **If more than one dose of a tetanus-toxoid containing vaccine is needed, either Td or Tdap vaccine can be used for those doses.** She should complete the 3-dose primary series at the recommended intervals."

In summary, the policy option under consideration is whether the recommendations should be changed to allow either Td or Tdap vaccine to be used in situations where only Td vaccine is currently recommended for the decennial booster, tetanus prophylaxis for wound management, and the catch-up immunization schedule, including in pregnant women. The proposed text has been presented for the policy option under consideration, and Dr. Havers invited input.

Discussion Points

Dr. Atmar pointed out that limb swelling 7 days after vaccination is entirely consistent with what has been observed and reported previously with acellular pertussis (aP) vaccines. It seems like this consideration is coming from a practical standpoint without a lot of safety information. The data presented are reassuring, but tens of thousands of people have not received this. He inquired as to whether the WG was unanimous in their endorsement of the recommendation.

Dr. Havers indicated that the WG was unanimous in their endorsement that either Td or Tdap should be allowed to replace Td. No one felt that the recommendations needed to stay the same. A couple of WG members favored a preferential recommendation for Tdap to replace Td. However, the WG as a whole felt that there was not enough evidence to support that.

Dr. Hunter said it makes sense that given the statistics showing how often Tdap is being used, they could assume that tens of thousands of people are already getting a second dose of Tdap. While this relies on a passive reporting system with VAERS, he found this reassuring as a WG member.

Dr. Frey recalled that they discussed in the past the number of children who are small for gestational age, and decided that this was not uncommon and it did not impact their thinking. She also inquired as to how much difference there was in the cost based on the economic analysis.

Dr. Bernstein recalled that there was a $10 price differential overall between the use of Tdap versus Td.

Dr. Havers noted that the CDC presented detailed economic analyses to the WG. The WG felt strongly that since they were not advocating for a preferential recommendation of Tdap over Td and that this change has been widely implemented, they were comfortable proposing this potential policy change regardless of the economic analysis and that it was not necessary to go into great detail during the full ACIP meeting. She shared the following table based on the CDC price list and commercial claims from MarketScan® for privately insured patients:

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Tdap is more expensive than Td

CDC Vaccine price list[1]	CDC cost per dose[2]	Incremental cost of Tdap over Td
Td (TDVAX™)[3]	$13.96	
Tdap (Boostrix®)[4]	$24.65	$10.68
Tdap (Adacel®)[4]	$24.49	$10.53
Commercial claims[5]	**Median cost**	
Td (n=61,468)	$27.38	
Tdap (n=716,638)	$44.07	$22.56

1. Source: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html, updated April 1, 2019
2. Indicates cost for 10 pack – 1 dose vial. 3. Vaccine cost includes $1.50 per dose Federal Excise Tax 4. Vaccine cost includes $2.25 per dose Federal Excise Tax 5. Source: Truven MarketScan databases, Outpatient Services Table, DY 2016

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To answer Dr. Frey's question about small for gestational age, Dr. Moro indicated that the reason they included the adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) was because these were the outcomes from a larger maternal Tdap safety study that already was published. At the time, these outcomes were of interest and also were included in the subgroup he presented of 187 women. That group was excluded from the larger study because they received multiple Tdap doses.

Dr. Messonnier clarified that Dr. Frey was asking whether there were data to show whether this number of adverse birth outcomes in this study is disproportionate compared to what would be expected in the general population not in the study.

Dr. Moro indicated that the rates were comparable to the background rates.

Dr. Havers added that they were asked to conduct a sub-analysis of the already published study in terms of closely spaced Tdap vaccines. In the sub-analysis of unpublished data, over 11,000 people received Tdap and then later received either Td or Tdap within 12 months of receiving their first Tdap. There was no difference in safety signals between those receiving additional Tdap versus those receiving additional Td. She expressed gratitude to Mike Jackson at Kaiser Permanente Northwest who performed this analysis specifically for the ACIP WG to evaluate this question.

Dr. Ault indicated that in terms of the pregnant population, he was representing the American College of Obstetricians and Gynecologists (ACOG) when they discussed Tdap the first time around 6 to 8 years ago. He was impressed with the amount of data there were from the 1940s, 1950s, and 1960s concerning pertussis-containing or tetanus-containing vaccines. This has been considered for a long time and also is the global norm for pregnant women to receive more than one dose of tetanus to prevent neonatal tetanus outside of the US.

Dr. Lee said she had wondered about the economic analysis as well, but in her mind it was more of a vaccine choice since it is not a preferential decision. In that case, she did not think an economic analysis was necessary.

Dr. Atmar asked whether they anticipated the extinction of Td use in this country if this recommendation is adopted and given that Tdap is being used widely already.

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Dr. Hunter said that based on his small experience in Milwaukee as a medical consultant to a local health department, Td would still be used in certain situations in clinics that are catching people up such as refugee clinics that administer multiple doses and have very strict cost restraints. His personal opinion is that for the average family or internal medicine clinic that is administering decennial boosters, it will be simpler to stock just one vaccine.

Dr. Baker (IDSA) noted that when Tdap was recommended for every pregnancy, there was a major ACIP discussion regarding safety because there were so little data. There are now robust data which demonstrate that Tdap is safe in pregnant women. One of the concerns was the arthus phenomenon. She asked whether Drs. Havers and Moro thought that the excessive limb swelling phenomenon in children and a few adults was an arthus phenomenon.

Dr. Moro indicated that arthus reactions are rarely reported in VAERS. From what he has seen in the VSD, it is rarely reported there as well.

Dr. Goldman (ACP) noted that from the internal medicine perspective and as a private practitioner, giving the Tdap every 10 years is practical. The purchasing cost is about the same, at least in the private sector, and this is what is being done now. Therefore, he is personally in favor of the recommended change.

Ms. Stinchfield (NAPNAP) commented that where she works at Children's Hospitals and Clinics of Minnesota, they saw some very severe cases of pertussis in their UCU this summer. At their critical care meeting the previous day, some of the extracorporeal membrane oxygenation (ECMO) national data were shared. For children with pertussis who go on ECMO, the survival rate is only 28%. Therefore, she is very supportive of adding Tdap to the recommendation.

Dr. Zahn (NACCHO) said that based on his local public health experience in Orange County in California, his gestalt was about the same as Dr. Hunter's that there would be a small but distinct utility for Td in the future. They receive the most questions about Td for healthcare workers (HCW) and people who will be around newborns. His presumption was that the proposed blanket recommendation would be for everyone, and that the WG was not considering particular groups.

Dr. Havers indicated that Dr. Weber from the Society for Healthcare Epidemiology of America (SHEA) is on the WG and that they specifically discussed whether HCW should be recommended to receive Tdap preferentially. She called upon Dr. Weber to elaborate.

Dr. Weber (SHEA) indicated that SHEA is very supportive of the recommendation. They think that virtually everyone will begin using Tdap in replacement of Td, so there is no need to call out healthcare personnel (HCP) specifically. The other issue is that the vaccine is not felt to be so protective. The recommendation is still to give antibiotic post-exposure prophylaxis. Based on those two issues, they did not feel the need to call out HCP and SHEA as a group is very supportive of this change.

Dr. Finley (AIM) indicated that state immunization programs follow ACIP guidance. When they have trouble following ACIP guidance, it creates a challenge. When they have said that providers need to carry Td, there has been waste following that and many do not want to carry it. The proposed recommendation would make life much easier for those providing guidance to primary care practitioners and others.

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Regarding Dr. Baker's comment, Dr. Talbot pointed out that adults occasionally have extensive limb swelling from certain vaccines, including aP. It is not a serious AE (SAE). It is uncomfortable, but has no long-lasting effects. It is important to recognize this so that when it does happen, they openly explain to their patients that this will resolve with no sequelae.

Dr. Havers posted the following proposed policy language for the vote:

- ❑ Recommendations should be changed to allow either Td or Tdap vaccine to be used in situations where only Td vaccine is currently recommended for:
  - Decennial Td booster
  - Tetanus prophylaxis for wound management
  - Catch-up immunization schedule, including in pregnant women

Dr. Bernstein made a motion to accept the 3 policy options as described, which Dr. Hunter seconded. No further discussion was offered and the vote was stayed until the voting session subsequent to the Public Comment period. The vote is included here for continuity.

Motion/Vote: Pertussis Policy Options

Dr. Bernstein made a motion to approve the proposed policy change to allow either Td or Tdap where only Td is currently recommended for the decennial Td booster, tetanus prophylaxis in the setting of wound management, and for additional doses of the catch-up immunization schedule for persons ≥7 years, including for pregnant women. Dr. Hunter seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot
0 Opposed:	N/A
0 Abstained:	N/A

VFC Pertussis Resolution

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

Dr. Santoli noted that yellow font/highlight in the presentation was used to indicate changes to the resolution in comparison to the prior approved version. She indicated that the purpose of this resolution was to update the language in the Tdap component of the resolution to be consistent with the most recent ACIP recommendations for routine and catch-up vaccination, as well as tetanus prophylaxis for wound management.

The eligible groups, Recommended Schedule and Intervals for the DTaP component, DTaP table notes, and Tdap Recommended Schedule and Intervals component were unchanged. The first Tdap table note is standard to make clear that what is said about brands is not meant to express any preference, the second note was updated to mirror the language in the ACIP recommendation, the third note was changed to reflect the language in the ACIP

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recommendation, the fourth note was not changed, the fifth table note was updated to use the same language as the ACIP recommendation and the addition of "Td or Tdap," the sixth note was not changed,

1) The use of brand names is not meant to preclude the use of other comparable licensed vaccines.

2) Persons aged 11–18 years should receive a single dose of Tdap, preferably at a preventive care visit at ages 11–12 years.

3) Catch-up immunization: Persons aged 7–18 years who have never been vaccinated against pertussis, tetanus, or diphtheria should receive a series of three tetanus and diphtheria toxoid-containing vaccines, which includes at least 1 dose of Tdap. The preferred schedule is a dose of Tdap , followed by a dose of either Td or Tdap at least 4 weeks afterward and another dose of either Td or Tdap 6 to 12 months later. Persons aged 7–18 years who are not fully immunized against pertussis, tetanus or diphtheria should receive 1 dose of Tdap (preferably the first) in the catch-up series; if additional tetanus toxoid–containing doses are required, either Td or Tdap vaccine can be used. The catch-up schedule and minimum intervals between doses are available at https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html

4) Adolescents who are pregnant should receive Tdap, irrespective of past history of Tdap receipt. Tdap should be administered from 27 through 36 weeks' gestation, preferably during the earlier part of this time period, although it may be administered at any time during pregnancy. If an adolescent did not receive Tdap during her current pregnancy and did not receive a prior dose of Tdap ever, then Tdap should be administered immediately postpartum. If an adolescent did not receive Tdap during her current pregnancy but did receive a prior dose of Tdap, then she should not receive a dose of Tdap postpartum.

5) Tetanus prophylaxis for wound management: A tetanus toxoid–containing vaccine is indicated as part of wound management if more than five years has passed since the last tetanus toxoid–containing vaccine dose. If a tetanus toxoid–containing vaccine is indicated for persons aged ≥11 years, Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus toxoid–containing vaccine is indicated for a pregnant woman, Tdap should be used. For nonpregnant persons with documentation of previous vaccination with Tdap, either Td or Tdap can be used if a tetanus toxoid–containing vaccine is indicated.

6) Td should be used if encephalopathy not attributable to another identifiable cause occurs within 7 days of administration of previous dose of pertussis-containing vaccine.

No changes were made to Recommended Dosages, Contraindications, and Precautions or the Statement Regarding Update Based on Published Documents.

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Discussion Points

Dr. Hunter made a motion to accept the wording for the VFC changes as presented, and Dr. Ault second the motion.

Motion/Vote: VFC Pertussis Policy

Dr. Hunter made a motion to accept the wording for the VFC changes as presented. Dr. Ault second the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot
0 Opposed: N/A
0 Abstained: N/A

Adult Immunization Schedule

Introduction

Paul Hunter, MD
Chair, Adult Immunization Work Group
Advisory Committee on Immunization Practices (ACIP)

Dr. Hunter described the immunization schedules as a tapestry woven from the threads of all of the individual recommendations on which ACIP votes and a quick way for clinicians, patients, and administrators to see what individuals need and how to put the pieces together. He reminded everyone that the Adult Immunization Schedule is presented for a vote every fall because ACIP's approval is necessary prior to publication of the schedule in February of the following year. In addition, the adult schedule is sent to the following partner professional medical organizations for approval:

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

New policy is not established in the proposed schedule; rather, the annual schedule reflects recommendations already approved by ACIP. In addition to bringing the threads together in the Adult Immunization Schedule, there is an effort to harmonize the Child/Adolescent and Adult Immunization Schedules.

Dr. Hunter indicated that for the remainder of this presentation, Dr. Freedman would discuss the proposed edits for the 2020 Adult Immunization Schedule. He explained that these edits are intended to incorporate ACIP recommendations and *Morbidity and Mortality Weekly Report* (*MMWR*) publications that have occurred since October 2018, and improve the readability and utility of the schedule into language that is easy to interpret for the busy provider. In addition to

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edits to improve harmonization with the Child/Adolescent Schedule, there are additional proposed edits to Tables 1 and 2. There are also content changes for the notes for the hepatitis A (HepA), human papillomavirus (HPV), pneumococcal, meningococcal, and Tdap.

2020 Adult Immunization Schedule

Dr. Mark Freedman
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Freedman indicated that the 2020 Adult Immunization Schedule has been updated to reflect recommendations published or voted upon since October 2018 including HepA vaccination for all persons living with human immunodeficiency virus (HIV) who are at least 1 year of age, HPV vaccination for all persons through age 26 and shared clinical decision making for those 27 through 45 years, updated language for MMR in HCP, shared clinical decision-making for pneumococcal conjugate vaccine-13 (PCV13) for immunocompetent persons 65 years and older, updated meningococcal recommendations, updated recommendations for the use of Tdap any time Td is indicated, and clarification of varicella indications for adults with HIV infection.

Changes that impact multiple portions of the schedule include minor edits throughout the notes section, which were made to improve harmonization between the Child/Adolescent and Adult Immunization Schedules. Minor wording edits were added to the footnote on the cover page to clarify there is no need to restart or add doses to a vaccine series if there are extended intervals between doses.

In terms of changes to Table 1, the Recommended Adult Immunization Schedule, the tetanus, diphtheria, and pertussis row now reads “Td or Tdap is an option for booster every 10 years” as presented earlier by Dr. Havers. The HPV row is combined in a single row reflecting the updated recommendation that HPV is now recommended for all adults through 26 years of age, and the blue color has been added indicating that consideration of HPV vaccination for persons 27 through 45 years is based on shared clinical decision-making. Within the pneumococcal conjugate row, the box for immunocompetent persons 65 years and older is now blue, indicating the updated recommendation for vaccination in this group is based on shared clinical decision-making.

Within the MenB row, a blue box has been added for those 19-23 years of age who are not at increased risk for meningococcal disease, which indicates the updated recommendation for vaccination in this group is based on shared clinical decision-making. A blue footnote key has been added indicating the vaccine is recommended on shared clinical decision-making, and the grey footnote key has been updated. The grey color indicates no recommendation/not applicable. Here is proposed Table 1 as described:

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Table 1 Recommended Adult Immunization Schedule by Age Group
United States, 2020

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV)	1 dose annually			
or	or			
Influenza live attenuated (LAIV)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td or Tdap booster every 10 yrs			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV) *(preferred)*			2 doses	
or			or	
Zoster live (ZVL)			1 dose	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination	27 through 45 years		
Pneumococcal conjugate (PCV13)	1 dose			65 years and older
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication			1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2 or 3 doses depending on vaccine			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Recommended based on shared clinical decision-making
No recommendation/ Not applicable

Regarding changes to Table 2, the Medical Indications Schedule, the tetanus, diphtheria, and pertussis row now reads, “Td or Tdap is an option any time a tetanus booster is recommended.” The HPV row is combined in a single row reflecting that HPV is now recommended for all adults through 26 years of age. In the HepA row, the box for all persons living with HIV at least 1 year old, regardless of CD4 count, is now gold, reflecting the new recommendation for this group. Lastly, the grey footnote key has been updated. The grey color indicates no recommendation/not applicable. Here is proposed Table 2 as described:

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications
United States, 2020

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200	HIV infection CD4 count ≥200	Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
IIV or RIV	1 dose annually										
or										or	
LAIV	CONTRAINDICATED					PRECAUTION				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 yrs									
MMR	CONTRAINDICATED	1 or 2 doses depending on indication									
VAR	CONTRAINDICATED	2 doses									
RZV *(preferred)*	DELAY				2 doses at age ≥50 yrs						
or					or						
ZVL	CONTRAINDICATED				1 dose at age ≥60 yrs						
HPV	DELAY	3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA					2 or 3 doses depending on vaccine						
HepB							2 or 3 doses depending on vaccine				
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT[3] recipients only			1 dose						

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
Delay vaccination until after pregnancy if vaccine is indicated
Contraindicated or not recommended —vaccine should not be administered because of risk for serious adverse reaction
No recommendation/ Not applicable

1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

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There are a few content edits in the *Notes* section. Within the HepA note, under *special situations*, an expanded definition of chronic liver disease (CLD) that is harmonized with the hepatitis B (HepB) definitions has been added. Additional indications for vaccination were added for persons with HIV infection and in settings for exposure, including health care settings targeting services to injection or non-injection drug users or group homes and non-residential day care facilities for developmentally disabled persons (individual risk factor screening not required). Lastly, clotting factor disorders has been removed as an indication for HepA vaccination.

Within the HPV note, under *routine vaccination*, HPV vaccination is recommended for all adults through age 26 years. Under *special situations*, for persons age 27-45 years, vaccination can be considered based on shared clinical decision-making.

Within the influenza note, under *special situations*, language for when live attenuated influenza vaccine (LAIV) is contraindicated has been reformatted into a bulleted list as shown here:

Special Situations

- **LAIV should not be used** in persons with the following conditions or situations:
    - History of severe allergic reaction to any vaccine component (excluding egg, see above) or to a previous dose of any influenza vaccine
    - Immunocompromised due to any cause (including medications and HIV infection)
    - Anatomic or functional asplenia
    - Cochlear implant
    - Cerebrospinal fluid-oropharyngeal communication
    - Close contacts or caregivers of severely immunosuppressed persons who require a protective environment
    - Pregnancy
    - Received influenza antiviral medications within the previous 48 hours

Language for vaccinating persons with a history of Guillain-Barré syndrome (GBS) within 6 weeks of previous dose of influenza vaccine now reads, “Generally should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza.”

Within the MMR section, under *special situations*, language for HCP has been clarified for those born in 1957 or later with no evidence of immunity to MMR and those born before 1957 with no evidence of immunity to MMR as shown here:

Special Situations

- **Health care personnel**:
    - **Born in 1957 or later with no evidence of immunity to measles, mumps or rubella**: 2-dose series at least 4 weeks apart for measles or mumps, or at least 1 dose for rubella
    - **Born before 1957 with no evidence of immunity to measles, mumps or rubella**: Consider 2-dose series at least 4 weeks apart for measles or mumps, or 1 dose for rubella

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Within the meningococcal note, under *special situations for MenB*, the new complement inhibitor ravulizumab was added to the list of indications for vaccination, guidance was added for MenB booster doses, and an updated recommendation was added for adolescent and young adults not at increased risk for meningococcal disease to be vaccinated based on shared clinical decision-making as listed here:

Special Situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, microbiologists routinely exposed to *Neisseria meningitidis***: 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- **Adolescents and young adults age 16 through 23 years (age 16 through 18 years preferred) not at increased risk for meningococcal disease**: Based on shared clinical decision-making, 2-dose series MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0, 6 months

Within the pneumococcal note, under *routine vaccination*, immunocompetent adults 65 years and older should receive 1 dose PPSV23 and 1 dose PCV13 is recommended based on shared clinical decision-making. The order of vaccines and spacing has not changed and is listed here:

Routine vaccination

- **Age 65 years and older** (immunocompetent): 1 dose PPSV23 is recommended. 1 dose PCV13 is recommended based on **shared clinical decision-making.**
    - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first
    - PCV13 and PPSV23 should be administered at least 1 year apart. PPSV23 should be administered at least 5 years after any previous PPSV23 dose
    - PCV13 and PPSV23 should not be administered during the same visit
    - Only 1 dose PPSV23 should be administered on or after the 65th birthday

Within the tetanus, diphtheria, and pertussis note, under *routine vaccination*, for those who previously did not receive Tdap at or after age 11 years, 1 dose Tdap then Td or Tdap every 10 years are recommended. Under *special situations*, those who previously did not receive primary vaccination series for tetanus, diphtheria, and pertussis should receive at least 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap, and another dose Td or Tdap 6-12 months after last Td or Tdap. Tdap can be substituted for any Td dose, but it is still preferred as the first dose. Td or Tdap can be given every 10 years thereafter. Information on the use of Td or Tdap as tetanus prophylaxis in wound management can be found at the listed web link.

Within the varicella note, under *special situations*, for persons with HIV-infection with CD4 counts of at least 200 cells/µL with no evidence of immunity, vaccination may be considered (2 doses, administered 3 months apart). This is just a clarification of the previous language.

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Discussion Points

Dr. Bernstein asked whether the statement "Previously did not receive primary vaccination series for tetanus, diphtheria, and pertussis" should read "or pertussis" rather than "and pertussis."

Dr. Freedman indicated that the language of the recommendation uses the word "and" and that he would check with Dr. Havers to determine whether it should be "and" or "or."

Ms. McNally expressed gratitude for the additional color to the schedule, observing that it adds clarity for consumers.

Dr. Lee thanked the WG for taking what turned out to be a very complex set of recommendations and trying to distill it. It was clear to her that the Adult Immunization Schedule is becoming increasingly complex. She indicated that she was still struggling with the implementation challenges, particularly with Table 2. She wondered how they could help sub-specialty providers who see primarily end stage renal disease (ESRD) or CLD ensure that these individuals are current on vaccines. Even though the schedule is distilled, it is still complicated to interpret. Going across, she appreciated the notes because the recommendations are clear from a vaccine-specific standpoint. However, from a population standpoint it is confusing for sub-specialists who are caring for these populations. She thought they should figure out how to partner with them to best protect these populations.

Dr. Sanchez requested further information about the contraindication for LAIV in those with cochlear implants.

Dr. Robinson clarified that there are some conditions outlined in the influenza notes that are not technically contraindications or precautions, but there is a lack of data on the use of LAIV in persons with those conditions. Cochlear implants falls within the groups in that paragraph.

Dr. Atmar had similar concerns about some of the other groups, such as those with asplenia. The guidance published earlier in 2019 notes that IDSA has made recommendations about some of these risk groups and that ACIP is gathering further information. It says "contraindicated" rather than "precaution," which bothered him.

Dr. Freedman clarified that the language that will be included in the schedule is, "LAIV should not be used." He inadvertently used the term "contraindication" in his discussion, which was misuse of the word. It is not listed as a specific contraindication.

Dr. Robinson noted that it appears in red on the table, which is why the legend for the red states "contraindicated or not recommended" because they did not want to introduce a new color to represent "should not be used." The color represents both of those scenarios.

Dr. Atmar pointed out that the guidance in the influenza recommendations notes that there have been concerns raised by other groups, but it does not state that it should not be used.

Dr. Kroger clarified that conditions that are contraindications also should not be used. They are labeled specifically as contraindications. Pregnancy is another contraindication specific to LAIV in the influenza statement. Cochlear implant is "should not be used." It makes sense that both conditions are listed on the schedule. They can double-check with influenza subject matter experts (SMEs) to ensure that the list is complete.

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Dr. Messonnier asked for clarification regarding whether the request was for more precision in the language to make clearer which conditions are considered “contraindications” and which are “should not be used.”

Dr. Talbot said she thought the concern was that there are HCW who refuse needles. LAIV is a major way that many hospitals vaccinate HCW. If there are any conditions for which there are not enough data or for which there is a precaution and a red box is used, no occupational health provider is going to give LAIV to that person who is a HCW. She thought an orange box would be the answer.

Dr. Messonnier noted that the issue seemed to be with how the influenza statement was being translated in the table and that the red color was a problem. They probably could not use orange because it is for precautions, but it seemed that another color was needed.

Dr. Cohn suggested that perhaps they could use orange with dots so that it was not in color but signified a difference.

Dr. Romero emphasized that this was further adding to the complexity of the reading of this document. Not all of this information can be transmitted through the table alone, which is why the notes are an integral part of the document.

Dr. Hunter stressed that they should be considering how to translate something already written upon which ACIP already had voted into the schedule, rather than trying to go back to change the actual recommendation.

Dr. Baker (IDSA) said she thought she heard someone say that the IDSA agrees with the contraindication for cochlear implants; however, she was unaware that this is true. She agreed with the conversation underway and emphasized that a contraindication should be for an immunocompromised person, which pregnant women are assumed to be for live vaccines due to the theoretical risks. For cochlear implants or even asplenia for influenza vaccines, she thought if there is a contraindication, this should be stated. Otherwise, it should be a precaution with dots or whatever they decide. The 2020 influenza statement should be consistent with the table.

Dr. Sanchez agreed because to him “should not be used” is the contraindication. If they do not have the data, that should be stated rather than saying that something is a contraindication.

Dr. Messonnier emphasized what Dr. Hunter reminded them of earlier, which was that this is about translating the recommendations upon which ACIP already voted into a statement. In the influenza statement on Table 2, under LAIV, there was a column with the statement “Contraindications and Conditions for Which Use is Not Recommended.” In order to change that, they would have to revote on the influenza statement, which was not up for consideration during this session. As a point of order, she suggested that they pause in order to obtain the precise language to compare to the recommended immunization schedule.

Dr. Weber (SHEA) pointed out that throughout the conversation, he heard people using the terms HCW and HCP interchangeably. SHEA feels strongly that the correct term is HCP, because it is important to remember that while students and volunteers are not workers, they do believe in protecting them as well. The ACIP in general has adopted HCP.

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To address Dr. Messonnier's comments, Dr. Lee wondered whether they could change the red box to state "contraindicated or not recommended." She also observed that flipping between Tables 1 and 2, it was clear that yellow were universally recommended vaccines by age group or by condition. However, because the purple was the same color, it was confusing to go back and forth between the two because it represented a risk-based or high-risk condition in Table 1 and an additional risk-based condition in Table 2. She worried that some people would be confused. For example, someone with ESRD and diabetes would default to yellow. In addition, the adult pneumococcal vaccines are some of the most complex recommendations. She realized that unlike the other vaccines, this is recommended in series of PCV13 + PPSV23 for people at high-risk or PPSV23 if someone has a risk condition. She wondered if it would help to clarify those two options by having PCV13 + PPSV23 on one line and PPSV23 on the second line rather than having just PCV.

Dr. Hunter said he would be very happy if specialists were looking vertically on Table 2 and were vaccinating more than they are, given that the majority of people who have specialist indications are not receiving their vaccines in primary care and public health settings. That is a struggle that those who educate clinicians have, and this is a systemic issue in that it is very difficult to carry vaccines. When that is not the majority of what specialists do, it is very difficult to keep that in mind. While he agreed with Dr. Lee's observation about this, he did not see a quick way of addressing it.

Dr. Messonnier pointed out that one of the things they have tried to work on with ACIP over the past couple of years was to try to differentiate ACIP's role from the role of the people who must implement the recommendations. Some members cross those lines because of their jobs. The schedule is a place where this tension is observed, because they are trying to fit the schedule into a way that gets toward implementation. CDC completely appreciates all of the feedback, but she was not sure that they could arbitrate this around the schedule itself. The schedule and decision-making are getting increasingly complex, and CDC and its implementation partners need to get more sophisticated at providing the tools that clinicians need to make it easy for them to do the right thing. That said, one of the tensions is that on one hand, they wanted the schedule simplified. However, on the other hand, some of the requests would make it more complex. They could add to the box that says "Contraindicated" the same language in the footnote that said, "Contraindicated or Not Recommended." It would make the words in the red box squishier, but it could be done if ACIP thought it was a better conveyance of what they meant. She thought it would be helpful to hear whether folks agreed with Drs. Lee and Talbot that the word "contraindicated" would be such an impediment to clinicians that it would be worth the extra complexity to add more words into the box.

Dr. Romero said that as the previous Chair of the Child/Adolescent WG and sitting on that WG, they were tasked with stripping the schedule to make it as compact as possible. They still spend a great deal of time doing that, and were now being asked to expand it again to fill the void they created by cutting down on the verbiage. He stressed that they could not have it both ways and must make a decision about what they wanted.

Dr. Lee emphasized that for some of the high-risk populations into which they were delving, sub-specialists have multiple points of contact with these individuals who do not necessarily see anyone in primary care. In addition, there is sometimes a reluctance if there is not a good understanding of where a patient is in the course of his or her disease. People can go under-vaccinated for long periods of time. As they begin to move into a more complex area, she said she would push them to think about how to avoid those missed opportunities. While she

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completely agreed with Dr. Messonnier's point about recommendations versus implementation, part of that relates to the implementation section of the EtR Framework.

Dr. Atmar thought the issue was the disagreement as to what the recommendations actually say as related to LAIV. He looked at the table and text of the recommendations and found that the language for some groups states that because there are no data, ACIP recommends recombinant influenza vaccine (RIV) or inactivated influenza vaccine (IIV) for these patients. It does not say that that LAIV is not indicated specifically. As Dr. Talbot noted, there may be some circumstances in which an injection may not be desired by the recipient, LAIV is an option, and there is not a safety issue.

Dr. Hunter reiterated that in his understanding and experience, subspecialists are not carrying vaccines in their practices and generally are not vaccinating.

Speaking as a subspecialists, Dr. Romero reported that every child who presents to their clinic has an extensive review of their immunizations based on the state health immunization record. Those vaccines that are deficient are available for and given to those children who need them.

Dr. Middleman (SAHM) noted that if Table 1 was supposed to be harmonized with the way that the Child/Adolescent Immunization Schedule worked, it was very difficult for her to understand how an annual influenza vaccine that should be given to everyone was the same color as the MMR vaccine, which would be considered a catch-up vaccine recommendation in childhood and adolescence. For her, the fact that there was no distinction between what should be given on a routine basis to adults versus what is being given to someone who perhaps has not had a vaccine or lacks documentation of a vaccine is problematic and separates the use of the Adult from the Childhood/Adolescent Immunization Schedule. She thought it was important to rethink the use of the colors and legends at the bottom of the tables. At the bottom of Table 2, purple stated, "Recommended vaccination for adults with an additional risk factor." It was not clear whether that meant an additional risk factor to diabetes if looking at diabetes, or if it meant with that risk factor. She thought the legends and colors could be better clarified.

Dr. Cohn noted that this issue comes up every couple of years. She thought that all of the points were good and emphasized that it could be difficult when only talking about it in October to decide on the schedule for the next year. She suggested that for next year, they could talk about some of these issues in meetings prior to October so that they could be discussed more and resolved prior to the next schedule.

In terms of the tension between increasing complexity, missed opportunities, and simplification, Dr. Bell emphasized that they were looking at a piece of paper. While the piece of paper is important because it hangs on bulletin boards everywhere, there are many other opportunities to make ACIP's messages clear on people's phones, tablets, et cetera to avoid missed opportunities. Perhaps for the future they could more explicitly direct people to tools that could reflect this type of complexity.

Dr. Goldman (ACP) pointed out that those in individual private practice who want to vaccinate patients are going to learn and understand the schedule. While from the public health perspective they want to make the schedule as easy as possible, they could not let the "perfect be the enemy of the good." After the learning curve, he found the schedule to be easy to read and digestible and liked it the way it was presented. While individual specialists may not learn it, the health system will learn the schedule and vaccinate from the specialty perspective. He

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stressed that there is going to be a learning curve, and that they cannot just “spoon feed” everyone.

Speaking as practicing physician, Dr. Fryhofer (AMA) complimented the WG on all of the time that went into developing the schedule. The way she looked at it was that the schedule is meant to draw one in rather than being the end-all. There also are the notes and the full recommendation. If too much writing is added to the schedule, people will not look at it. She emphasized that everyone should enter their immunizations into the immunization system so that they all know what their patients need. She still sees patients in her primarily adult practice who were not vaccinated with MMR. Having it in yellow is a reminder that this is something important that people need. She agreed with Dr. Atmar that they need to get the details about LAIV worked out. Her office has standing orders for influenza vaccine. She does not want to give a patient the wrong vaccine and have a problem, but she would appreciate clarification as a practicing doctor. However, she did not think working on this schedule during this session was the time to address this.

Dr. Bernstein reminded everyone that the Adult and Child/Adolescent Immunization Schedules are trying to translate the actual policy. They are not creating policy. To echo what Dr. Atmar said, it is important to utilize the language specifically used in the current policy. Referring to the pneumococcal note, under *routine vaccination*, he thought the third bullet should be the first bullet. He thought it was important to first emphasize that they should not be administered during the same visit and that they should be a year apart.

Dr. Messonnier said it sounded like the biggest tension pertained to the language regarding LAIV. She requested that they contact the Influenza WG Chair so that they could check the language to ensure that they could justify the way it was presented. Regarding harmonization between the Adult and Child/Adolescent schedules and in thinking about how the word “contraindicated” on the Adult schedule was disconcerting, she checked the Child/Adolescent schedule. In Table 3 in the Child/Adolescent schedule, there are not words. She asked whether people preferred that the words be removed from the bar in the Adult schedule as well. It would be harmonized and also would offer the opportunity to direct people to look at the language underneath, which makes a clearer case for whether it is contraindicated or not recommended. Perhaps they also could switch the order so that “not recommended” appeared first.

Dr. Talbot thought that would help a lot and as long as it was truly contraindicated if it was in red.

Dr. Hunter recommended keeping the text in the yellow and purple boxes to prevent people from having to go to the notes.

Dr. Robinson suggested removing the “contraindicated, precaution, and delay” portions for those and leave the additional information in the rest of the boxes as it appeared.

Dr. Hunter suggested that they should review the table with all of the proposed changes incorporated before moving forward with a vote.

Dr. Cohn suggested also moving the formal vote to the next morning in order to incorporate all of the changes for ACIP’s review prior to voting.

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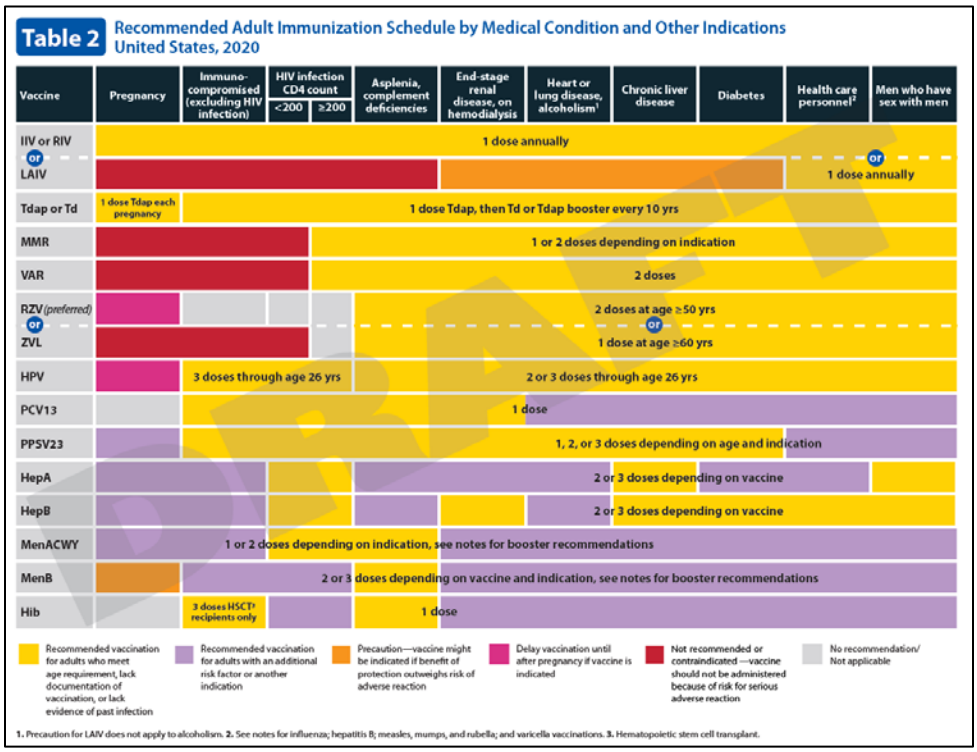
Revised Adult Immunization Schedule

Dr. Mark Freedman
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

On the second day of the meeting, Dr. Freedman highlighted the changes made to Table 2, the Medical Indications Schedule, based on the previous day's deliberations. This is the revised version of the table after the text from within the boxes for red (contraindication), orange (precaution), and pink (delay until after pregnancy), with the text for the red color key modified to read, "Not recommended or contraindicated – vaccine should not be administered because of risk for serious adverse reaction." In addition, the wording was removed from the boxes:



Some content edits also were made in the Notes section based on the previous day's comments. Within the HPV note, a new *Shared Clinical Decision-Making* subsection was created. The text in this block was the same that was previously under *Special Situations* the previous day, and describes the recommendation for persons 27-45 years. They are recommended to receive 2 or 3 doses based on shared clinical decision-making, with the number of doses dependent on age at initiation of vaccination or underlying medical condition:

Shared Clinical Decision-Making

- **Age 27-45 years based on shared clinical decision-making**: 2- or 3-dose series as above

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Within the meningococcal note under a new *Shared Clinical Decision-Making* subsection for MenB, only the text related to the recommendation on shared clinical decision-making was moved. The other recommendation regarding booster doses would remain under *Special Situations.* The new complement inhibitor, ravulizumab, was added to the list of indications for vaccination, and guidance was added for a MenB booster dose 1 year after primary series completion and to revaccinate every 2-3 years as long as the risk remained. The updated recommendation was added for adolescents and young adults not at increased risk for meningococcal disease to be vaccinated based on shared clinical decision-making:

Shared Clinical Decision-Making for MenB

- **Adolescents and young adults age 16 through 23 years (age 16 through 18 years preferred) not at increased risk for meningococcal disease**: Based on shared clinical decision-making, 2-dose series MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0, 6 months

Within the pneumococcal note, under the new *Shared Clinical Decision-Making* subsection, immunocompetent adults 65 years and older should receive 1 dose PPSV23. 1 dose PCV13 is recommended based on shared clinical decision-making. The 3 sub-bullets were reordered as shown here:

Routine vaccination

- Only 1 dose PPSV23 should be administered on or after the 65th birthday

Shared Clinical Decision-Making

- Age 65 years or older (immunocompetent): 1 dose PCV13 is recommended based on shared clinical decision-making.
    - PCV13 and PPSV23 should not be administered during the same visit
    - If both PCV13 and PPSV23 are to be given, PCV13 should be administered first
    - PCV13 and PPSV23 should be administered at least 1 year apart. PPSV23 should be given at least 5 years after any previous PPSV23 dose

Discussion Points

Dr. Fryhofer (AMA) said that speaking as a practicing physician, Table 2 is like an introduction and is a “go to” document. She thought that removal of the writing was a disadvantage for practicing physicians or physicians trying to do a quick check. If the schedule is printed in black and white or a printer is low on ink, it may not be possible to discern the colors. Therefore, she advocated for replacing the wording.

Dr. Atmar was still troubled by the terminology for the red box. For some of the vaccines, such as LAIV, the issue was not due to a recognized risk for SAEs. It was putatively because there were no data, at least at this time this was reviewed several years ago by the WG. He reminded everyone that the LAIV statement says that RIV or IIV should be administered. It does not say “Do not administer.”

Dr. Kroger clarified that the influenza statement lists a number of conditions that are immunosuppressive. There also is another discussion about what conditions should be considered immunosuppressive. For the influenza statement, cochlear implants and CSF leaks are listed under the header of *Immunosuppression*. In the table, immunosuppression is listed as a contraindication. That is the logic by which this decision was made.

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Dr. Atmar maintained that the logic was flawed and that this should be revisited. Another inconsistency in the Child and Adolescent Immunization Schedule is that the only live-attenuated vaccine for which there is a red box is LAIV, which is somewhat inconsistent as well.

Dr. Lee requested clarification for the definition of “contraindication” as it relates to what is listed on the package insert versus ACIP’s definition, and whether it was acceptable to be inconsistent.

Dr. Kroger replied that FDA and ACIP have not always been 100% consistent historically. However, there is a sentence in *General Best Practices* that states, “A contraindication (increases the risk of an adverse reaction) . . .”

Dr. Messonnier said she thought that the larger issue was that they needed a longer conversation regarding whether ACIP using language differently from FDA is inadvertently confusing, for which they did not have ample time during the remainder of this meeting.

Dr. Fink (FDA) added that FDA would agree that in situations where the same language is used to define different sets of circumstances than appear in the published inserts is confusing.

Dr. Bernstein recalled that someplace in the tables there was a suggestion that the interpretation of the tables also should include a review of the notes. Given that, he wondered whether the language after “Not recommended” or “Contraindicated” was even needed. Perhaps that could be shortened since people are supposed to read the notes as described on the first page of the schedule.

Dr. Cohn reminded everyone that they could vote to approve the general schedule for next year, and that there still would be an opportunity for the members to review the schedule before it moves forward in terms of small language changes. Because the goal is to try to interpret policy, some of the issues will be worked on throughout the process of production and in terms of next year’s general schedule for issues that cannot be addressed this year. She emphasized that they were voting to approve the general schedule—not every detail.

Dr. Kroger added that there would be 1 to 1.5 weeks before the schedule would go to the Director.

Dr. Lee suggested describing MMR and Varicella on Table 1 in the adult schedule at “Catch-Up.”

Dr. Freedman indicated that “Catch-Up” is not a term that is typically used for adults because if they are not vaccinated, they just need the vaccine. Therefore, it is recommended as a general recommendations rather than a catch-up vaccine.

Dr. Lee asked whether if an adult is already vaccinated they would be given another round of vaccines.

Dr. Freedman replied that they would not unless there is some additional risk, such as an outbreak setting.

Dr. Messonnier pointed out that one problem is that people use these schedules very differently. As a result, there could be as many tweaks as people. She asked whether ACIP could at least come to consensus about whether they wanted the words on or off of the colors.

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Dr. Cohn added that since the word “contraindication” seemed to be problematic, perhaps one option would be to use the phrase “not recommended.”

Dr. Szilagyi agreed with that suggestion and said that, as a clinician, he liked the words on the color.

Dr. Hunter moved to approve the schedule as shown, with the exception of reinserting the words and instead of “contraindicated” using “not recommended” in the red boxes.

Dr. Romero reiterated that the changes would be made based on the vote and would be distributed to the ACIP members for a final review.

Motion/Vote: Adult Immunization Schedule

Dr. Hunter made a motion to approve the schedule as shown, with the exception of reinserting the words over the colors and using the phrase “not recommended” instead of “contraindicated” in the red boxes. Dr. Bell seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot
0 Opposed:	N/A
0 Abstained:	N/A

Child and Adolescent Immunization Schedule

Introduction

Henry Bernstein, DO, MHCM, FAAP
Chair, Child and Adolescent Immunization Schedule WG
Professor of Pediatrics, Zucker School of Medicine at Hofstra/Northwell
Cohen Children’s Medical Center New Hyde Park, New York

Dr. Bernstein introduced this session on behalf of the Child and Adolescent Immunization Schedule WG. He first took a brief moment to recognize one of the WG’s CDC contributors, Dr. Raymond Strikas, who is retiring later this year. In his over 30 year career, Dr. Strikas has had the opportunity to work on different subject areas. Luckily, he has had worked with ACIP for the last 7 years. During this time, he served as CDC lead for the Child and Adolescent Immunization Schedule WG for 2 years; was a contributing member of the Adult Immunization Schedule, Zoster, and Pneumococcal WGs; and briefly served as acting ACIP Secretariat. Dr. Bernstein said that he first had the privilege of learning of Dr. Strikas in 1986 when he was a fellow in the laboratory of a polio virologist. Dr. Strikas’s original first paper out of the CDC, *Temporal and Geographic Patterns of Isolates of Nonpolio Enterovirus in the United States, 1970-1983*, has stood the test of time. It served then and still serves today as the reference point for this particular topic, is cited in numerous articles, and is a major contribution of the

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epidemiology of this disease. It is very germane currently in the face of the acute flaccid myelitis (AFM) epidemic. Dr. Bernstein thanked Dr. Strikas for everything that he has done, for the work that he has contributed, and for his lasting legacy and offered him best wishes for an awesome retirement.

In terms of the Child and Adolescent Immunization Schedule, Dr. Bernstein reminded everyone that the schedule is presented for a vote every fall because ACIP's approval is necessary prior to publication of the schedule in February of the following year. ACIP approval also is necessary before its partners (AAP, AAFP, ACOG, and ACNM) review and approve the schedule. Of note, this is the first year that the ACNM will be listed as an approving organization for the Child and Adolescent Immunization Schedule. ACIP welcomes them and their input. As a reminder, no new policy is established by this schedule; rather, it reflects a summary of ACIP recommendations.

Dr. Bernstein indicated that for the remainder of this presentation, Dr. Robinson would discuss the proposed edits for the 2020 Child and Adolescent Immunization Schedule. These edits are intended to incorporate ACIP recommendations and *MMWR* publications that have occurred since October 2018, and improve readability and utility of the schedule into language that is easy to interpret for the busy provider. He noted that Dr. Robinson's presentation would highlight proposed edits to Tables 1, 2, and 3 as well as content changes or clarifying edits for multiple notes (DTaP, Hib, HepA, HepB, Influenza, MenACWY, MenB, Polio, and Tdap). He explained that the session would conclude with discussion of the proposed edits and a vote for both the child/adolescent and adult schedules.

2020 Child and Adolescent Immunization Schedule

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

Dr. Robinson reviewed the updates for the 2020 Child and Adolescent Immunization Schedule. This is a list of the ACIP votes relevant to the Child and Adolescent Immunization Schedule that have occurred since the October 2018 ACIP meeting. Content edits based on the recent votes for HepA, MenB, and Tdap vaccines were discussed by the WG group and incorporated into the proposed 2020 schedule. Clarifying edits for the influenza note also were incorporated into the proposed schedule:

- Influenza vaccination (June 2019)
  - 2019–20 Influenza vaccine recommendations
- Hepatitis A vaccination (June 2019)
  - Recommendation for routine catch-up vaccination for all children and adolescents age 2 through 18 years
- Meningococcal B vaccination (June 2019)
  - Recommendation for booster doses for those at increased risk
- Tdap vaccination (October 2019)
  - Vaccination of persons who received Tdap at 7–10 years of age
- Edits to tables and notes of other vaccines as needed for clarity

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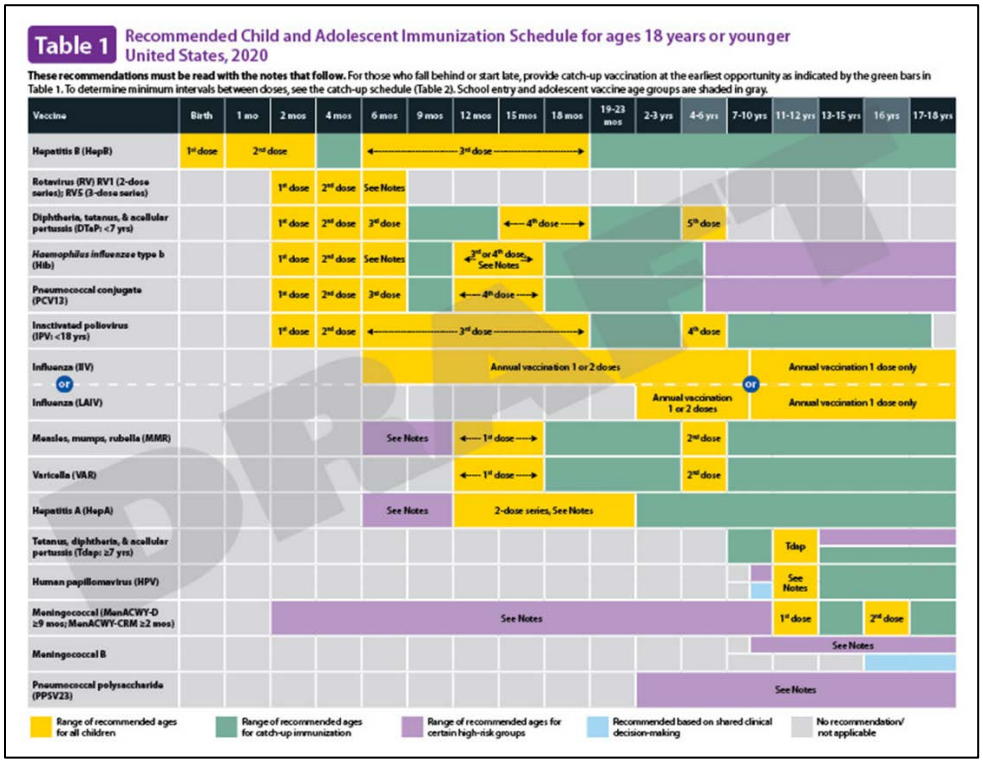
On the cover page, ACNM has been added as an approving organization for the Child and Adolescent Immunization Schedule.

For Table 1, in the HepA row, the bar representing vaccination for those 2 through 18 years has been changed from a split purple and green bar to solid green bar. This denotes the recommendation for routine HepA catch-up vaccination for all children and adolescents through 18 years of age. The MenACWY row has been moved to appear just above the MenB row.

Within the legend, the texts for the blue and gray boxes have been edited. The blue box now reads “Recommended based on shared clinical decision-making” and the phrase “not applicable” has been added to the gray box. The legend for these colors is harmonized with the Adult Immunization Schedule:



There is one minor edit for Table 2. “ACWY” has been added next to “Meningococcal” to clarify that these catch-up recommendation apply only to MenACWY and not MenB:

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Table 2 Recommended Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who are More Than 1 month Behind, United States, 2020

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with Table 1 and the notes that follow.**

Children age 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days.	4 weeks	4 weeks Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	4 weeks	4 weeks	6 months	6 months
Haemophilus influenzae type b	6 weeks	No further doses needed if first dose was administered at age 15 months or older. 4 weeks If first dose was administered before the 1st birthday. 8 weeks (as final dose) If first dose was administered at age 12 through 14 months.	No further doses needed if previous dose was administered at age 15 months or older. 4 weeks If current age is younger than 12 months *and* first dose was administered at younger than age 7 months, *and* at least 1 previous dose was PRP-T (ActHib, Pentacel, Hibativ) or unknown. 8 weeks *and* age 12 through 59 months (as final dose) If current age is younger than 12 months *and* first dose was administered at age 7 through 11 months; OR If current age is 12 through 59 months *and* first dose was administered before the 1st birthday, *and* second dose administered at younger than 15 months; OR If both doses were PRP-OMP (PedvaxHIB; Comvax) *and* were administered before the 1st birthday.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	No further doses needed for healthy children if first dose was administered at age 24 months or older. 4 weeks If first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) If first dose was administered at the 1st birthday or after.	No further doses needed for healthy children if previous dose administered at age 24 months or older. 4 weeks If current age is younger than 12 months and previous dose given at <7 months old. 8 weeks (as final dose for healthy children) If previous dose given between 7-11 months (wait until at least 12 months old); OR If current age is 12 months or older and at least 1 dose was given before age 12 months.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	4 weeks	4 weeks if current age is <4 years. 6 months (as final dose) if current age is 4 years or older.	6 months (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	4 weeks			
Varicella	12 months	3 months			
Hepatitis A	12 months	6 months			
Meningococcal ACWY	2 months MenACWY-CRM 9 months MenACWY-D	8 weeks	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal ACWY	Not Applicable (N/A)	8 weeks			
Tetanus, diphtheria, tetanus, diphtheria, and acellular pertussis	7 years	4 weeks	4 weeks If first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) If first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	Routine dosing intervals are recommended.			
Hepatitis A	N/A	6 months			
Hepatitis B	N/A	4 weeks	8 weeks *and* at least 16 weeks after first dose.		
Inactivated poliovirus	N/A	4 weeks	6 months A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	4 weeks			
Varicella	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

Within Table 3, the vaccination by medical indication table, the columns within the HepA row have been changed to all yellow to denote that routine vaccination is recommended irrespective of medical indication. As in Table 1, the MenACWY row has been moved to appear just above the MenB row. Additionally, the pregnancy column of the MenACWY row has been changed from purple to yellow. This is to indicate that pregnancy is not deemed a reason to withhold the recommended adolescent dose of this vaccine, and that routine vaccination should be administered if indicated. Lastly, the legend for the gray box has been modified to add "not applicable" to be consistent with the legend for Table 1:

Table 3 Recommended Child and Adolescent Immunization Schedule by Medical Indication United States, 2020

Always use this table in conjunction with Table 1 and the notes that follow.

VACCINE	INDICATION									
	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count[1]		Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease	CSF leaks/ cochlear implants	Asplenia and persistent complement component deficiencies	Chronic liver disease	Diabetes
			<15% and total CD4 cell count of <200/mm3	≥15% and total CD4 cell count of ≥200/mm3						
Hepatitis B										
Rotavirus		SCID[2]								
Diphtheria, tetanus, & acellular pertussis (DTaP)										
Haemophilus influenzae type b										
Pneumococcal conjugate										
Inactivated poliovirus										
Influenza (IIV)										
or										
Influenza (LAIV)						Asthma, wheezing: 2-4yrs[3]				
Measles, mumps, rubella										
Varicella										
Hepatitis A										
Tetanus, diphtheria, & acellular pertussis (Tdap)										
Human papillomavirus										
Meningococcal ACWY										
Meningococcal B										
Pneumococcal polysaccharide										

Vaccination according to the routine schedule recommended; Recommended for persons with an additional risk factor for which the vaccine would be indicated; Vaccination is recommended, and additional doses may be necessary based on medical condition. See Notes; Contraindicated or use not recommended—vaccine should not be administered because of risk for serious adverse reaction; Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction; Delay vaccination until after pregnancy if vaccine indicated; No recommendation/ Not applicable

1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the General Best Practice Guidelines for Immunization "Altered Immunocompetence" at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Table 4-1 (footnote D) at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.
2 Severe Combined Immunodeficiency
3 LAIV contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months.

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In terms of relevant edits to the notes section, within the DTaP note, language has been added to clarify the circumstances under which a 5th dose of DTaP is not necessary. The addition of the highlighted language is also harmonized with similar language that appears in other notes with catch-up guidance, including the polio note. Within the Hib note, a bullet has been added to clarify that catch-up vaccination is not needed for previously unvaccinated children age 60 months and older who are not at high risk of Hib disease.

Within the HepA note, a bullet has been added to the catch-up vaccination section to reflect the recommendation for routine catch-up vaccination of all children and adolescents 2 through 18 years of age who have not previously received HepA vaccine. Additionally, the *Special Situations Section* has been removed as all persons recommended to receive vaccination through 18 years irrespective of other indications. Within the HepB vaccination note, a *Special Situations Section* has been added. This section outlines the groups for whom revaccination may be recommended and refers to the HepB ACIP recommendations for additional details.

The influenza note has been reformatted to more clearly present the recommendations of which children are recommended to receive 2 doses of influenza vaccine and which children are recommended to receive 1 dose of influenza vaccine. Additionally, the section of the influenza note that outlines the situations under which LAIV should not be used has been reformatted to present this information in an easier to read, bulleted list.

Within the *Special Situations Section* of the MenACWY note, the term “complement inhibitor use” will be used where relevant to refer to all medications in this class such as eculizumab and ravulizumab. Also, information has been added to this section which outlines the recommendations for adolescent vaccination of children who received MenACWY prior to age 10 years. The sub-bullets outline the recommendations for children in whom booster doses are not recommended and those in whom booster doses are recommended. Within the MenB notes, a reference to the *MMWR* publication for the booster doses recommendations has been added. This harmonizes the presence of similar recommendations in the MenACWY note.

The “inactivated poliovirus vaccination” note has been renamed “poliovirus vaccination” as the note also contains information regarding oral polio vaccine (OPV). The note will be moved to the appropriate alphabetical place within the notes section. In addition, detailed information regarding which doses of OPV can count as trivalent OPV (tOPV) has been added.

Within the Tdap note, “or Tdap” has been added as a place holder as a vaccine option for booster doses and pending an ACIP vote. Finally, clinical guidance for children who received Tdap or DTaP between 7-10 years of age has been added to the note as mentioned in the earlier Tdap session by Dr. Havers.

Discussion Points

Dr. Hunter noted that for the Adult Immunization Schedule, MenACWY in pregnancy is purple. However, Dr. Robinson indicated that the MenACWY box would be changed in the Child and Adolescent Schedule from purple to yellow.

Dr. Robinson explained that for children, there is a routine recommendation for MenACWY at adolescent age. In those instances, pregnancy would not be considered a reason to withhold the vaccination. However, for adults, there is no routine MenACWY recommendation. It is all indications-based.

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Dr. Poehling said she liked how in Table 3 the MenACWY and MenB are placed together. She wondered whether it would be possible to include HepA and HepB together in Table 3 as well.

Dr. Robinson explained that the order of Table 3 is based on the order of Table 1. The reason that HepA and HepB are separated is that the goal was to have a progression in the yellow boxes from the first recommended vaccine and down through the adolescent vaccines to enable the reader to follow along from left to right. However, consideration could be given to moving HepB if ACIP felt passionate about this.

Dr. Talbot said that on Table 3, she would have placed Tdap right under DTaP to indicate a change based on a medical condition.

Recalling Dr. Lee's point about the difficulty in the adult schedule on Table 2, Dr. Bell noted that there were longitudinal lines on Table 3 in the Child and Adolescent Schedule. She wondered whether it would be possible to do that on the adult schedule as well. This would make it somewhat easier to look down a column.

Dr. Robinson noted that Dr. Freedman gave this a "thumbs up."

Dr. Eckert (ACOG) asked for further information about the shared clinical decision-making for HPV vaccine for 9 year olds.

Dr. Robinson indicated that for Table 1, when the box was originally introduced for 9 to 10 year olds, it was purple. This was the recommendation for a high-risk child. It is known that for HPV, those who have been victims of sexual abuse or assault are definitely recommended to receive it at 9 to 10 years of age. However, they received feedback that it also made it seem like the HPV vaccine could not be used routinely in 9 year olds. The HPV notes are clear that the series can be started at age 9 if indicated. This box was placed to denote that the high-risk indication is not needed to start the vaccine at age 9. This is consistent with the ACIP recommendation.

Dr. Lee suggested that for simplicity, it would be great to think about other opportunities for harmonizing the adult and child/adolescent schedules. She noticed the wording was slightly different for the same color across the two schedules.

Dr. Robinson responded that they could consider how to best harmonize those while keeping the intent as it should be for both schedules.

Dr. Kimberlin (AAP) said that while he realized it could not be done across the entire table, to channel Dr. Larry Pickering, whether the dash signifies "to" or "through" should be clarified. Perhaps as statement could be may someplace in the document to signify that a dash is inclusive of the year that follows the dash.

Dr. Robinson indicated that in the *Additional Information* section, there is a bullet stating that a dash should be interpreted as "through." They could further expand upon that if needed.

Dr. O'Leary (PIDS) pointed out that they seemed to be going down a "slippery slope" of increasing shared clinical decision-making. In all of the other cases, this was voted upon at ACIP. In the case of HPV, AAP recommends vaccination at this age. CDC sort of recommends vaccination. However, it is not in specifically in the language that it is shared clinical decision-making. He thought that yellow might be better than shared clinical decision-making.

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Along those lines, Dr. Bernstein said he thought that would perhaps be revisited at some point. Different groups have different recommendations pertaining to HPV vaccine recommendations. He emphasized that ACIP was creating the schedule not to make policy, but rather to reflect current ACIP recommendations. The intent of the addition of the blue area was to point out to people that it is an opportunity to give the HPV vaccine at an earlier age, but it is not a yellow recommendation and that is not the current ACIP policy. Rather than including a lot of text in the Child and Adolescent Immunization Schedule notes, the links to the text have been included. That might be helpful in the Adult Immunization Schedule as well, because there seemed to a lot of narrative in the notes in the adult schedule, some of which could be abbreviated by including the links.

Dr. Cohn emphasized that they were trying to be consistent with having the blue acknowledge where they specifically voted for shared clinical decision-making. There are other places in the schedule that say “you may do this” or “you may do that” from prior to implementing the EtR Framework. They should further consider what the most consistent color should be for that specific recommendation.

Dr. Messonnier called upon the CDC Lead for the Influenza Vaccines WG to answer the question pertaining to cochlear implants.

Dr. Grohskopf explained that cochlear implants and persistent cerebrospinal (CSF) fluid-oropharyngeal communication are considered what CDC calls a “do not recommend,” which equals contraindications. Several years ago, it became apparent that there were only two label contraindications for LAIV use that are in the package insert: salicylate and aspirin use and severe hypersensitivity or anaphylaxis. However, they have said not to use LAIV for other conditions for a number of years. It was suggested to them after discussions with several other groups that they have a concise table with a column of contraindications, that also includes conditions in which LAIV should not be used. Immunocompromised conditions are included in there. While the column does not specifically list cochlear implants or persistent CSF oropharyngeal communication, these are noted in the text. For next season, one thing they could do would be to add those two conditions specifically to the table. They are considered a breach of immunity and is why they are in the “do not recommend” category.

Regarding the suggestion about included more white lines on the adult schedule, Dr. Fryhofer (AMA) pointed out that there are a lot of single doses. It was not clear whether this would make it easier or more complicated, but she wants things to be easy.

Dr. Coyle (AIRA) said she did not see anything in the HPV recommendations for shared clinical decision-making.

Dr. Robinson clarified that the recommendations for HPV do not specifically state “shared clinical decision-making.” I just indicates that HPV vaccine can be started at age 9.

Dr. Coyle (AIRA) thought that should be indicated by yellow.

Dr. Robinson indicated that they could have an internal discussion with the HPV SME and ACIP members to determine the best color for that box.

Dr. Cohn reminded everyone that the plan was to consider and incorporate all of the comments and present revised schedules prior to making a motion to vote.

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Dr. Kimberlin (AAP) asked whether leakage following a cochlear implantation was permanent. It seemed like recipients would be dying frequently from bacterial meningitis if that was the case. He requested clarification regarding whether a cochlear implant always yields persistent CSF communications.

Dr. Grohskopf indicated that cochlear implants and persistent CSF communications are described as two separate issues. It is not necessarily a CSF leak following cochlear implants. The “do not recommend” pertains to persistent CSF oropharyngeal communications.

Dr. Maldonado (AAP) indicated that she looked it up and the incidence of CSF in cochlear implantation is reported to be between 1% and 5% in large case series.
Dr. Romero indicated that in a recent discussion with their Ear, Nose, and Throat (ENT) Specialist in his center, he was told that the question of the leak and associated problems with the CSF were more closely associated with the original types of cochlear implants that were used and that this is not so much a problem today as it was in the past.

Dr. Sanchez agreed that this issue was with the original implants and is no longer an issue with the current implants, and stressed that this should be stated clearly. He personally does not consider them to be a contraindication and “do not recommend” or “do not use” signifies a contraindication. If it is because they do not have the data, that should be stated instead.

Dr. Grohskopf indicated there is a paragraph in the guidance specifically noting that there is a lack of data that for those two conditions and that other vaccines are available, which is the reason for it not being recommended. The WG reviewed these two topics several years ago. At the time, the thinking and rationale were that there simply was not enough data to move on it and there are alternative vaccines. They do plan to take this back to the WG to assess whether additional data have become available.

Dr. Cohn suggested also moving the formal vote to the next morning in order to incorporate all of the changes for ACIP’s review prior to voting.

Revised Child and Adolescent Immunization Schedule

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

On the second day of the meeting, Dr. Robinson presented the Child and Adolescent Immunization Schedule with the revisions suggested the previous day incorporated. For Table 1, there was discussion the previous day about the HPV row for 9 to 10 year old persons. The WG now proposed to have the blue box, but with an expanded definition of the meaning of the blue box similar to the red box for “contraindicated.” The definition of the blue box would read, “Recommended based on shared clinical decision-making or *can be used in this age group.”

For Table 3, similar to the adult schedule, the order of the language was changed to “Not recommended” or “Contraindicated.” The definition also will be changed as discussed after the meeting.

In the influenza note, condition under which LAIV should not be used was changed from a paragraph format to a bulleted format to be consistent with how similar language is presented elsewhere in this schedule.

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In the MenB note, the *Clinical Discretion* section will now be named *Shared Clinical Decision-Making* for consistency with the new language and between the Child and Adolescent and Adult Immunization Schedules.

Discussion Points

In terms of the HPV line, Dr. Bernstein asked whether it would be possible to separate the language associated with the asterisk so that it is more easily identified. He had some difficulty finding it.

Dr. Robinson indicated that they could move that down to the next line.

Dr. Szilagyi thought this was a good change and followed the policy that ACIP set.

Dr. Messonnier asked whether anyone had a preference for inclusion of words or having no words in the boxes.

Dr. Fryhofer (AMA) said that speaking as an internist, she does not see these children.

Dr. Poehling said that speaking as a pediatrician who uses the schedule, it has never caused her problems so she would like it to remain as-is.

Dr. Bernstein moved to adopt the recommended Child and Adolescent Immunization Schedule for 2020 with the changes incorporated. Dr. Frey seconded the motion.

Dr. Cohn thanked the Adult Immunization WG and the Child and Adolescent Immunization WG leads who worked hard overnight to adopt the suggested changes.

Motion/Vote: Child and Adolescent Immunization Schedule

Dr. Bernstein moved to adopt the recommended Child and Adolescent Immunization Schedule for 2020 with the changes incorporated. Dr. Frey seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot
0 Opposed:	N/A
0 Abstained:	N/A

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Influenza

Introduction

Robert L. Atmar, MD
Chair, Influenza Work Group
Baylor College of Medicine

Dr. Atmar reminded everyone that during the June 2019 ACIP meeting there were presentations on influenza surveillance and vaccine effectiveness (VE) updates, an overview of 2018-2019 influenza vaccine safety surveillance, and the proposed recommendations for the 2019-2020 influenza season.

In terms of WG activities and discussions since June 2019, the 2019-2020 ACIP Influenza Statement was published on August 23, 2019. The WG has had a series of discussions to develop a protocol for a systematic review of influenza vaccines for older adults, including selection of relevant comparisons and outcomes. The WG heard a presentation of Phase 3 trial data for quadrivalent high-dose inactivated influenza vaccine (IIV) for persons 65 years of age and over. Fluzone® High-Dose (trivalent high-dose IIV) has been licensed for this population since 2009.

The agenda for this session included the following topics:

- ❑ US Influenza Activity Update
- ❑ QIV-HD Clinical Development and Phase 3 Safety and Immunogenicity Study Results
- ❑ Summary and WG Considerations

Influenza Surveillance Update

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

Ms. Brammer presented updates on international influenza activity and recent US influenza activity, and briefly discussed the Southern Hemisphere vaccine recommendations.

In terms of Southern Hemisphere influenza activity for the 2018-2919 season as reported to the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS), all possible influenza viruses have been circulating. There are differences by country. Although Australia had H1 activity during their summer months leading into their influenza season, their season was predominantly influenza A(H3N2) viruses with some influenza B. In contrast, New Zealand also had predominantly H3 among their As, but they had more influenza B Victoria lineage viruses. New Caledonia had a very strong and early H1 seasons, followed by a second wave that was mixed with H3 and B/Victoria. To round it out, South Africa had an almost exclusively A(H3N2) season.

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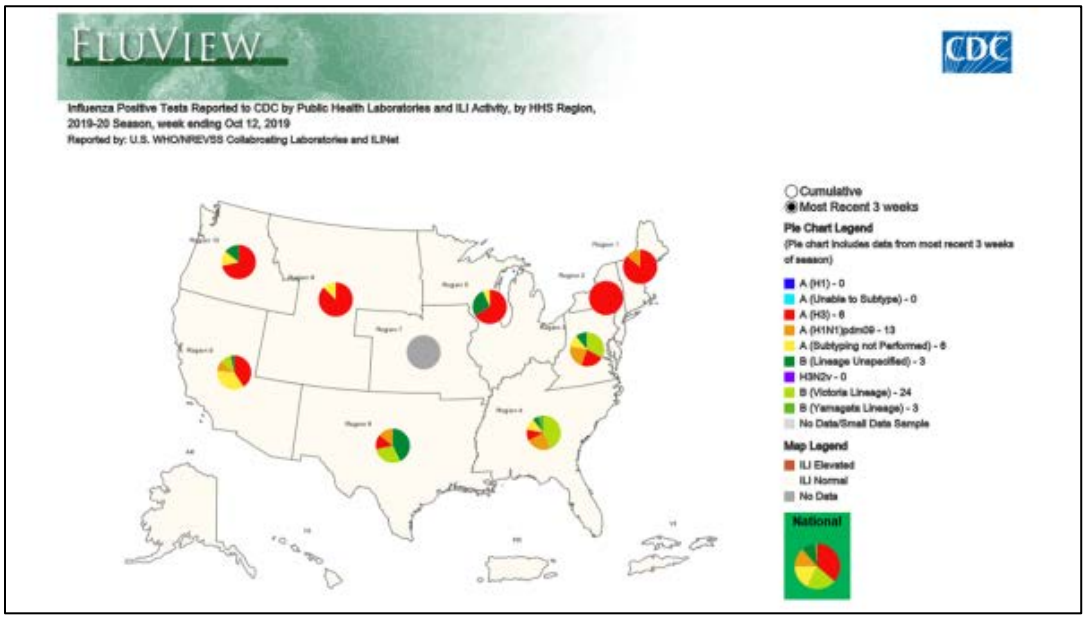
There was quite a contrast in select South American countries. Brazil had an A(H1N1)-predominant season with some A(H3N2) and some B activity, with the Bs being predominantly B/Victoria. Chile also had an H1 predominant season with some H3 activity. But at the end of their season, they had a pretty substantial influenza B wave. What is unusual about this is that the predominant influenza B virus they saw was B/Yamagata, which has been pretty rare over the last year.

Moving on to US influenza positive activity as reported to CDC by clinical laboratories across the country from September 30, 2018 through October 12, 2019, in recent weeks influenza activity has been increasing slightly as would be expected during this time of year. The majority of viruses reported recently have been influenza B viruses, which is somewhat unusual for this time of year. During the first 2 weeks of this season, 71% of the viruses reported have been influenza B. Among the influenza B positives that have been reported, 85% come from Region 4, which is the Southeast US.

In terms of influenza positive tests reported to CDC by public health laboratories across the country, there still has been a lot of influenza B activity reported recently. These have been predominantly B Victoria lineage viruses. Overall, A(H3N2) viruses have been more frequently reported. For the first 2 weeks of the season, 68% of the viruses reported by public health laboratories have been influenza A and only 32% have been influenza B. Among the influenza A viruses that have been subtyped, 73% have been A(H3N2) viruses. Among the influenza B viruses with lineage information, 95% have been the B/Victoria lineage viruses.

This map shows the relative proportion of viruses in each region:



This map includes only 2 weeks of data and is only 176 viruses, but it shows that Region 4 in the Southeast is B predominant. Region 6 is also B predominant, but it is mostly Louisiana and Texas contributing those data. Up the East Coast is more influenza B. However, influenza A predominates across the North and over to the West Coast. Thus, there are some pretty marked differences geographically at this time.

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Looking more closely at the genetic and antigenic characterization of the influenza A(H3N2) viruses collected from May 19, 2019 through September 28, 2019 (Summer Weeks 21-39), note that these data include influenza viruses submitted by both international and US laboratories and tested at CDC. All of the H1N1 viruses belong to the 6B.1a single genetic subclade group. Of those that have been antigenically tested, 96% are similar to the cell propagated 2019-2020 Northern Hemisphere vaccine virus component, which is an A/Brisbane/02/2018-like virus. The B/Yamagata viruses all also belong to the single genetic group known as Y3, and all of them are similar to the cell propagated Northern Hemisphere vaccine component that remains a B/Phuket/3073/2013-like virus.

The recently tested influenza A(H3N2) viruses (n=427) belong to either clades 3C.2a (83%) or 3C.3a (17%). There are multiple subclades currently circulating within the 3C.2a clade. The majority belong to subclade 3C.2a1. The 3C.2a1 viruses predominated in Australia during their influenza season that is just coming to a close, but 3C.3a viruses predominated among H3 viruses in South America. If the antigenically characterized H3 viruses, 70% are similar to the cell culture-propagated 2019-2020 Northern Hemisphere vaccine virus component (A/Kansas/14/2017 that belongs to the 3C.3a clade). While ferret antisera clearly distinguish antigenic differences between 3C.2a and 3C.3a viruses, there is some cross reactivity between the two groups of viruses, hence the 17% 3C.3a viruses but 70% antigenically similar. Again, these data include influenza viruses submitted by both international and US laboratories and tested at CDC.

The B/Victoria lineage viruses all belong to either clade V1A (4%) or subclades V1A.1 (24%) and V1A-3Del (72%). The V1A.1 viruses antigenically characterized were similar to the cell culture-propagated 2019-2020 Northern Hemisphere vaccine component (B/Colorado/06/2017). Ferret antisera raised against recent V1A.1 viruses had reduced reactivity with V1A and V1A-3Del viruses, indicating that there are some antigenic differences between the B/Victoria lineages subclades. Sera from humans vaccinated with V1A.1 virus cross-reacted well with V1A-3Del viruses, which are the predominant viruses circulating recently.

In terms of the percentage of visits for influenza-like illness (ILI) reported by the US outpatient Influenza-like Illness Surveillance Network (ILINet), 1.5% of patient visits for the first 2 weeks of this season have been for ILI. This appears to be higher than what has been observed at the start of previous seasons, but some new sites were added this season. With the addition of those sites, the baseline increased from 2.2% to 2.45. Therefore, this increase is believed to represent a different mix of providers reporting rather than increased activity. Looking at ILI at the state-level, Louisiana already had high ILI activity by Week 41 while the Virgin Islands had low activity. All of the remaining jurisdictions are seeing minimal activity. The activity in Louisiana is associated primarily with B/Victoria lineage viruses. Looking at the geographic spread within each state, Louisiana again stands out as the one state reporting regional influenza activity. In addition, 3 states reported local activity (California, Nevada, and Kentucky). The majority of states reported sporadic activity, and three states reported no influenza activity.

Based on pneumonia and influenza mortality data from the National Center for Health Statistics (NCHS), the percentage of death certificates with pneumonia or influenza listed is low as would be expected with low influenza activity. Based on these data for the week ending October 5, 2019, 4.7% of death certificates had pneumonia or influenza listed. This is well below the epidemic threshold of 5.7% for that week. So far for the 2019-2020 season, there have been no influenza-associated pediatric deaths reported. However, 2 influenza-associated pediatric deaths were reported in September. Both of those were due to A(H3N2) viruses.

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In terms of the recommendation for the 2020 Southern Hemisphere influenza vaccine, the WHO committee met at the end of September to make recommendations and they recommended the following:

- ❑ It is recommended that the following viruses be used for trivalent influenza vaccines in the 2018 Southern Hemisphere influenza season:
  - A/Brisbane/02/2018 (H1N1)pdm09-like virus (in the current US vaccine)
  - A/South Australia/34/2019 (H3N2)-like virus (belongs to the 3C.2a1 subclade and differs from the US vaccine)
  - B/Washington/02/2019-like virus (B/Victoria lineage V1A-3Del)

- ❑ For quadrivalent vaccines containing 2 B components:
  - Above 3, plus B/Phuket/3073/2013-like virus (B/Yamagata lineage)

It is important to keep in mind that these vaccine recommendations are made for what is expected to circulate in the Southern Hemisphere season during what will be the US summer of 2020.

To summarize, overall influenza activity remains low in the US. The numbers so far are small, but influenza A(H3N2) viruses are predominant in the US overall. However, there is a lot of variability by region. It is too early to tell what viruses will be predominant for the season. Frequently, summer influenza activity does not predict what is going to occur in the US influenza season. While 2 of the 4 vaccine components were updated for the Southern Hemisphere, recent laboratory data suggest that the components selected for the Northern Hemisphere vaccine still appear to be appropriate for the US season.

Discussion Points

Dr. Lee said she did not really appreciate the geographic variability until she saw this presentation. She wondered whether it would be possible to predict the genetic antigenic characteristics of influenza viruses by region in the US based on travel patterns from other countries.

Ms. Brammer said it is very difficult to predict which genetic groups will predominate regardless of geography, which is illustrated by the fact that different subtypes can predominate in places that are fairly close like Australia and New Zealand. There are methods whereby all of the worldwide genetic data are entered to try to predict which among those will emerge and predominate. However, she has not seen those data on a finer geographic level.

Ms. Stinchfield (NAPNAP) asked whether the pediatric deaths that occurred in September were counted in last year's season, and whether international travel was considered as a source since these were so early.

Ms. Brammer responded that those do count in the 2018-2019 season, although whether that is correct is up for question. There is concern that those that the viruses that caused illness early in September could be travel-related.

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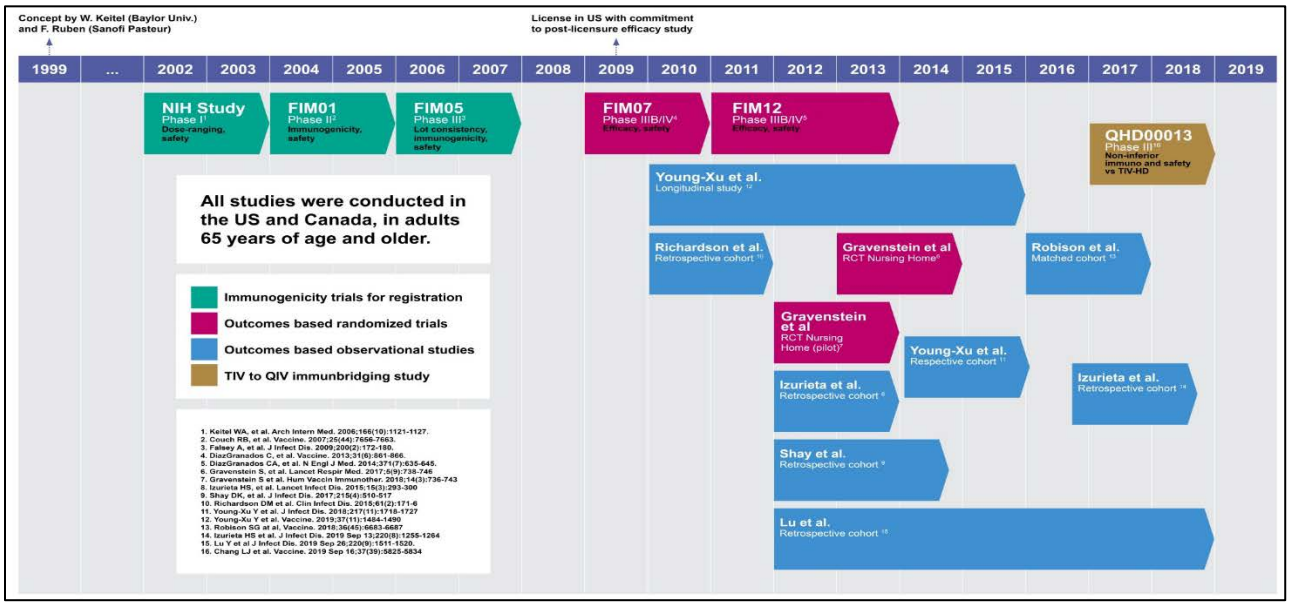
QIV-HD Clinical Development and Phase 3 Safety and Immunogenicity Study Results

Lee-Jah Chang, MD
Director Clinical Development, Sanofi Pasteur

Dr. Chang thanked the WG and ACIP for inviting him to present Sanofi Pasteur's data. In terms of background, Sanofi Pasteur's quadrivalent high-dose influenza vaccines (QIV-HD) builds off of their currently existing licensed trivalent high-dose influenza vaccine (TIV-HD) that has been available in the US since 2010. Over 115 million doses of TIV-HD have been sold since licensure, and about 2 out of 3 vaccinated adults ≥65 years of age in the US received Fluzone® HD vaccine during the 2018-2019 season (~22 million doses). As with most other vaccines, their high-dose vaccines is the last one to be transitioned over to Sanofi Pasteur's quadrivalent formulation. During this session, Dr. Chang shared their QHD00013 data, which is the study used to immunobridge from the trivalent to the quadrivalent formulation in order to ensure that there is good coverage for both B influenza lineage strains (Victoria and Yamagata). To demonstrate the strength of the data that the QIV-HD vaccine is building off of, shown in the table below are all of the key studies that have been generated since licensure as well as real-world evidence data that have been generated. Note that the colors denote that there are different study designs, with different populations evaluated in these studies (community-dwelling, nursing homes, veterans):



They also examined multiple endpoints aside from the traditional ILI endpoint, including influenza hospitalization, pneumonia hospitalization, pneumonia/influenza hospitalization, cardiorespiratory hospitalization, and all-cause hospitalization in a new meta-analysis conducted and presented at Options X in Singapore in August. It shows all of the most recent RCT and observational studies shown in the table above [Lee et al. Meta-analysis and Systemic Review. Options X for the Control of Influenza. Aug 19, 2019].

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Transitioning to the QHD00013 study, there were 2670 adults ≥65 years of age. Most of the subjects (N=1777) received QIV-HD and randomization was 4:1. There were two different TIV-HD formulations. The TIV-HD1 was the licensed product for that season (Victoria B lineage). The TIV-HD2 contained the alternate B lineage (Yamagata B lineage) in order to perform comparisons with the QIV-HD group. The primary objective of the study was to demonstrate non-inferior immunogenicity between the two groups. The study was conducted at 35 sites across the US during the 2017-2018 Northern Hemisphere season. The high-level demographics were balanced for gender, age, and racial origin. There were more females than males in the studies, about a third of the subjects were ≥75 years of age, and most subjects were Caucasian.

In terms of safety, there were no related deaths or AEs of special interest in any of the groups. Similar levels of solicited reactions were reported for the solicited injection site and solicited systemic reactions, with low Grade 3 reactions for both groups. Unsolicited AEs were also similar for the QIV-HD and TIV-HD groups. Splitting out solicited reactions by local and systemic, pain was the most commonly reported local reaction and myalgia was the most common systemic reaction in both groups.

To summarize the safety results, while higher percentages for some solicited reactions were observed for QIV-HD, the overall reactogenicity profile was comparable to TIV-HD. The QIV-HD and TIV-HD study groups showed similar rates of unsolicited events, AEs leading to study discontinuation, SAEs, fatal SAEs, and AEs of special interest. One related SAE occurred in a subject who reported small fiber neuropathy diagnosed 42 days after QIV-HD vaccination. This individual had other concomitant etiologies that were documented, one of which was a viral illness the week prior to the start of the neuropathy and the other a recently diagnosed vitamin B12 deficiency that resulted in being started on supplementation. The sponsor assessment was to consider it unrelated to the study vaccine given the other more likely etiologies and symptom improvements with vitamin B12 supplementation; however, it was considered related due to the investigators' judgment.

Regarding the two key immunogenicity results, non-inferiority was defined as the lower bound of the confidence interval being greater than 0.667. All of the lower bounds were above 0.667. By geometric mean titers (GMTs), the QIV-HD and TIV-HD formulations were considered non-inferior. The other endpoint was seroconversion rates, which were defined as non-inferior if the lower bound of the confidence interval was greater than -10%. The lower bound for all four of the strains were greater than the cutoff margin.

One of the secondary endpoints was to demonstrate the benefit of having the additional B strain, so they looked at superior immune responses for the GMTs and seroconversion rates. Those lower bounds were defined as greater than1.5 for the GMTs and >10% for the seroconversion rates. For both B/Brisbane and B/Phuket groups, there were superior immune responses by both GMTs and seroconversion rates.

To summarize the overall key study results, no safety issues were observed with QIV-HD in adults 65 years of age and older. Safety profiles between QIV-HD and TIV-HD were similar. Regarding the immunogenicity results, the primary objective was met in that QIV-HD was non-inferior to TIV-HD by GMTs and seroconversion rates for all 4 strains. The secondary objective was met in that QIV-HD induced an immune response superior to that induced by the TIV-HD that did not contain the corresponding B strain. The study results demonstrated that addition of a second influenza B strain in QIV-HD did not impact the safety or immunogenicity of the other 3 strains in subjects 65 years of age and older.

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In terms of next steps for QIV-HD, the Common Technical Document (CTD) has already been submitted. The Center for Biologics Evaluation and Research (CBER) action date is November 4, 2019. Assuming that QIV-HD receives licensure, HCPs will be able to pre-order in the first quarter of 2020. TIV-HD will be entirely replaced by QIV-HD for the 2020-2021 influenza season.

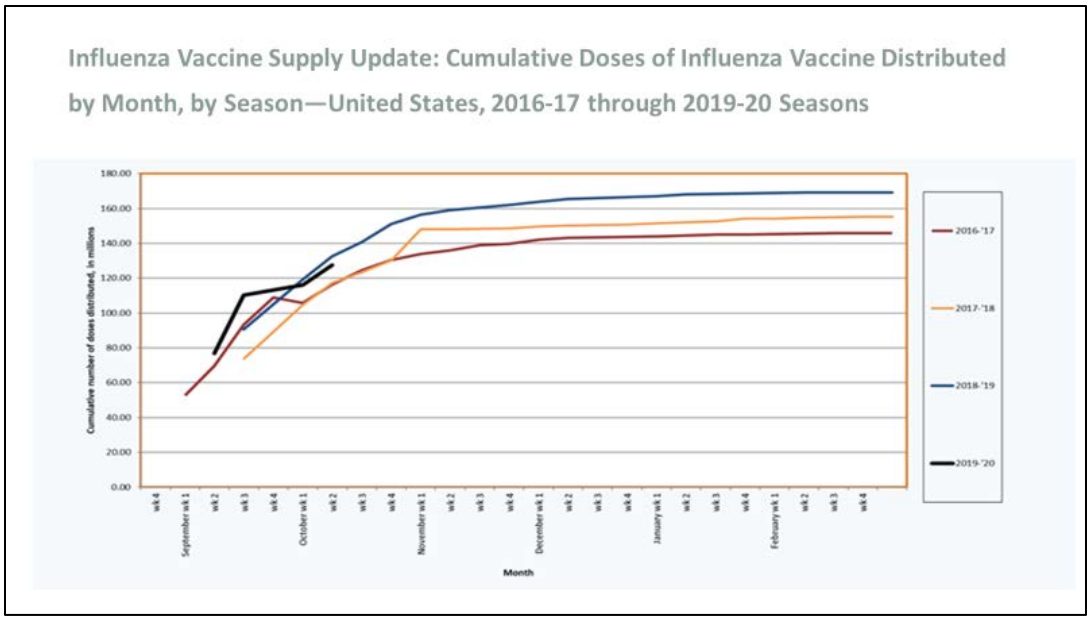
In conclusion, Dr. Chang emphasized that Sanofi Pasteur remains committed to the study of the performance of its influenza vaccines and their ability to reduce influenza and its associated complications across seasons and settings in order to understand the differences each vaccine brings.

Influenza Work Group Considerations

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

Dr. Grohskopf thanked the WG members for being extremely generous with their time and mental energy on their twice a month calls and beyond, as well as the CDC staff who contribute regularly to the calls every month twice a month and often deliver presentations to the WG.

Before discussing the WG considerations over the last several months, Dr. Grohskopf shared a brief influenza vaccine distribution update. She shared the following data assembled by Dr. Santoli and her group in ISD:



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As a reminder, the WG reported during the June 2019 ACIP meeting that selection of the H3N2 component of the 2019-2020 Northern Hemisphere season had been delayed. It was delayed by about a month until March 22, 2019. There were some questions about whether that might have implications for supply, and a slide was shared at that time that summarized the projected start dates for distribution of the vaccine from the various manufacturers and anticipated a mid-August to early-September timeframe. The above table summarizes influenza vaccine supply in terms of cumulative doses distributed by month over the course of 4 seasons. The most recent season that just began is represented by the short black line, with the previous 3 seasons to that. By October 11, 2019, approximately 127.6 million doses had been distributed. Compared to the recent 3 previous seasons for the same time period, this is somewhat less than last season but is more than 2017-2018 and 2016-2017. As a reminder, it is anticipated based on manufacturer estimates that a total of 162 to 169 million doses will be distributed this season. As a reminder, these are the types of influenza vaccines:

IIV	Inactivated Influenza Vaccine
ccIIV	Cell Culture-Based Inactivated Influenza Vaccine
aIIV	Adjuvanted Inactivated Influenza Vaccine
HD-IIV	High-Dose Inactivated Influenza Vaccine
RIV	Recombinant Influenza Vaccine
LAIV	Live Attenuated Influenza Vaccine

In terms of some basic context and history about the recommendations for influenza vaccination for older adults and also influenza in general for older adults, older adults have been recommended to receive routine annual influenza vaccination since the early 1960s. The 1960 *Surgeon General's Statement on Influenza Immunization* was one page long, illustrating that times were simpler back then. In that statement, it is noted that several groups were considered to have contributed the most to excess mortality and morbidity during the previous pandemic in 1957. One of those groups was all persons 65 years of age or older. This is one age group for which the recommendations have been consistent since 1960. Older adults are still recognized as being generally at higher risk for increased severity of illness with influenza and also death. As an example, data from CDC's FluView Interactive showing cumulative hospitalizations rates over the course of the last 4 influenza seasons illustrate that those 65 years of age and older tend to have the highest hospitalization rates.

At the time of the Surgeon General's statement in 1960, there had not been nearly the diversity of influenza vaccines that are currently available. This graphic offers a snapshot of how things have developed in roughly the last 2 decades:

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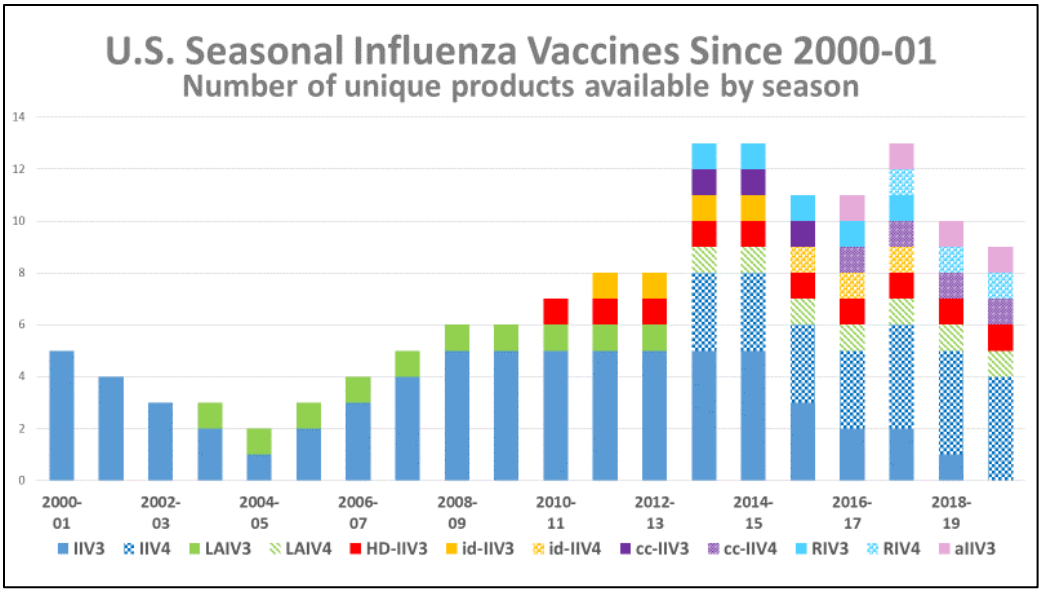

For the current season, a total of 9 individual types of vaccines will be available. The high-dose and the adjuvanted vaccines are licensed specifically for individuals 65 years of age and older.

FLUAD® and FLUZONE® High-Dose were developed specifically for this age group, with features that were intended to help promote a stronger immune response in this age group. Not only is this age group at higher risk of contracting influenza, but also tends not to respond as well to vaccines. FLUZONE® High-Dose has a higher antigen content and FLUAD® has MF59 adjuvant. Though not licensed specifically for those 65 years of age and older, Flublok® also has been studied specifically in this population. There tends to be more than one vaccine that is appropriate by age indication. ACIP recommends simply that a licensed, age-appropriate influenza vaccine should be used. No preferential recommendations are made for any specific influenza vaccine for any age group, including those 65 years of age and older, where there is more than one vaccine that is appropriate and available for the given recipient.

The fact that there are many vaccines available and the growing body of literature that is starting to compare specific vaccine types against one another raises some significant questions regarding what can be said about whether one is more suitable for any given population age group. Older adults is one of those groups for whom this is being pondered. There are some challenges for influenza in particular in terms of assessing the relative benefits of specific vaccines for older adults. One is that there simply is a large variety of available vaccines, 8 of which are appropriate for this age group by licensed indications. While there is a growing canon of studies comparing individual vaccine types, the data are limited for some relevant comparisons that would help inform this question. There also are a number of factors related to influenza itself. The virus changes and the relative effectiveness of different vaccines varies from season to season. Therefore, it is not possible to be certain that results from one or a few high-quality studies will generalize across all or most influenza seasons. This landscape is unlikely to get any less complicated.

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This table summarizes some of the data on high-dose, adjuvanted, and recombinant vaccine for older adults, with the caveat that these are the studies that have examined laboratory-confirmed influenza outcomes and is not a comprehensive literature review:

HD-IIV3, aIIV3 and RIV4 for Older Adults

Summary of studies examining laboratory-confirmed influenza outcomes:

Study Year published Ages	Season(s)	Comparison	Design	N	Relative Efficacy/effectiveness
DiazGranados 2013[1] ≥65 years	1 2009-10	HD-IIV3 vs SD-IIV3	RCT	~9,100	Not evaluable because of pandemic
DiazGranados 2014[2] ≥65 years	2 2011-12, 2012-13	HD-IIV3 vs SD-IIV3	RCT	~32,000	24.2% (95% CI = 9.7–36.5)
Dunkle 2017[3] ≥50 years	1 2014-15	RIV4 vs SD-IIV4	RCT	~8,600	30% (95% CI = 10–47)
Van Buynder 2013[4] ≥65 years	1 2011-12	aIIV3 vs SD-IIV3	observational	227	63% (95% CI = 4–86)

[1] DiazGranados CA et al, Vaccine 2013;31:861-866
[2] DiazGranados CA et al, N Engl J Med 2014;371:635-645
[3] Dunkle LM et al, N Engl J Med 2017;376:2427-2436
[4] VanBuynder PG et al, Vaccine 2013; 31:6122-6128

These studies have been summarized in the ACIP Influenza Statement for the last couple of years. In each case, at least one study uses a laboratory-confirmed influenza outcome that suggests that there might be some benefit. There is an RCT for high-dose vaccines that covered two seasons, one for recombinant vaccine that covered a single season, and an observational study for the adjuvanted vaccine that covered a single season. In each case, these studies compared the index vaccine to a standard dose unadjuvanted inactivated influenza vaccine. At present, there is a dearth of data on these vaccines compared to one another in studies with laboratory-confirmed influenza outcomes. Importantly, there are other studies that examine non-laboratory-confirmed influenza outcomes.

The WG had a number of discussions in the early part of the summer about planning a systematic review to examine the question, “Do the relative benefits and harms of HD-IIV, aIIV, and RIV as compared with one another and with other influenza vaccines favor the use of these vaccines over others for persons aged 65 years and older?” One consideration is that the landscape does continue to change. One of these vaccines will be quadrivalent at some point that may be licensed, and there are likely to be other changes as seems to be the case with influenza and the vaccines in general. However, the WG felt overall that it is time to start summarizing this literature in a systematic fashion and with the understanding that it probably would have to be updated over time.

Therefore, a systematic review/meta-analysis is planned for influenza vaccines in older adults. As it is currently framed, the population of interest is adults aged ≥65 years. The intervention vaccines will include trivalent and quadrivalent high-dose IIV, adjuvanted IIV, or RIV that are US-licensed or that are similar in formulation and manufacture to US-licensed vaccines. The comparators include other trivalent or quadrivalent influenza vaccine (US-licensed or similar in formulation/manufacture to US-licensed), non-influenza control vaccines, placebo, and no vaccine. The efficacy/effectiveness and safety outcomes of interest are anticipated to be finalized in early November and include:

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- Efficacy/Effectiveness
  - All influenza A and B, with a sub-analysis stratified by virus type and subtype as feasible (not all papers report these)
  - Influenza-associated outpatient/emergency visits
  - Influenza-associated hospitalizations
  - Influenza-associated deaths

- Safety
  - Systemic and injection site adverse events
  - Serious adverse events
  - Guillain-Barre syndrome
  - Severe hypersensitivity or anaphylaxis

Inclusion/Exclusion criteria will include the following:

- Peer-reviewed literature with no language restriction
- Publication dates from 1990 forward, with a rationale that the adjuvanted vaccine was licensed in Europe in 1997
- Include:
  - Randomized studies (including cluster-randomized)
  - Retrospective case-control and cohort studies
  - Prospective cohort studies
- Exclude:
  - Case series, case reports, registry reports without comparator information
  - Studies/data on vaccines not licensed in the United States
  - Animal studies
  - Studies/data for which entire population falls outside of designated age range
  - Duplicate reports
  - Interim reports superseded by final reports

This review is anticipated to be somewhat more complicated than the last time this topic was reviewed in 2015, at which time there was only on relevant comparison for this age group of high-dose versus standard dose. This time there are at least 3 relevant comparisons. The systematic review/meta-analysis is anticipated to begin in November, with updates presented as available during future ACIP meetings.

Discussion Points

Dr. Frey inquired as to whether there was any sense of the uptake of adjuvanted vaccine versus high-dose in terms of what people prefer.

Dr. Grohskopf indicated that she did not have any specific information in terms of trends over time for the uptake of adjuvanted vaccine. There is an FDA-authored paper that is an analysis of CMS data for the 2017-2018 season. The intent of that paper was primarily to compare egg-based versus non-egg-based vaccines, but it did cite the approximately breakdown of the various vaccine types for that season. The population was comprised of approximately 13 million CMS Medicare beneficiaries ≥65 years. As she recalled, vaccine was approximately 65% high-dose. This is a snapshot and does not reflect trends over time.

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Dr. Foster (APhA) recalled that a couple of years ago, FluMist® was analyzed but the other regular types of doses were not. Here again, they were not planning to specifically assess the various products through a total comparison. He expressed his hope that someday, this would be done. He also recalled that there was considerable discussion last year about the effectiveness of cell-based versus egg-based products. However, that was not mentioned in the comparison to determine whether that was a factor.

Dr. Grohskopf indicated that the WG discussed this specifically. One of the issues is that there are increasing data for the cell-based vaccine over time. There is somewhat more specific data for this age group concerning the other vaccines. Because there already are 3 vaccines of interest, the analysis will be somewhat complicated. Therefore, the plan is to focus on those 3. The cell culture-based vaccine also had the interesting distinction that the upcoming season will be the first season during which not only is the virus propagated in eggs for manufacturer and large-scale production, but also this is the first season in which all the reference viruses provided to manufacturers also are cell-derived viruses. It is anticipated that the WG will want to revisit this in the future, but the task already is very large with the vaccines available that are most applicable and germane for this age group.

Dr. Hunter requested confirmation regarding whether there was a plan to compare recombinant versus adjuvanted versus high-dose. Instead, they would be lumped into one group and compared to everything else. In terms of the timeline, he expressed concern that these data would not be available in time for the votes related to the upcoming season.

Dr. Grohskopf clarified that if they can find the data, these will be compared to each other. This is what she meant to convey by the fact that there will be at least 3 relevant comparisons. Ideally, the aim is to have the analysis completed by February. However, she emphasized that it is a complicated undertaking.

Dr. Messonnier said her understanding was that there are 8000 articles to begin with. While every effort will be made to have this completed by February, she said she did not want to over-promise. To make a distinction between what the ACIP WG is doing and what the overall Influenza Division is doing in terms of egg- and cell-based vaccines, in addition to the proposed analysis, the Influenza Division has increased the network of sites in which they evaluate influenza vaccines in an attempt to enhance the granularity at which they can examine the distinctions of cell- versus egg-based vaccines. They also have added immunogenicity studies. Outside of the ACIP process, they will continue along the same path discussed a year ago, which is that they need a bigger database in order to provide the kind of data in which ACIP is interested.

Dr. Atmar asked whether it would be possible to expand on immunogenicity. This needs to be done and there has been discussion about the advantages of having that information available.

Dr. Fry, Branch Chief of the Epidemiology and Prevention Branch in the Influenza Division, indicated that they have several studies with immunogenicity outcomes that are focused on different groups. One is in older adults. There is one year with 5 arms. In the second year, they re-randomized. They revaccinated for a third year with the same vaccine, so they assess repeat vaccination effects and potential differences if vaccines are switched. There is an ongoing study in Hong Kong looking at that. The first year's data were just presented at Options X and should be published soon. There are several studies in younger age groups and HCP. The analyses focus on not only initial vaccination effects, but also repeat vaccination effects because they think this will be an important consideration for all of these vaccines. They also are trying to

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tease out some of the immunologic differences, which are still softer outcomes for them. They would be happy to present those studies to the WG or the full ACIP during a future meeting.

Dr. Bernstein recalled that earlier they heard that it was a surprise about the B lineages, especially the Yamagata lineage. He wondered at what point they would expect to have only quadrivalent vaccines available for adults, especially for adults ≥65 years.

Dr. Grohskopf said they know what potentially is on the horizon for the high-dose vaccine based on the Sanofi Pasteur presentation from earlier. There has not yet been a WG presentation on the adjuvanted vaccine. It would be best for Seqirus™ to address this. At this point, the high-dose and adjuvanted vaccines for this season are the last 2 trivalent vaccines. It would be anticipated that those would change to quadrivalent at some point.

Dr. Sylvester from Seqirus™ reported that they do have a quadrivalent adjuvanted product that is in front of the FDA at this time. The action data is February 2020. He hopes to present those data during the February 2020 ACIP meeting.

Dr. Frey inquired about intradermal vaccines, which have not been mentioned.

Dr. Grohskopf indicated that the intradermal vaccine is not currently available in the US. A higher dose intradermal vaccine has been licensed in some other countries. The plan is to include other influenza vaccines broadly. The case of the intradermal vaccine is interesting because it is relevant since it is licensed, but it is not available. They could include this, but it is not anticipated that there would be as many literature citations for that vaccine. It is something the WG can think about.

Ebola Vaccine

Introduction

Sharon Frey, MD
Chair, Ebola Vaccine Work Group
Saint Louis University Medical School

Dr. Frey introduced the new Ebola Vaccine WG. She indicated that the Ebola Vaccine WG's terms of reference are to: 1) review the available data on the rVSVΔG-ZEBOV-GP vaccine and inform domestic vaccine policy options for ACIP consideration; and 2) inform recommendations for use of the rVSVΔG-ZEBOV-GP vaccine in pre-exposure vaccination of healthy adults ≥ 18 years of age at occupational risk for exposure to Ebola virus (species *Zaire ebolavirus*).

This WG's activities are divided into 2 phases. During Phase 1, the WG will review vaccination data for healthy non-pregnant, non-lactating adults ≥18 years of age without immunocompromising conditions; and identify US populations at occupational risk for exposure to Ebola virus (species *Zaire ebolavirus*). In Phase 2, the WG will identify areas of further research to inform potential future vaccination recommendations.

This session included presentations on Ebola Virus Disease (EVD); Ebola vaccine safety, efficacy, immunogenicity; the WG's perspective on vaccine data; and WG next steps.

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Ebola Virus Disease

Mary Choi, MD, MPH
Viral Special Pathogens Branch
Centers for Disease Control and Prevention

Dr. Choi reported that on August 1, 2018, the Ministry of Health confirmed an outbreak of EVD in North Kivu province in Eastern Democratic Republic of Congo (DRC). The virus responsible for the outbreak belongs to the *Zaire ebolavirus* species. This outbreak is the 10th EVD outbreak in the DRC and is the largest to ever have occurred there. As of September 29, 2019, cases have been reported in 29 health zones and now 3 provinces, North Kivu, Ituri, and South Kivu. Over 3000 cases and over 2000 deaths have been reported to date. In addition, 165 HCW have been infected in the course of this outbreak.

In terms of background, EVD is a deadly disease caused by infection with one of 4 viruses within the genus and are listed here:

- Ebola virus *(species Zaire ebolavirus)*
- Sudan virus *(species Sudan ebolavirus)*
- Tai Forest virus *(species Tai Forest ebolavirus)*
- Bundibugyo virus *(species Bundibugyo ebolavirus)*

The natural reservoir for the virus is unknown. However, based on studies done on similar virus, it is likely fruit bats. For the remainder of this presentation, Dr. Choi focused on the Ebola virus species *Zaire ebolavirus*.
Since 1976 when the virus was first discovered, there have been 28 reported outbreaks of EVD. The *Zaire ebolavirus* species is responsible for 18 (64%) of these outbreaks. These outbreaks have resulted in over 31,000 cases and over 12,000 deaths. In addition, Ebola virus is responsible for the two largest EVD outbreaks, the 2014 West Africa outbreak and the current DRC outbreak. Untreated, the mortality rates for Ebola virus infection have been reported to be as high as 70% to 90%. Ebola virus infection has the highest mortality rates among the 4 viruses within the genus that are known to cause disease in humans.

In an infected person, Ebola virus can be found in all body fluids, including: Amniotic Fluid, Blood, Feces/Vomit, Saliva, Breast Milk, Semen, Sweat, Tears, Urine, and Vaginal Secretions. The virus is transmitted through contact through a break in the skin, mouth, eyes, and/or mucous membranes with the body fluids of a person that is sick or has died of EVD. The signs and symptoms of EVD are non-specific and are listed here: Bleeding (epistaxis, injection sites), Abdominal Pain, Diarrhea, Fatigue, Fever, Headache, Muscle pain/Joint Pain, Rash, and/or Vomiting. Although bleeding can certainly be seen in EVD, in general, it is seen in less than 50% of cases. It is important to note that a person who is infected with Ebola virus is not contagious until symptoms appear.

Here is a graphic depicting the progression of illness in EVD:

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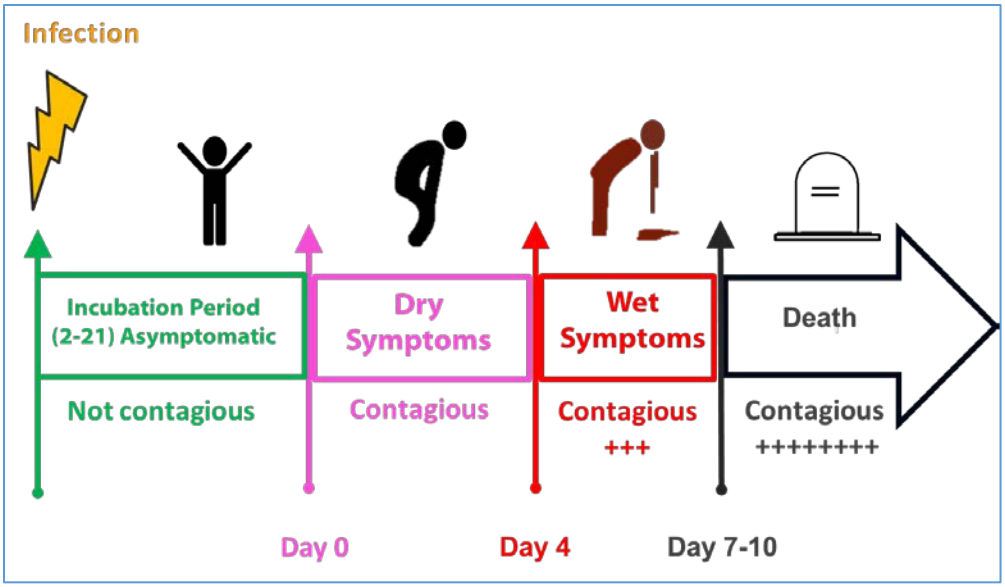

Following infection, there an incubation period. During the incubation period, the infected individual has no signs or symptoms of EVD and they are not contagious. The incubation period is between 2 and 21 days, but on average is between 8 and 10 days. The first symptoms that appear are called “dry symptoms” and include fever, headache, muscle aches, and joint pain. Once signs and symptoms appear, the patient is contagious and is capable of transmitting the virus to others. At around day 4 of illness, patients develop diarrhea and vomiting or what are called “wet symptoms.” At this point, the patient is very contagious with high amounts of virus in the vomit and stool. Without treatment, most infected individuals will die 7 to 10 days after illness onset. The concentration of Ebola virus in the body is highest at the time of death.

The true incidence of sequalae amongst EVD survivors is unknown because until the 2014 outbreak in West Africa, the outbreaks were small as were the number of survivors. However, the handful of studies that have looked at this issue have found that sequalae tend to vary over time and that for the most part, symptoms resolve over time as well. In one study, the most commonly reported sequalae at 6 months were arthralgia, myalgia, abdominal pain, fatigue[1] and at 2 years were uveitis, headache, joint pain, cataracts, and muscle pain.[2] With regard to mortality in survivors, one study looking at EVD survivors in Guinea found that they had a 5-fold greater mortality than the general population within 1 year of discharge from an Ebola treatment unit. The exact reason for this increased mortality was not known. Some verbal autopsies were done and it was speculated that this was due to renal disease as a sequalae of severe EVD.[3] Finally, it is known from West Africa and previous studies that Ebola virus can persist in immunoprivileged sites such as the testes, aqueous humor of the eye, the brain, placenta, and breast milk [[1]Rowe et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of Congo; [2]Prevail III Study Group. A longitudinal study of Ebola sequelae in Liberia; [3]Keita et al. Subsequent mortality in survivors of Ebola virus disease in Guinea: a nationwide retrospective cohort study Lancet Infect Dis. 2019].

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With regard to immunity, the duration of natural immunity against Ebola virus infection in survivors is unknown. However, a few studies have found that some survivors continue to have high levels of specific IgG antibodies to the Ebola virus glycoprotein and neutralizing activity at 11[1] years and 40 years[2] after recovery. It should be noted that natural immunity is postulated to be species-specific. It also is important to note for the work going forward that the immune correlate for protection in humans against Ebola virus infection is unknown, but is thought to be a combination of humoral and cell-mediated immunity [[1]Corti et al. Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody; [2]Ebola virus neutralizing antibodies detectable in survivors of the Yambuku, Zaire outbreak 40 years after infection].

There are no FDA approved treatments for EVD at this time. Previous studies from West Africa have shown that early supportive care alone can scientifically improve chances of survival, with mortality rates as low as 40%. In November of 2018, the DRC conducted a randomized clinical control trial looking at 4 different experimental therapies. On review of the data in March of 2019, two therapeutic agents, Regeneron and mAB114 were found to reduce mortality rates to 29% and 34% in all-comers respectively. Mortality rates were further reduced to about 10% in individuals who presented to care early.

There have been 11 individuals treated for EVD due to Ebola virus in the US. All 11 individuals were associated with the 2014-2016 EVD outbreak in West Africa. Of these 11, for 7 individuals the diagnosis of EVD was made overseas and they were medically evacuated to the US for further care. For 4 of the 11 individuals, the EVD diagnosis was made in the US. Of the 11 individuals, 2 (18%) died. Of the 11 cases, there was one instance of secondary transmission in which 1 person who was diagnosed with EVD in the US transmitted the virus to 2 nurses who cared for him in a community hospital. The 11 EVD patients were treated at 5 hospitals in the US. For 8 individuals, treatment was initiated at a Special Pathogen Treatment Center(Emory, Nebraska, NIH, or Bellevue). For 3 individuals, treatment was initiated at a community hospital, but they were later transferred to Special Pathogen Treatment Centers.

One question the WG is exploring pertains to the groups at potential occupational risk, which include the following:

- ❑ Laboratory personnel who directly handle cultures and diagnostic samples from animals contaminated or infected with replication-competent Ebola virus
- ❑ HCP at US Special Pathogen Treatment Centers caring for an EVD patient
- ❑ Personnel responding to an EVD outbreak

Looking at these groups in more detail, laboratory personnel who could come into contact with Ebola virus can be split into two categories: individuals working with the virus in Biosafety Level 4 (BSL-4) laboratories and individuals working in Laboratory Response Network (LRN) laboratories. There are 10 BSL-4 laboratories in the US, with an estimated 350 to 400 laboratory and support staff. These laboratories are listed here:

CDC, Georgia	Galveston National Laboratory, Texas
Georgia State, Georgia	Shope Laboratory, Texas
NIH, Maryland	Texas Biomedical Research Institute, Texas
USAMRIID, Maryland	Rocky Mountain Laboratories, Missouri
National Emerging Infectious Disease Laboratories, Massachusetts	National Biodefense Analysis and Countermeasures Center, Maryland

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Within the BSL-4 population, individuals at potential occupational risk include individuals who handle cultures/animals contaminated or infected with replication-competent Zaïre ebolavirus (ZEBOV) for research purposes, and individuals who handle diagnostic or clinical specimens containing replication-competent ZEBOV.

The LRN is a network composed of local, state, federal public health, food testing, veterinary diagnostic, and environmental testing laboratories. These facilities are affiliated with federal agencies; military installations; and international, state, and local public health departments. At this time, 57 LRN laboratories have the capacity to test for Ebola virus. To date, 37 laboratories have tested clinical samples collected from suspect or confirmed EVD patients in the US.

As mentioned earlier, individuals working at Special Pathogen Treatment Centers are also at potential occupational risk. In terms of what these centers are and how they fit into the US preparedness efforts, in response to the US EVD cases during the 2014 west Africa outbreaks, the Department of Health and Human Services (HHS) created a nationwide regional treatment network to care for patients with Ebola and other special pathogens. There are 4 tiers of facilities, which are listed here:

Type	Number	Role
Frontline healthcare facilities	4845	Has necessary materials/staff to care for suspect/confirmed EVD patient for at least 12-24 hours
Ebola Assessment Hospital	217	Has necessary materials/staff to care for suspect/confirmed EVD patient for up to 96 hours
Ebola Treatment Center	63	Has necessary materials/staff to care for suspect/confirmed EVD patient for up to 7 days
Regional Special Pathogen Center	10	Able to treat simultaneously at least two patients with Ebola for duration of illness

The first level are the frontline healthcare facilities. There are approximately 4800 of these facilities, which include places such as emergency departments (EDs) and urgent cares. These facilities should have the necessary materials and staff to care for a suspect or confirmed EVD patient for at least 12-24 hours. Going down the above list, the number of facilities in each tier decreases and the duration time during which they have the capacity to care for a suspect or confirmed EVD patient increases.

The highest tier are the regional Special Pathogen Treatment Centers. There are 10 regional Special Pathogens Treatment Centers in the US, with an approximate total of 500 healthcare workers and support staff. These facilities have specialized high-level isolation units equipped with infrastructure, laboratory capabilities, and staff to care for patients with highly hazardous communicable diseases. They have the capacity to treat simultaneously at least two patients with Ebola for the duration of illness.

Finally, persons responding to EVD outbreaks also are at potential occupational risk for exposure to Ebola virus. The number of US-based organizations responding to an outbreak will vary by size and location of the outbreak. During the 2014 West Africa outbreak, over 4000 US government personnel deployed in response to that outbreak, including for domestic EVD cases.

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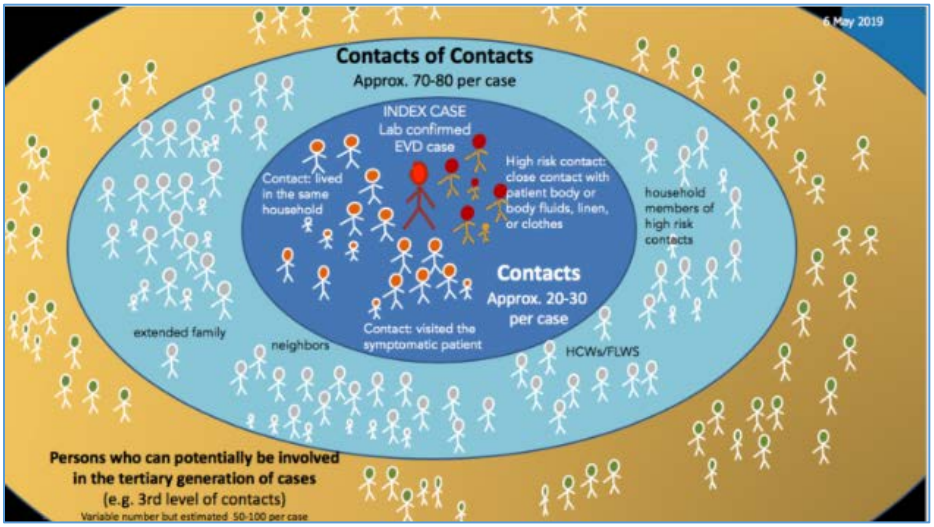
There is a recombinant vesicular stomatis virus-based Ebola virus vaccine. It is a live-attenuated vaccine that initially was developed by Public Health Agency Canada (PHAC) and NewLink Genetics. Merck now holds the intellectual rights. The vaccine is currently being used in the DRC outbreak. As the outbreak has evolved, there has been an evolution in how the Ebola vaccine is being used in this outbreak. Initially, individual eligible to receive the vaccine were adults and children 1 year of age or older. The dose given was the 1 ml dose, and the vaccine was administered using a ring vaccination strategy in which contacts and contacts of contacts were vaccinated. Based on the dynamics of this outbreak, by June of 2019, eligibility was expanded to include pregnant woman after the first trimester and lactating women. In addition, eligibility criteria were expanded in the pediatric population to include children greater than 6 months of age. The dose of vaccine was changed to the ½ ml dose and ring vaccination was expanded to include a third ring. A second vaccine, the adeno MVA-BN Filo (Ad26.ZEBOV/MVA-BN), was approved by the DRC in September 2019.

Here is a graphic on the ring vaccination strategy being used in DRC:



In the middle of the graphic, there is a red stick figure that represents the confirmed case. Individuals associated with this case are offered vaccination using a 3-ring strategy. The first ring is the contacts of the case, shaded here in dark blue. These individuals can include those who lived with the case while the case was symptomatic. These individuals also can include those who visited the case when the case was symptomatic. The second ring is the contacts of contacts, shaded here in light blue. These are individuals who associated with the contacts of the confirmed case. These individuals can include extended family and neighbors. The third ring is another step removed from the case and can include people who live in the same geographic area.

To summarize, Ebola virus (species *Zaire ebolavirus*) infection causes severe illness with high morbidity and mortality. Ebola virus is responsible for 64% of EVD outbreaks, with over 31,000 people infected and over 12,000 deaths. The current outbreak is the largest in DRC and is still ongoing. US personnel at risk for occupational exposure include laboratory personnel, HCP at Special Pathogen Treatment Centers, and persons responding to EVD outbreaks.

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Discussion Points

Dr. Lee inquired as to what prompted expansion to the third ring, given that it seemed the second ring would be sufficient for most types of outbreak control.

Dr. Choi indicated that it had to do with security. There were areas in which it was very difficult to vaccinate the case. For example, some cases did not want to cooperate with the response. The addition of the third ring was done previously, but is now being done more systematically. In order to delineate the ring, a case must identify his or her contacts. When that does not occur, a ring does not open. By opening up the third ring, people who live in the same geographic area can be vaccinated. Resistance in a community is not homogenous. There are pockets in communities who do want to be vaccinated. By opening up the third ring, there is an avenue to do so.

Dr. Hunter noted that there was no discussion about any vaccine side-effects or implementation with HCP in the US. Working in local public health, he has had the opportunity to interact with laboratory staff about exposures such as an exposure to brucella. There are quite a variety of responses from individual laboratory staff regarding their personal risk and how long they are willing to take medications. Depending upon the level of recommendations in the 4 tiers of hospitals and the variety of responses that will occur, ACIP will have to give guidance on risk and potential vaccine complications. He expressed hope that the WG would be focusing on this issue.

Dr. Frey indicated that the WG has met only a couple of times and have not gotten to all of the discussion points. However, they will be talking in more detail in the future about the risk groups and how they think they should be managed.

Dr. Bernstein inquired as to how people who manifest dry symptoms are removed from the other contacts, given that they become increasingly contagious and their symptoms move quickly.

Dr. Choi indicated that in an outbreak, there is a confirmed case and a list of their contacts is obtained. These are individuals who are exposed to the patient while they are symptomatic. Questions are asked to try to delineate the timeframe. Teams then follow each contact every day for 21 days after their last exposure to the case. By checking on them daily using a standardized checklist of all of the symptoms, it is possible to find them the moment they develop symptoms. The contacts also are given contact information to call if they develop symptoms. As soon as an alert is raised, a special team will take the patient from the community to a designated facility where they will be tested.

Dr. Messonnier added that this is an exceedingly complicated outbreak in a conflict zone, which causes a lot of logistic challenges. There is some urgency around the first question posed, which regards people from the US who will be responding to the outbreak, working with specimens, and potentially caring for patients. CDC asked the WG to come to a rapid solution with regard to that relatively narrow issue, because it is anticipated that there will be a rapidly licensed vaccine for which they want to be equipped to move quickly on a recommendation because there are people who are at risk. She asked that ACIP try to focus on that issue first, given the anticipated pressure on the WG to reach a resolution quickly.

Dr. Hunter pointed out that if they focus on that issue, the question becomes, “Who is in and who is out in terms of who will really be at risk?”

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Dr. Choi indicated that the WG will be discussing and working through this. She specified generally who these groups are. Certainly, persons responding to an outbreak is not a homogenous population. CDC has been responding to Ebola outbreaks since 1976 and has not had anyone get infected. However, the 11 individuals who were affected during West Africa were HCP. Risk is not uniform and that will be addressed by the WG.

Dr. Szilagyi asked whether anyone through travel with dry or wet symptoms who infected anyone in the US or another country, which could be another at-risk population.

Dr. Frey said this would pertain to contact tracing, although the timeframe for the disease process is narrow and people die very quickly. There are mechanisms to address this, though not perfect.

Ms. McNally requested additional information about the second vaccine approved by the DRC with regard to the difference in the vaccines and the reason for the development of the second vaccine.

Dr. Choi indicated that the Merck vaccine is a single dose vaccine, while the second vaccine from Johnson & Johnson (J&J) is a prime-boost vaccine. The time between the doses is 0 and 56 days, which is one of the differences. That vaccine also protects against the *Zaire ebolavirus* species because of the way that the Ad26.ZEBOV/MVA-BN-Filo boosts, there was some theoretical thought that maybe it could protect against other species. However, that still needs to be evaluated. No animal data have been published to show that it cross-protects against the other species of Ebola virus. There have been some studies on the safety and immunogenicity of that vaccine that are ongoing. The idea in the DRC is to use it in an area that is not yet affected by the outbreak, but is within a zone of risk.

Dr. Messonnier noted that neither vaccine is licensed and asked under what mechanism they are being used in the DRC.

Dr. Choi indicated that both vaccines are will be administered under a “Compassionate Use” mechanism.

Dr. Frey added that the rVSV∆G-ZEBOV-GP vaccine is much further along in its investigations and data collection than the Ad26.ZEBOV/MVA-BN-Filo vaccine, which is why the WG is currently focusing on the rVSV∆G-ZEBOV-GP vaccine.

Safety and Immunogenicity of Ebola Zaïre Vaccine (rVSV∆G-ZEBOV-GP)

Beth-Ann Coller, PhD
Executive Director, Global Clinical Development
Merck

Dr. Coller expressed gratitude to CDC and ACIP for the opportunity to speak to them about the vaccine that Merck refers to as V920, which is somewhat easier to say than rVSV∆G-ZEBOV-GP. She presented a brief background on the vaccine, some non-clinical data, and an overview of clinical development in terms of efficacy data, validated immunogenicity data, and safety.

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As Dr. Choi mentioned, this vaccine initially was developed by PHAC. In the context of the 2014 West Africa Ebola outbreak, a number of private and public institutions became involved in the development and contributed in major and significant ways to the evaluation of this vaccine. This included colleagues at CDC, WHO, Medecins Sans Frontieres, and many other groups. Merck was proud to be a part of this collaborative development program in the Fall of 2014.

V920 is a live, attenuated, recombinant vesicular stomatitis virus (rVSV)-based, chimeric-vector vaccine, for which the VSV envelope protein was deleted and replaced (ΔG) by inserting only the envelope glycoprotein (GP) of ZEBOV. The surface of the virus looks like Ebola, but the interior proteins are all VSV. V920 is administered as a 1.0 mL dose by the intramuscular (IM) route. Because the development was done in the context of an outbreak with a great sense of urgency, there was not time to develop a thermostable type formulation. Therefore, V920 has to be stored frozen between -80ºC and -60ºC. Data have been generated to support the fact that the vaccine can be stored and/or transported at 2ºC to 8ºC for up to 2 weeks. Once thawed, it cannot be refrozen.

A number of preclinical studies were conducted to support licensure. PHAC conducted groundbreaking work prior to the outbreak to demonstrate that the vaccine had a high potential for efficacy in non-human primate (NHP) studies. This positioned the vaccine to go into Phase 1 clinical trials in the Fall of 2014. In parallel to clinical development, Merck contributed to the safety, immunogenicity, and efficacy database to support and better understand how this vaccine works. In terms of pharmacology, there are efficacy evaluation in monkey challenge studies, including dose ranging down to 300 plaque-forming units (pfu). Immunogenicity was assessed in separate studies in monkeys in addition to the challenge studies. Regarding toxicology, repeat-dose toxicity studies have been conducted in mice and monkeys. Biodistribution and persistence study have been conducted in monkeys. Developmental and reproductive toxicity studies have been conducted in rats. Because this is a genetically modified organisms based on a VSV backbone, a detailed environmental risk assessments was done to assess the ability of the virus to replicate in arthropod cell cultures and relevant vector species and evaluate the potential for infectivity and transmission in swine.

In terms of the results for two of the NHP studies that were conducted to assess the immunogenicity and efficacy of this vaccine in the context of cynomolgus macaque challenge models, collaborators at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) conducted studies AP-14-009 and AP-15-001-02. AP-14-009 was conducted in advance of or in parallel with some of the Phase I studies. This examined the same dose range as in the first Phase 1 studies from $3x10^6$ to $1x10^8$ pfu. There was 100% survival in the two highest dose levels, and 1 animal succumbing to the EVD in the lowest dose range of $3x10^6$. In a follow-on study intended to better understand correlates of protection, which are not understood for EVD or this vaccine, study AP-15-001-02 focused on a dose de-escalation to look for breakthrough. Happily in one way and unhappily in another, there was 100% survival all the way down to 300 pfu. The vaccine appears to be highly efficacy even at low doses in NHP. However, it has not been terribly helpful in informing correlates of protection.

In parallel to pre-clinical work and in the context of an outbreak, a considerable number of clinical evaluations were launched in 10 countries across 3 continent, including 5 countries in Africa including the 3 countries involved in the outbreak (Guinea, Sierra Leone, Liberia) as illustrated by this map:

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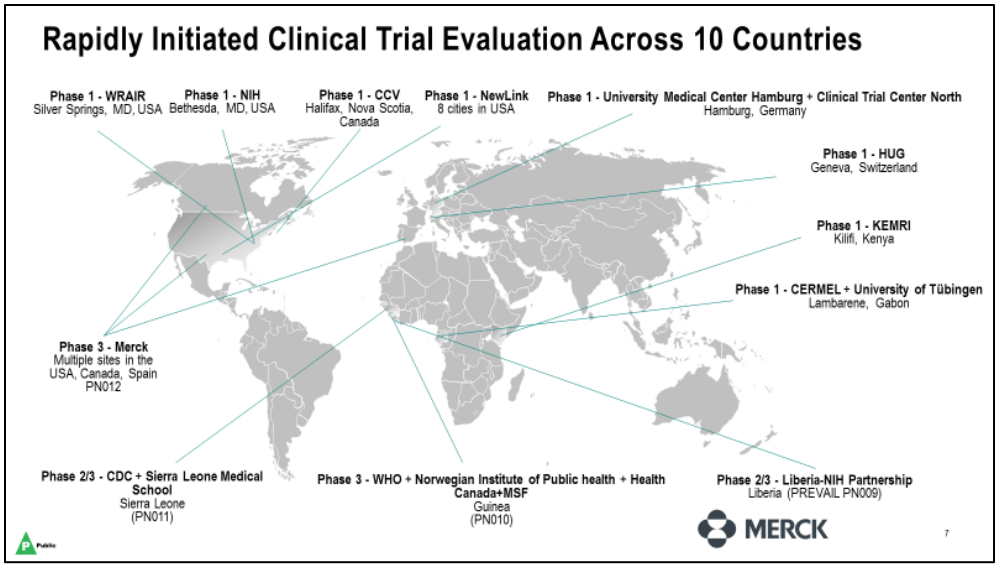

In fact, there were 13 clinical trials conducted in the context of the outbreak. There were 8 Phase 1 studies in which nearly 800 adult and 40 pediatric subjects received V920, and 5 Phase 2 clinical trials. This all happened very rapidly. The 8 Phase 1 trials began in the Fall of 2014 and by January 2015, a decision was made on the dose to take into the Phase 2/3 trials. The Partnership for Research on Ebola Virus in Liberia (PREVAIL) study sponsored by NIH and conducted in collaboration with the Liberian government began in February 2015, the Ebola ça Suffit trial in Guinea began in March 2015, and the Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) trial sponsored by CDC began in Sierra Leone April 2015. In total, more than 15,000 people were vaccinated with doses ≥ $2x10^7$ through these trials.

The Ebola ça Suffit trial in Guinea was the combination of a public health intervention of ring vaccination, which was used to help eradicate smallpox, and an RCT. The contacts of contacts of an index case (rings) were identified and then the rings were cluster randomized into immediate or delay vaccination 21 days later. In fact, it was this trial that was able to generate cases and assess the efficacy of the vaccine. The ring vaccination trial final efficacy results were published in early 2017. The point estimate of VE was 100% with a 95% confidence interval ranging from 63.5% to 100% with a p-value of 0.0471. That primary analysis represents the results from all vaccinated in the immediate arm versus all people who were eligible and consented on Day 0 in the delayed arm. The WHO also conducted a number of other types of analyses, all of which were consistent with evidence of efficacy. In the efficacy analysis, there were 0 cases of EVD from 10 days post-vaccination in the immediate arm. The delayed arm had 10 cases in 4 clusters. The 10 days post-vaccination is important because it was not clear exactly what time points to use to define the start of the efficacy assessment. The WHO looked at the typical time for the incubation period, which is typically captured as 2 to 21 days. By day 10, the majority of people who will present with EVD already have presented. The other equation was to allow time for vaccine induce an immune response and actually have an effect. Day 10 was defined as the time point to assess efficacy. Importantly, there were no cases of EVD occurring in any subjects whether they were in the immediate group, delayed group, or later in the trial in the non-randomized group from Day 10 post-vaccination onward [Henao-Restrepo AM, et al. Lancet. 2017;389:505-518].

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Immunogenicity was not assessed in the Ebola ça Suffit trial. The investigators were not able to collect blood samples, so there is no direct link between immunogenicity and efficacy. However, the other trials that were conducted in West Africa in Liberia, Guinea, and Sierra Leone and the study sponsored by Merck and conducted in the US, Canada, and Europe all examined immunogenicity. On Day 1 compared to Day 28, there was a clear immune response across all studies. They were validated by galactomannoprotein enzyme-linked immunosorbent assay (GP-ELISA) GMTs, which showed a robust response across all of the studies that were maintained down to Day 180 with a slight decline and then maintained out to Month 12 as well. The results from the US, Canada, and Europe tend to be higher than the results from the other studies. This is believed to be attributable primarily to the fact that the samples that came from the 3 epidemic countries had to be gamma irradiated before they could be tested in a BSL-2 laboratory in the US. Studies have shown that gamma irradiation resulted in about a 20% drop in the titers in those samples. Seroresponse rates also were quite high across all of the studies and were maintained out to Month 12.

Durability of the response is also an important topic. This was lacking in the efficacy trial because the Ebola ça Suffit trial looked out to only Day 84. After that, there were no more Ebola cases. Therefore, it is very important to examine the durability of the immune response. Based on the results from the study in the US, Canada, and Europe, out to 2 years there is good durability. While there is a slight decline over time, there is good durability of immune responses.

In terms of overall safety conclusions, the safety data in healthy, non-pregnant adults suggest an acceptable safety profile that in the context of demonstrated efficacy supports a positive benefit-risk ratio. V920 is generally well-tolerated in healthy, non-pregnant subjects 18 years of age and older, which is the indication that Merck will be seeing. Very few vaccine-related SAEs have been reported to date. That includes the efforts from the DRC that Dr. Choi referred to in which more than 230,000 people have received the vaccine under Compassionate Use. Injection-site reactions are very common, but are generally mild to moderate in intensity and of short duration. Systemic AE are reported more commonly in vaccinated subjects than placebo recipients include: headache, pyrexia, fatigue, myalgia, arthralgia, arthritis, chills, sweats (hyperhidrosis), nausea, abdominal pain, and rash. This is a live virus vaccine, so it replicates. The majority of joint events were mild to moderate in intensity and resolved in days (arthralgia) to weeks (arthritis); however, a few subjects reported arthritis of prolonged duration and/or with recurrences/sequelae. Skin- and mucosal-related AEs including rash with and without vesicles and mouth ulcers have been observed in V920 recipients. These have been generally mild to moderate in intensity and of short duration. Vaccine virus shedding is not frequent in adults and is more frequent in children. Secondary transmission has not yet been evaluated as part of the V920 program. Additional studies in children and HIV+ adults and adolescents have started, but data from these studies are not yet available. With limited data, safety in pregnant women has not been established.

With regard to regulatory status, Merck is pursuing licensure of this vaccine in the US. It is currently under review with the FDA, with a decision timeframe for March 2020. However, an earlier decision is anticipated. It also is under review in the European Union (EU). A positive opinion was issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) on October 18, 2019, and the European Commission is expected to make a final decision on that in the near future. It also is under review by 14 at-risk African countries and the WHO Prequalification group. This is typically done in series, but in this case, Merck has been working with all of these organizations to have them occur in parallel. The

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EMA has been collaborating with the WHO Prequalification group and the 14 African countries to conduct a parallel collaborative review.

The indication Merck is seeking is based on the efficacy data from the WHO's Ring Vaccination Trial, so the indication is quite focused on adults ≥18 years of age in reactive use settings. Ultimately, Merck hopes to seek supplementary indications based on immunobridging, trying to establish a correlate of protection, to look at immunobridging in children in the Partnership for Research on Ebola VACcinations (PREVAC) study, in HIV+ adults and adolescents in the African-Canadian Study of HIV-Infected Adults (ACHIV) study, and to assess durability of the immune response to support general use prophylaxis.

As mentioned earlier, access to V920 is being accomplished primarily under Compassionate Use or Expanded Access clinical protocols, including the protocol that is ongoing in the DRC. There also are some Emergency Decrees and Authorizations in some countries that allow vaccination of HCP prior to deployment. Within the US, there is an ongoing clinical trial that is being sponsored by the NIH for at-risk personnel at occupational risk of exposure of Ebola. The vaccine is being used in the North Kivu outbreak where more than 230,000 people have received the vaccine. In April 2019, the WHO conducted an interim analysis of efficacy and effectiveness in the DRC of the data to date and found that those data are consistent with the data from the Ebola ça Suffit trail, suggesting a high level of efficacy for the vaccine.

In summary, strong preclinical data, including evidence of protection after a single dose, positioned V920 to be an important candidate for development in response to the 2014-2016 Ebola outbreak. Merck, working in collaboration with a large number of partners, has advanced V920 through Phase 1, 2, and 3 clinical trials including more than 16,000 subjects. V920 was demonstrated to be highly efficacious in a randomized, controlled, ring vaccination trial conducted in Guinea. Clinical trials results also demonstrate the immunogenicity and safety of V920. Marketing Authorization Applications (MAAs) are under review in the US and EU. The WHO's Prequalification team has been included in a collaborative review of the EU dossier to expedite prequalification, together with select African countries, determined by past and current outbreak risk, to support expedited registrations in those respective countries. Merck is committed to ensuring vaccine availability in advance of product licensure in the face of an ongoing outbreak in the DRC.

Discussion Points

Dr. Romero asked how long the vaccine is stable at room temperature, whether they were able to parse the immunogenicity data for children, and how low in age they intend to go down under the regulatory strategy.

Dr. Griswold-Coller indicated that they have data to support holding the vaccine at 2^0 to 8^0 for 2 weeks after thawing. They have limited immunogenicity data from children that came from the Phase 1 trial in Gabon. The PREVAC Trial sponsored by the NIH is a large trial that is ongoing in West Africa in which approximately 1400 children have been enrolled to receive either the Merck vaccine or the Johnson & Johnson vaccine. Those are the type of data that would be utilized to support a supplemental indication for children. The lowest group for which use in children would be sought is 1 year of age.

Dr. Frey expressed interest in Merck's past licensure in terms of timing, particularly with regard to how realistic March 2020 is and whether they have discussed the terms and type of licensure with the FDA.

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Dr. Griswold-Coller replied that they are in active discussions with the FDA. They are working with a rolling submission that started last year, so FDA has been receiving pieces of the dossier since October 2018. The final component was submitted in July 2019, which started the review clock. FDA has granted Merck a priority review upon which the March 2020 date was granted. However, it was her understanding that the FDA is doing everything in their power to make a decision sooner. Merck is still actively answering questions as the FDA reviews the dossier.

Dr Maldonado (AAP) inquired about the number of children who have been studied to date, and whether they have any hypotheses as to why the number cases and deaths are higher than what were predicted from animal models in other trials.

Dr. Griswold-Coller indicated that the number of children in the dossier are very limited at 234 who were included in the Ebola ça Suffit trail and the Gabon Phase 1 trial. The PREVAC trial will provide a significantly greater number of children, but those data are not expected to be available for another couple of years. Tens of thousands of children have been vaccinated in the DRC, the data for whom will be provided to the regulators when they become available to Merck. The WHO is in the middle of an outbreak, so Merck anticipates that it will be a number of years before those data will be finalized and they can do a clinical study report. In terms of cases and deaths, the level of efficacy estimated is still very high as it appears that the vaccine has a very high level of efficacy. It is hard to go against 100%, which is a very high bar that has been seen in animals and in the Ebola ça Suffit trail. Those numbers are relatively small, but from everything they are hearing, the vaccine is still very highly efficacious.

Dr. Messonnier extended her compliments to Merck, given this incredible journey to get to a vaccine that is now before the FDA for licensure. The issue at hand for ACIP consideration is the first recommendation consideration, which pertains to people in the US who are at risk. In the event that ACIP makes a recommendation, she wondered whether there were any concerns about potential supply issues based on what is occurring globally since so many countries are now considering this vaccine.

Dr. Griswold-Coller said anticipates that this vaccine will be stockpiled by Biomedical Advanced Research and Development Authority (BARDA). Merck has worked closely with BARDA, which has been an amazing partner and funder for this work. It is anticipated that BARDA will be purchasing licensed doses and also has supported the production of large numbers of investigational doses that are supporting outbreak responses. The idea is that this would go into the Strategic National Stockpile (SNS), which differs from the VFC stockpile, and would be available for US personnel who are deemed at risk and who ACIP may recommend to receive the vaccine. Merck's vision, and the vision of the US Government as well, is that this will not be a vaccine that will be sold to individual doctor's offices, healthcare providers, and state departments of health. It would be provisioned to and distributed by the US government. Merck anticipates that there will be another stockpile, which will be more of the global stockpile that will be purchased by UNICEF and GAVI and governed through the WHO.

In terms of the immunogenicity data, Dr. Bernstein asked whether they had settled on 10^7 or 10^8 or if it did not really matter.

Dr. Griswold-Coller indicated that it was not linked to the dose. When she was comparing across the various bars, those were all the 2×10^7 dose. The difference for gamma irradiation was between samples from Africa versus samples from the US, Canada, and Europe. The samples from West Africa had to be gamma irradiated. There were data for the 1×10^8 dose

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that was tested only in the trial in the US, Canada, and Europe. Essentially, there is no dose response seen at those dose levels. In fact, the specifications for the vaccine that will be released are going to be between those two doses—the highest dose tested and the lowest dose that showed efficacy.

Dr. Hunter recalled that approximately 24% of people have some amount of arthritis after the vaccine, and he wondered whether that could be due to some of the individuals having had Ebola itself.

Dr. Griswold-Coller clarified that it was 24% in one trial, but was 5% or less in all of the other trials. They do not believe that this could be due to someone having had Ebola. Almost all of those cases were in developed countries, and there was almost no arthritis seen in the African countries. They conducted a post-hoc analysis looking for risk factors to try to understand. In fact, being female or having a history of damage to the joints was associated with a 2- to 3-fold increased risk of developing arthritis after receiving the vaccine. They think that those kinds of risk factors may exist. They do not understand why the rates were so much higher in the Geneva trial. They did use a different definitions of arthritis and they used imaging, which was not typically done in other studies.

Dr. Atmar asked about detection of the virus in people who have been vaccinated by PCR, which may or may not be viable versus by culture. In terms of the some of the transmission studies planned, particularly since this is initially going to be indicated for healthy adults, he wondered whether there were any plans to assess transmission to sexual partners. He thought they read that there were some cases from skin biopsies or aspirate in which live virus has been detected.

Dr. Griswold-Coller indicated that it was her recollection that all of the viremia and shedding assessments have been done based on PCR, so no data are available looking for live virus. That is partly limited by the sampling. The samples often are collected and put immediately into TRIZOL®, which then eliminates the ability to detect live virus. Nobody actually has looked for live virus. She was pretty sure that the virus detected from biopsies that Dr. Atmar mentioned was detected by PCR. They validated the PCR assay to be accepted for synovial fluid and so forth. They talk about detecting the virus, but to be precise, it is detecting viral ribonucleic acid (RNA). In terms of transmission to sexual partners, they have not looked specifically at whether there is virus present in semen. In the NHP biodistribution study, the only places where virus was detected out past Day 1 was in lymphoid organs. They are not sure whether that was live virus or residual that was left in the organs. They do not have data on the possibility for sexual transmission [*Post-Meeting Note from Dr. Griswold-Coller: In checking back in Geneva, they did isolate some viruses by culture*].

Dr. Frey requested clarification about the shedding being detected from the mouth, and that PCR positivity was noted in at least one or two vesicles.

Dr. Griswold-Coller clarified that they looked for shedding in saliva or oral fluids and urine. It was detected more frequently in saliva compared to urine. In adults, it is not frequent in either of those body fluids. In children, it was much more frequent. A relatively small number of vesicles were tested. They were aware of the results from the Geneva trial. In the Merck-sponsored Phase 3 trial, skin and join items were specifically solicited events and were referred to a dermatologist or rheumatologist for sampling and fairly significant work-ups were done. The numbers of subjects who actually had vesicles was not huge, and a small number were positive. The small number detected suggested to Merck that it was probably viral-mediated.

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Dr. Hunter noted that the clinical and epidemiologic characteristics of the transmission of the vaccine virus would be related to the stomatis virus, and not related to how Ebola virus gets transmitted.

Dr. Griswold-Coller said that they expected the trophism of the virus to be dictated by the surface glycoprotein, which should be Ebola. However, they do see these vesicles for example and this does suggest that, in fact, what they are seeing is the profile of the vaccine as a hybrid between the two viruses that make it up.

In terms of cell-mediated immunity, Dr. Frey wondered what kind of studies Merck may have done regarding CD4 and CD8 cells and whether they had looked at innate immunity. In some parts of the world, particularly in the DRC and war torn areas, nutrition is not likely as good as it should be. With that in mind, she wondered whether that might play a role in the antibody response to the vaccine.

Dr. Griswold-Coller indicated that they do not have any data on the potential effect of nutrition. The immune responses that they detected in Liberia, Sierra Leone, and Guinea were pretty robust with the 20% hit that they took with the gamma irradiation. In terms of cell-mediated immunity, there was early work done by PHAC and other that suggest that there is not a huge impact of this vaccine on inducing cell-mediated immunity. Therefore, they believe that the vaccine is driven primarily through antibodies. As would be expected with an antibody-driven response, CD4 depletion studies suggest that depleting CD4 can impact an antibody-driven response. For innate immunity, there are data from NHPs. The group at the NIH Rocky Mountain Laboratories (RML) have conducted studies that suggest that perhaps early protection with the vaccine may be linked to induction of innate immunity because there seems to be protection before there are even robust detectable immune responses.

Dr. Hunter asked whether the fact that there was not much cell-mediated immunity or memory meant that the next time there is an outbreak, people deploying to the next response would have to be revaccinated.

Dr. Griswold-Coller said that to her, cell-mediated immunity was perhaps separate from CD8. There is evidence of CD4 responses. With the durability, there is evidence of memory. They are continuing to look for evidence of durability of protection, which is an open question.

Work Group Interpretation and Next Steps

Mary Choi, MD, MPH
Viral Special Pathogens Branch
Centers for Disease Control and Prevention

Dr. Choi indicated that the WG has met twice at this point. During their last WG meeting, Dr. Griswold-Coller did provide a longer presentation of her presentation given during this session. The WG was able to begin some initial discussions regarding their thoughts on the interpretation of MERCK data. In general, there appears to be encouraging evidence for the effectiveness in prevention of EVD when administered in an outbreak setting using a ring-vaccination strategy. There appears to be an acceptable safety profile as well. The issue of arthritis as an AE in a subset of study participants in Europe and the US raised concern among the WG members, given the population for whom ACIP potentially would be making policy recommendations. The WG also needs to consider the fact that there is no known immune

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correlate for protection. As Dr. Griswold-Coller noted, IgG antibodies tend to persist after vaccination.

The WG will be further discussing the issue of virus dissemination and replication (skin, joints), and the fact that the Phase 1 study showed that this can occur and persist for up to 2 to 3 weeks after vaccination. There was evidence of seeding of rVSV-ZEBOV into joints as demonstrated by detection of rVSV DNA in synovial fluid, and there was replicating rVSV-ZEBOV recovered from skin vesicles. Some of these events after vaccination appeared to be a pathophysiology of chimeric rVSV-ZEBOV vaccine that may include features attributable to both its VSV backbone and ZEBOV glycoprotein components, which may play a role in the development of arthralgia and arthritis that have been noted.

Anticipated next steps for the WG are to continue to evaluate and discuss the immunogenicity and safety data, to start the Grading of Recommendation Assessment, Development and Evaluation (GRADE) and Evidence to Recommendations Framework (EtR), given this data with the US population pre-exposure scenario in mind. The WG will present policy options, with an anticipated vote on policy options, pending vaccine licensure, in February 2020. There is a potential for an emergency meeting in the event the vaccine is not licensed by February 2020.

Discussion Points

Dr. Fink (FDA) indicated that the FDA is diligently working to complete a thorough review and arrive at a licensing decision well ahead of the March date.

Dr. Lee requested clarification of what the policy option might be in terms of whether the focus would be just on HCP. In the Merck presentation, there was an initial indication of adults ≥18 years of age in reactive use settings. She assumed that US HCP would be included as part of the reactive use setting, but wanted to confirm that this was part of the anticipated policy option. She also wondered whether they would see potential risks for the initial populations.

Dr. Messonnier said that there are larger issues, but the urgency that CDC feels is a narrower group than the indication for the smaller population of laboratorians in the US, HCP who work in healthcare facilities who may be asked to care for Ebola patients, and those traveling overseas to respond to outbreaks.

Dr. Choi added that this is why they talked about the phases in the beginning. The WG's initial push at this moment, based on the current outbreak in the DRC and what Merck is seeking licensure for, is to make some recommendations for policy for very specific populations and then continuing that work in the second phase of the WG.

In terms of potential risks for the initial populations of interest for which the WG would make policy recommendations, Dr. Frey clarified that they are talking about people who are at least 18 years old, non-pregnant and non-lactating females, non-immunocompromised hosts, and people who are at risk in the US who are working in laboratories or overseas. They also will discuss whether there are different risks for different people. Depending upon what they decide, they will be consenting different risk categories. They have not had the opportunity to have this conversation yet, as they have met only twice. The WG just heard the Merck presentation the Friday before this ACIP meeting. The plan is to engage in detailed discussions about all of these issues.

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Dr. Choi added that in choosing the WG members, they had this issue in mind and have invited relevant individuals to help inform the WG's decisions.

Dr. Messonnier emphasized that this is a really complicated issue. They highly value being able to ask ACIP about difficult policy questions, to come to a rapid conclusion, and make a rapid recommendation if possible. If it is not, they understand. They just need to be transparent about why they cannot reach a resolution if that is the case. One thing she heard loud and clear was that for ACIP, it is not just about the immunogenicity and safety. There are a variety of practical implementation issues that need to be worked out before ACIP makes a recommendation in terms of specific risk groups, family, sexual partners, access to vaccine, etcetera.

Dr. Frey emphasized that the WG is fully aware of the ask and is working very hard to provide this information to ACIP by the February meeting.

Vaccine Safety

Introduction

Frank DeStefano, MD, MPH
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

Dr. DeStefano described CDC's vaccine safety monitoring systems, shared an example of HPV vaccine safety monitoring as a case study, and described broader national and international vaccine safety monitoring and research efforts.

Vaccine safety is a major consideration in all phases of the vaccine life cycle from initial vaccine development to pre-licensure studies and clinical trials and eventually after licensure. It is the after licensure phase where CDC and FDA safety monitoring begins. While Dr. DeStefano focused on the ISO's work, he acknowledged that there are several other agencies within HHS, other governmental agencies and organizations, and organizations outside government, including the vaccine manufacturers who are involved in the vaccine safety enterprise.

ISO uses three main systems to monitor and evaluate vaccine safety: VAERS, VSD, and Clinical Immunization Safety Assessment (CISA). Communication and response to inquiries from the public, physicians, and others is a cross-cutting function of ISO. VAERS is a spontaneous reporting system, or passive surveillance system. CDC co-manages VAERS with the FDA. It has a standard reporting form that anyone can submit (HCP, patient, parent, etcetera). The fillable PDF form collects information about the patient, HCP and reporter, AEs, vaccines received, and pre-existing medical conditions. Other information that is collected includes date of vaccination, AE onset date, vaccine type, lot number, and dose number. All reports are accepted without judgment on causality. CDC encourages reporting as soon as possible, but there is no time limit on reporting. The other main mechanism for reporting is an online form that includes the same fields as the PDF form. Well over half of the forms completed currently are done online, which is the preferred mechanism.

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To put the number of reports received in VAERS in context of the number of vaccine doses distributed, 164.3 million non-influenza vaccines were distributed in 2017, with 29,937 AE reports to VAERS or 1 report for every 5488 doses distributed. Currently, there are about 50,000 total reports per year. Influenza vaccines are separated out, given that this is by far the most common vaccine administered and that there are differences by age. Influenza vaccine reports include more older individuals; whereas, the reports for non-influenza vaccines have a higher proportion of infants and children. There were 159.1 million influenza vaccines distributed during the 2018-2019 season, with 11,138 AE reports to VAERS or 1 report for every 14,284 doses distributed.

A variety of methods are used to evaluate and analyze the VAERS reports. The first step is to code the signs, symptoms, and diagnoses using a standardized coding system known as the Medical Dictionary for Regulatory Activities (MedDRA). A more in-depth clinical review is conducted of reports, including medical records when available, for all serious reports and selected conditions of special interest. Trends and patterns of reports and reporting rates are assessed. Empirical Bayesian data mining analyses are done to detect disproportional reporting for vaccine-adverse event pairings to ensure that nothing has been missed.
As a spontaneous reporting system, VAERS has a number of strengths and limitations. It is important to be aware of the purposes for which it can and cannot be used. The primary strengths of VAERS are that it is national in scope, accepts reports from anyone, rapidly detects safety signals, can detect rare AEs, and data are available to the public. Its limitations include reporting bias, inconsistent data quality and completeness, lack of an unvaccinated comparison group, and general inability to assess causality. As a hypothesis-generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems.

The main system ISO relies on to conduct population-based surveillance and epidemiologic research is the VSD. The VSD was established in 1990 as a collaboration between CDC and several integrated healthcare organizations. There are currently 8 integrated healthcare organizations participating in the VSD, including: Kaiser Permanente Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Colorado, HealthPartners, Marshfield Clinic Research Institute, and Harvard Pilgrim. The VSD collects medical care and demographic data on over 12 million persons per year, links vaccination data to health outcome data, and is used for surveillance and research.

The VSD uses the infrastructure of the participating healthcare organizations beginning with their computerized databases to conduct initial analyses. Key to that are their computerized immunization registries. The databases are linked by de-identified study IDs that allows for linkage of an individual's immunization records to a variety of other types of other computerized data, including diagnoses from outpatient, ED, and hospital discharges. There is also access to other types of information as needed. Importantly, there also is access to individual medical records. That is important because medical record review is often necessary to validate the computerized diagnosis codes or obtain additional clinical details. VSD covers all of the members of the participating healthcare organizations. As such, information is available on both vaccinated and unvaccinated individuals and when they were vaccinated.

It is possible with the VSD to conduct follow-up studies as well, such as descriptive analyses (e.g., background rates, vaccination coverage), cohort studies, case-control studies, or self-control studies. VSD is also beginning to explore some data mining techniques, such as tree-temporal scan data mining. One of the main innovations of the VSD in recent years, particularly for near real-time surveillance, has been Rapid Cycle Analysis (RCA) for near real-time

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monitoring. RCA is a powerful surveillance tool that allows for near real-time vaccine-safety monitoring using sequential monitoring techniques. It employs an automated analysis of ICD-coded diagnoses from administrative data, which tend to be refreshed weekly. The system was designed to detect statistical signals (values above specified statistical thresholds). When a statistical signal occurs, CDC conducts a series of further evaluations, including traditional epidemiologic methods. Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment. Not all statistical signals represent a true increase in risk for an AE.

The third main project in ISO is the CISA project that involves participation of 7 medical research centers, including Boston Medical Center, Cincinnati Children's Hospital Medical Center, Columbia University, Duke University, Johns Hopkins University, Kaiser Permanente Northern California, and Vanderbilt University. CISA provides access to vaccine safety experts and experts in several other clinical disciplines and has two main purposes, which are to: 1) assist US healthcare providers with complex vaccine safety questions about their patients; and 2) conduct randomized clinical research that tends to be about specific vaccine safety questions, and may require in-person interaction with study subjects and sometimes collection of laboratory specimens.

To illustrate how these systems are used, Dr. DeStefano presented a case study of HPV vaccine. HPV vaccine has a well-established safety record. He first shared a timeline of CDC/ISO HPV vaccine safety monitoring activities and selected publications. With the introduction of the 9 valent HPV vaccine (9vHPV), ISO re-initiated VAERS and VSD monitoring of the safety of that expanded vaccine. Focused studies of vaccine safety questions or conditions also were conducted. The findings of all of these studies were published.

This table of the Top 10 reported signs and symptoms after 9vHPV vaccine in VAERS represents a fairly typical table that is generated from the VAERS reports:

Top 10 reported signs and symptoms[1] after 9vHPV in VAERS, Dec 2014-Dec 2017

Non-serious (n=7,058)	N (%)
Dizziness	529 (7)
Syncope	488 (7)
Headache	355 (5)
Injection site pain	316 (4)
Injection site erythema	314 (4)
Nausea	313 (4)
Pyrexia (fever)	283 (4)
Loss of consciousness	273 (4)
Injection site swelling	266 (4)
Pallor	235 (3)

Serious[2] (n=186)	N (%)
Headache	63 (34)
Dizziness	50 (27)
Nausea	48 (26)
Fatigue	42 (23)
Pyrexia (fever)	35 (19)
Asthenia (weakness)	34 (18)
Vomiting	33 (18)
Syncope	29 (16)
Abdominal pain	26 (14)
Loss of consciousness	26 (14)

[1] As coded using the MedDRA preferred terms (PT); more than one code may be assigned to a single event
[2] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

The reports are divided into serious and non-serious. In this case, the vast majority of reports were non-serious. The leading symptoms reported tend to be local reactions or systemic reactions. There is sometimes confusion about what the percentages mean in these tables. Looking at the example of syncope for which there were 488 (7%) reports, the 7% does not

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mean that 7% of people who received HPV vaccine experienced syncope. Instead, that represents 7% of the 7058 non-serious reports filed in VAERS for that vaccine. It is important to keep this proportion in mind because it also is what is meant when they talk about disproportionality.

VAERS Empirical Bayesian data mining is a sophisticated statistical method that can conduct disproportional reporting analyses, and analyzes thousands of MedDRA-preferred terms (PTs) to look for possible associations. Disproportional reporting was identified for syncope. This is not considered a signal, because syncope also was disproportionally reported for 4vHPV vaccine and is a known and labeled AE for any injectable vaccine. Other PTs signaled but did not represent an AE. Instead, these represented a drug administered to a patient of inappropriate age and other administration errors. No other disproportional reporting for 9vHPV vaccine was noted.

In summary, VAERS received 7244 reports following 9vHPV vaccine during the study period from December 1, 2014 through December 31, 2017. Most (97%) reports were non-serious. Approximately 29 million 9vHPV vaccine doses were distributed in the US. No new safety signals or unexpected patterns were observed. The conclusion was that the safety profile of the 9vHPV vaccine is consistent with data from pre-licensure trials and post-licensure data on the 4vHPV vaccine.

RCA also was conducted on the 9vHPV vaccine using a prospective cohort design. The surveillance period was from October 4, 2015 through October 3, 2017. The analysis included male and female health plan members 9 through 26 years of age enrolled in one of 6 participating VSD sites. This table lists the pre-specified AEs that were selected to be monitored based on findings from pre-licensure studies, from similar vaccines, and reports in the literature. Data were obtained from various outpatient clinic, inpatient or ED settings:

Pre-specified Adverse Events

Adverse event	Setting	Post-vax window	Primary comparison group
Syncope	OP, ED, IP	Day 0	Concurrent
Injection site rxn, w/ and w/o day 0	OP, ED, IP	0-6, 1-6 days	Concurrent
Allergic Reactions	OP, ED, IP	0-2 ED, IP 1-2 for OP	Concurrent
Seizure	ED, IP	0-42 days	Concurrent
Anaphylaxis	OP, ED, IP	0-2 days	Concurrent
Appendicitis	ED, IP	1-42 days	Historic
Pancreatitis	ED, IP	1-42 days	Historic
Guillain-Barré Syndrome (GBS)	OP, ED, IP	1-42 days	Historic
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	OP, ED, IP	1-180 days	Historic
Stroke	ED, IP	1-42 days	Historic
Venous Thromboembolism (VTE)	OP, ED, IP	1-42 days	Historic

*Historical comparison is based on VSD data from 2007-2014. Concurrent comparison is based on non-HPV vaccination visits during the surveillance period.

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Importantly for these analyses, a risk interval must be defined. That basically depends upon the AE in terms of what would be considered a biologically plausible window for a possible condition to be related to vaccination. There also has to be a comparison group for determination of possible more frequent occurrence of an AE. Depending upon the vaccine and such, that comparison group may vary. In summary of the findings from the VSD RCA, statistical signals

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occurred for several AEs after 9vHPV vaccine. Syncope and injection site reactions were expected and all other signals were further investigated. Signals for allergic reaction, pancreatitis, and appendicitis were not confirmed after further evaluation. That is, review of the medical records did not result in verification of the diagnosis. For example, several were determined to be a rule out diagnosis and not an incident event.

As mentioned earlier, evaluations also are conducted of specific conditions or safety questions. An example of evaluating a specific outcome would be reports of death following receipt of HPV vaccine. Death is the most concerning AE. There is a frequent misconception that VAERS death reports represent causal associations. However, a report filed to VAERS does not signify that the vaccine was the cause. A VAERS report only indicates a temporal relationship that an AE occurred sometime after a vaccination. An evaluation was performed of mortality reports following 4vHPV vaccine in VAERS for a surveillance period of January 2009 through December 2015 to see what could be discerned. During this period, 92 reports of death were submitted to VAERS. Of these, 61 were hearsay reports. That is, the person reporting did not have direct information so no medical information could be verified. An example of a hearsay report would be someone who saw mention of a death in social media. There were 2 reports that mentioned a cause of death (COD), but no patient or contact information were provided so it was not possible to obtain additional information. Ultimately, additional follow-up information was obtained that allowed for verification of 29 of the reports of death. The VAERS review of confirmed death reports found no pattern with respect to time after vaccination, combination of vaccines administered, or the diagnoses at death. The interpretation was that the VAERS data did not suggest a possible causal association with vaccination.

To look at this in a more systematic fashion epidemiologically, a VSD study was conducted to evaluate death among individuals 9 through 26 years of age from 2005 to 2011 in which medical records and coroners' reports were reviewed. There were 13 deaths identified within 0-30 days following 4vHPV vaccine. Of these deaths, 9 were due to external causes such as injuries, 2 were definitely unrelated to vaccination, and 2 did not have sufficient evidence to confirm or rule out a causal association. Based on these 13 deaths and the number of HPV vaccines that had been administered in VSD, the rate of mortality following 4vHPV vaccine was estimated to be 11.7 deaths per 100,000 persons per year. According to US published death rate for all causes among persons 15 through 24 years, the death rate should be 67.6 deaths per 100,000 persons per year. That is, a substantially lower death rate was found in VSD following 4vHPV vaccination. A large part of this is thought to be due to the healthy vaccinee effect. This possibility was addressed in a further analysis restricted to vaccinated individuals in VSD. The risk of death was not increased during the 30 days following 4vHPV vaccination compared to more distant time periods [McCarthy et al. Vaccination and 30-day mortality risk in children, adolescents, and young adults. Pediatrics 2016].

In summary of VAERS and VSD findings on HPV vaccine, no new safety concerns were identified in either VAERS or VSD RCA. Epidemiologic studies in VSD found no increased risks for autoimmune and neurologic conditions, venous thromboembolism, mortality, or pregnancy-related conditions. A few studies are still in progress in VSD on Postural Orthostatic Tachycardia Syndrome (POTS), Complex Regional Pain Syndrome (CRPS), and Chronic Fatigue Syndrome (CFS). The evidence for these has come primarily from case reports, case series, and expert reviews. Most of the reviews by experts and specialty societies have concluded that there is no evidence to suggest a causal association with these conditions. These conditions are heterogeneous and have a variable symptomatology, so it would be difficult to work out algorithms to identify these conditions in fully automated data. Therefore, feasibility studies are currently underway to determine whether these conditions can be

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identified reliably in the VSD to be able to study them and determine some epidemiologic measures.

In recent years, there has been an increasing focus on vaccine safety monitoring and research worldwide, as well as an increasing number of publications related to vaccine safety. International studies also have played an important role in evaluating the safety of HPV vaccine. A number of epidemiologic studies have been published on a variety of conditions that have been suggested at one point or another to possibly be related to HPV vaccination. Some of these were conducted in VSD. Several of the key studies come from Europe, particularly from the national registries and healthcare databases of countries such as Denmark and Sweden and large healthcare databases from England and France. None of these studies found increased risks related to any of the HPV vaccines for any of the conditions studied.

In conclusion, pre-licensure activities form the foundation of vaccine safety. The US has a comprehensive and robust vaccine safety monitoring system, which is essential to maintaining public confidence in vaccines. It also must be recognized that science is not sufficient in maintaining acceptance of vaccines. There is important work to be done in terms of communication, policy, and other factors. CDC is beginning a new strategic framework that is known as “Vaccinating with Confidence” with a goal of strengthening vaccine confidence and preventing outbreaks of vaccine-preventable diseases in the US.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that the previous week, CDC released its annual childhood and kindergarten data on immunization coverage. It is reassuring that coverage remains high overall in 2 year olds; however, it is disturbing that 20 states now have MMR coverage of less than 90% and there are communities with far lower coverage than that. This clearly puts these states and communities at risk. In addition, there are still disparities. Coverage is lower for children without private health insurance, living below the poverty level, or living in rural areas. This is especially disturbing given that there is the Vaccines For Children (VFC) safety net that should cover those children. Similarly, national coverage of kindergarteners remains near 95%. The proportion of children with an exemption increased slightly for the second year in a row, but it is still very low. Conversely, a number of states have children in what is known as the “grace period.” This is a situation in which a child begins school but does not have an appointment with the pediatrician until the next week, so the child is entered into a grace period. Many states and education departments do not have the resources to follow-up on those children, so the number of children in a grace period are actually higher than the number of children with an exemption in many states. They are trying to encourage support to close those grace period gaps.

In September 2019, CDC published its influenza vaccination coverage estimate for last season. Overall, overage was lower than desired at 62.6% among children 6 through 17 years of age. However, that is a 5% increase compared to the previous year. Among adults, coverage was 45%. That is an increase of 8% over the previous year. It is always nice when influenza coverage increases. However, it is important to remember that the previous season was a bad influenza season with a lot of pediatric deaths. That received a lot of publicity, when generally results trend up the year afterwards. Increasing coverage by even 5% would prevent another

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4000 to 10,000 hospitalizations annually depending upon the influenza season, so those small improvements in influenza vaccination coverage remain very important.

In addition, in September 2019, CDC published a *Vital*signs™ on maternal vaccination. *Vital*signs™ is CDC's way to harness the power of the communication enterprise at the agency to get out a message. This was an *MMWR* highlighting the importance of vaccinating pregnant women with Tdap and influenza vaccine, which is good for the mom and baby. It is important to build that infrastructure. AGOG has been very supportive of these efforts; however, not every obstetrician is prioritizing vaccination. It is known that even for obstetricians who do prioritize vaccination, moms present with many misconceptions about vaccines already. Therefore, it is important to do a better job in the whole of immunizations. It also is known that attitudes around vaccines are set frequently when moms are pregnant or in the first few weeks after they deliver their babies before they see their pediatrician for their first appointment. Therefore, that time period is very important in terms of ensuring that accurate information is provided to pregnant women and their families.

The President signed an Executive Order in September 2019 titled, "Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health." It promotes actions to improve the effectiveness of influenza vaccines and promotes influenza vaccination. In the interest of time, Dr. Messonnier did not go into detail but indicated that this order is published online. Many of the principles included in the order focus on improvement of immunization coverage and incremental improvements in the vaccines, as well as the long-term issues surrounding having a faster better vaccine for pandemic response.

Dr. Messonnier pointed out that it was World Polio Day, which is an opportunity for the world to end polio. Dr. Romero added that there will soon be an announcement about the total eradication of Poliovirus Type 3, which would now mean that Poliovirus Types 2 and 3 are eradicated and eradication is pending for Type 1.

Dr. Messonnier recognized Dr. Carol Baker, the liaison representative for IDSA, because she was recently elected into the National Academy of Medicine (NAM). This is one of the highest honors.

Department of Defense (DoD)

Dr. Deussing reported that the Military Health System (MHS) transition efforts continue to progress. These enterprise-wide changes will be aided by a new "Department of Defense Instruction for Immunizations" which will lead to increased vaccine oversight and accountability.

In terms of specific DoD vaccine programs, Dr. Deussing has reported on DoD's Yellow Fever (YF) vaccine supply challenges over the past several years. The DoD continues to experience some intermittent supply constraints; however, they fortunately have returned to unrestricted ordering in support of operational and travel requirements.

The DoD has begun exploring the potential utility of the newly licensed JYNNEOS™ smallpox vaccine for Force Health Protection. Also new and of note, the DoD will begin utilizing the Southern Hemisphere influenza vaccine for service members assigned to duties within the Southern Hemisphere. In regard to seasonal influenza, the DoD has initiated its annual influenza vaccination campaign with the goal of vaccinating over 90% of Active Duty, Select Reserve Forces, and HCP by January 15, 2020.

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During the last ACIP meeting, Dr. Deussing provided an update on the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD or (PAIVED) study, which is co-chaired by the Immunization Healthcare Division (IHD) and the Uniformed Services University's (USU's) Infectious Diseases Clinical Research Program (IDCRP). As a reminder, this is a prospective comparative effectiveness study, randomizing participants to recombinant, cell culture, or egg-based influenza vaccines. They are initiating the second research year adding three new sites this season for a total of 14, and increasing target participants from 10,650 to 15,000. Dr. Deussing looks forward to providing an update on this study's progress during future ACIP meetings.

The IHD's South Atlantic Region Vaccine Safety Hub (RVSH) recently presented research identifying major risk factors and most effective treatment pathways associated with Shoulder Injury Related to Vaccine Administration (SIRVA). This data represents the largest case series related to SIRVA available to date.

Since June, the IHD has conducted seven on-site Immunization Lifelong Learners Course (ILLC) and Immunization Lifelong Learners Short Courses (ILLSC) for more than 400 students. They also have several other educational products for military medical personnel, including a comprehensive Immunization Tool Kit reference booklet, on-site assessments of clinics' immunization practices, and online training modules.

Department of Veterans Affairs (DVA)

Dr. Califano reported that the VA completed the update for its "2019-2020 Seasonal Influenza Clinical Preventive Services Immunization Guidance Statement." Updates included the composition changes for the 2019-2020 influenza season, and updated tools and resources to assist VA clinicians with implementing this guidance.

Food and Drug Administration (FDA)

Dr. Fink reported that FDA will convene its Vaccines and Related Biological Products Advisory Committee (VRBPAC) on November 8, 2019 to discuss approaches to demonstrating effectiveness for chikungunya vaccines. They will not be discussing any specific vaccine candidates, although manufacturers of vaccines currently in clinical development will be presenting during the meeting. The announcement for the meeting was posted in the *Federal Register*.

On September 24, 2019 FDA approved a new vaccine called JYNNEOS™ manufactured by Bavarian Nordic. This vaccine is a 2-dose series indicated for prevention of smallpox or monkeypox in adults 18 years of age and older who are at risk of either of those two diseases. The demonstration of effectiveness was based on a package of data that included immunological comparison to the licensed smallpox vaccine, ACAM2000, with regard to vaccinia neutralizing antibody responses. The package also included animal data specifically showing that the vaccine protected NHP against monkeypox challenge. For safety, the vaccine was evaluated in over 8000 pre-licensure trial subjects and compared to over 1000 placebo-control subjects. The vaccine was reviewed and approved under FDA's Priority Review program because it is a non-replicating vaccine, it does not carry with it some of the serious potential complications related to replicating or conventional smallpox vaccines.

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Health Resources and Services Administration (HRSA)

Dr. Rubin reported that the National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In Fiscal Year (FY) 2018, 1238 claims were filed with the VICP. In that same FY, $199.6 million was awarded to petitioners and $26.9 million was awarded in attorneys' fees and costs. This includes fees for compensated, dismissed, and interim cases). As of September 25, 2019, over 1230 claims were filed with the program, and $222.1 million was awarded to petitioners and for attorneys' fees/costs. As of September 25, 2019, HRSA had a backlog of 854 claims alleging vaccine injury awaiting medical review. More data about the program can be obtained on the HRSA website. As of September 25, 2019, the Countermeasures Injury Compensation Program (CICP) compensated 39 claims totaling $5.5 million.

Indian Health Service (IHS)

Ms. Doss-Walker reported that IHS has been exploring ways to improve childhood immunization coverage rates among IHS federal facilities. This summer, IHS conducted key informant interviews and administered a national survey among providers who administer vaccines to American Indian and Alaska Native (AI/AN) children within IHS. This included physicians, physician assistants, clinical and public health nurses, and pharmacists to assess their knowledge, attitudes, and practices around childhood immunizations. Their input and recommendations on how to improve childhood immunization rates and potential successful interventions were solicited and findings are currently being analyzed. The hope is that the survey results will help inform potential interventions, and IHS looks forward to sharing the findings during the next ACIP meeting.

In addition, IHS is currently transitioning the forecasting system within its electronic health record (EHR), Resource and Patient Management System (RPMS), from the Texas Children's Hospital Immunization Forecasting Software (TCH Forecaster) to the Immunization Calculation Engine (ICE) Forecaster in 2020. Internal testing is currently underway, and IHS anticipates a national release in early spring. This impacts almost 200 IHS facilities across the country, and will help to ensure that these facilities have the most up-to-date and accurate ACIP recommendations to provide patient care.

National Institutes of Health (NIH)

Dr. Beigel reported that as usual, NIH has numerous ongoing Phase 1 and Phase II studies across the infectious disease spectrum. He emphasized that this was not intended to be an inclusive update, but would instead highlight a few high-level items that might be of interest to the ACIP. A few months ago, NIH started a study for using licensed influenza vaccines with novel adjuvants across manufacturers, which has been a barrier in the past. This is two different licensed vaccines, two different adjuvants, and an unadjuvanted arm. They believe this will be very informative about how vaccines and adjuvants interact, and how to boost the immune response.

Earlier in the week, NIH started an influenza challenge study. This work was very prominent in the 1990s, was absent in the 2000s, and was rekindled. This provides a way to test novel vaccines and therapeutics in a human controlled infection model. This is very exciting and they are looking forward to much more work with this.

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Several large programs were recently awarded. The first is Collaborative Influenza Vaccine Innovations Centers (CIVICs) to advance the development of novel influenza vaccines, which has its own manufacturing and clinical cores. Another is the Sexually Transmitted Infections Cooperative Research Centers (STI CRC) program, with a focus on the development of vaccines to control and prevent STIs. The awardees are a very distinguished group of academic centers that hopefully will move this field forward. Finally, there are large awards for the Immune Mechanisms of Protection Against Mycobacterium Tuberculosis (IMPAc-TB) Centers, which are working on better tuberculosis (TB) vaccines that are thought to be critical for control of TB.

Office of Infectious Disease Policy and HIV/AIDS (OIDP)

Dr. Beckham provided an update on OIDP activities. OIDP is responsible for developing the National Vaccine Plan (NVP). As such, they are in the process of developing the updating plan. As a part of this effort, OIDP has been seeking input from their stakeholders and HCP. The National Vaccine Advisory Committee (NVAC) also was charged by the Assistant Secretary for Health (ASH) to provide input into the goals and priorities of the 2020 NVP. NVAC developed a draft report on their recommendations on the goals and priorities on the next 5-year plan. NVAC voted on this in September 2019, and also provided input to OIDP on stakeholders. OIDP posted a Request for Information (RFI) seeking input from the public on ways to strengthen and improve the vaccination system across the lifespan, communicate priorities for insuring safe and effective vaccination, and the optimal use of vaccine. The RFI comment period was scheduled to close at the end of the day at 5:00 PM Eastern Time.

In August 2019, OIDP concluded the HHS Regional Adult Immunization Stakeholder Meeting Series. That effort was developed in support of a National Adult Immunization Plan (NAIP). Over the past 2 years, the initiative brought together nearly 500 immunization stakeholders from almost every state across the country to discuss strategizing and collaborating around immunization at the local, state, and regional levels. In collaboration with HHS regional offices, the 10 regional meetings sparked a number of activities that are poised for impact at the regional and national levels. A few of those examples include re-establishing immunization coalitions in Illinois and Minnesota; training stakeholders on how to use immunization registries to optimize HPV vaccination in New Jersey, New York, and New York City; and developing and strengthening partnerships among state health departments and departments of corrections to enhance vaccination among correctional facility populations. They also gathered a number of promising practices throughout the initiative, which they plan to share in the final report on the website in the next few months.

NVAC has been incredibly busy in addition to working on the NVP priorities, goals, and recommendations for that report. NVAC is working to support two additional charges that the ASH, Admiral (ADM) Brett P. Giroir, gave them. One of those is to develop a comprehensive set of recommendations to lay the foundation for an effective national strategy for ending immunization disparities in the US to ensure that all Americans have an equal opportunity to benefit from life-saving vaccines. The second is to write a report to assess the determinants of vaccination confidence across the lifespan, with suggestions for HHS to improve confidence in all recommended vaccines. The next NVAC meeting will take place at the Humphrey Building in Washington, DC on February 13-14, 2020.

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Orthopoxvirus Vaccine

Beth Bell, MD MPH
ACIP Orthopoxviruses Vaccine Work Group Chair
University of Washington

Dr. Bell presented an overview of the newly forming Orthopoxviruses Vaccine Work Group (WG). By way of background, *poxviridae* are a family of deoxyribonucleic acid (DNA) viruses that infect a broad range of hosts. The *orthopoxvirus* genus includes several species that cause disease in humans, including:

- *Variola virus* (causative agent of smallpox)
- *Vaccinia virus* (principal source of smallpox vaccine)
- *Monkeypox virus* (cause of multiple outbreaks in Africa and imported cases to other countries, including the US)
- Cowpox virus (endemic in Europe)
- Newly discovered species (*Akhmeta virus*, *Alaskapox virus*)

A number of settings have been well-recognized where occupational exposures can occur. This includes diagnostic laboratorians who directly handle specimens from persons with suspect orthopoxvirus infections; research personnel use replication-competent orthopoxviruses in biomedical research; and healthcare personnel (HCP) in the US who either administer *Vaccinia virus* vaccine (e.g., to military personnel), or would treat patients with smallpox or monkeypox due to accidental or intentional exposures.

Serious infections have occurred during laboratory and research work, such as ocular vaccinia in a laboratory worker and needlestick inoculation of a researcher using vaccinia virus as a vector. Clearly, vaccination with an orthopoxvirus vaccine can prevent these infections. Vaccinia virus vaccine provides cross-protective immunity against other orthopoxviruses, facilitated smallpox eradication as the main component of smallpox vaccine, and currently is recommended by ACIP for use in laboratory and HCP at risk for occupational exposure to orthopoxviruses.

The brand name of the first generation vaccinia virus vaccine was Dryvax®, which was manufactured by Wyeth Laboratories, Inc. Dryvax® was propagated in calf skin and was updated in the ACIP Statement in 2001. In 2015, the second generation vaccine with the brand name ACAM2000™, manufactured by Acambis, Inc.™, replaced Dryvax®. It is propagated in tissue culture and is made from a purified clone of the strain that was used to make Dryvax®. Importantly, it has a safety profile that is similar to that of Dryvax®. As just reported by Dr. Fink from the FDA, a third generation vaccine by Bavarian Nordic, JYNNEOS™, was licensed in September 2019. JYNNEOS™ is an attenuated, live, replication-deficient vaccinia virus that can be used in persons for whom ACAM2000™ is contraindicated.

The new WG is being formed to update ACIP recommendations for use of JYNNEOS™ to prevent orthopoxviruses in persons at risk for occupational exposure. Planned WG activities are to: 1) review available data about safety and effectiveness of JYNNEOS™, including among persons with atopic dermatitis, immunocompromising conditions, pregnancy, and people who have household contacts who fall into these categories—the major groups for whom

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ACAM2000™ is contraindicated; 2) consolidate US recommendations for vaccination of persons who may have occupational exposures to orthopoxviruses; and 3) identify areas in need of further research for informing potential future vaccine recommendations to prevent *orthopoxvirus* infection.

In terms of the tentative timeline, work has been underway to determine the scope of the WG and collect available data. November and December 2019 will be spent continuing to identify the WG members. WG meetings are anticipated to begin by January 2020, and ACIP can expect to begin hearing detailed presentations by the June 2020 meeting. The new guidelines are anticipated to be published in 2021. The WG Co-Leads are Agam Rao, MD and Brett Petersen, MD, MPH. The next steps will be to begin identifying WG members, reviewing data, and convening WG meetings.

Discussion Points

Having dealt indirectly with a case of monkeypox in the clinical setting in Milwaukee, Dr. Hunter indicated that he has had some experience with this. He wondered whether the vaccine had been studied in Western Africa with people who could have been exposed to monkeypox.

Dr. Petersen indicated that CDC currently has an ongoing clinical study evaluating this vaccine in the DRC in a province where monkeypox is endemic. The goal of the study is to assess the safety and immunogenicity of the vaccine, as well as to identify any exposures or incidents of infection to try to provide evidence of effectiveness specifically in this population at risk. In the first phase of the study, which was recently completed, 1000 HCP in this province were vaccinated and they were monitored for 2 years for AEs, exposures, and infections with monkeypox.

Dr. Hunter said that he knows from personal experience from interacting with the laboratory at the City of Milwaukee Health Department that samples are sent out to laboratories on a regular basis to prepare them to deal with orthopox exposures, and they also engage in tabletop exercises. With that in mind, he suggested inclusion of laboratory workers on the WG.

Dr. Bell indicated that the LRN is engaged in this effort, which is always an important group to include for these kinds of conditions.

As mentioned earlier, Dr. Fink (FDA) pointed out that it is important to remember that the term “contraindication” might differ in ACIP’s recommendations versus FDA labeling. There are clear differences in safety risks between ACAM2000™ and other replicating smallpox vaccines as compared to the newly licensed smallpox vaccine. ACAM2000™ is contraindicated per FDA labeling only in severely immunocompromised individuals who would not benefit from the vaccine.

Dr. Bell acknowledged that this newly formed WG would offer the opportunity to address the issue of the difference in terminology so as to avoid confusion. In the ACIP recommendation, there is a different way of looking at who should receive ACAM2000™.

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Dengue Virus Vaccine

Introduction

Robert Atmar, MD
Chair, Dengue Vaccines WG
Advisory Committee on Immunization Practices

Dr. Atmar reported that in addition to a review question and issues that arose during the June 2019 ACIP dengue vaccines session, since June the WG has discussed the following topics:

- ❑ Dengue vaccines in seronegative individuals, with new insights from vaccine trials and laboratory research
- ❑ Development of a perspective on partially effective vaccines, primarily in persons who are seropositive
- ❑ DENGVAXIA® implementation feasibility in Puerto Rico in children 9 through 16 years of age
- ❑ Orientation of new members to previous WG discussions
- ❑ Cost-effectiveness of CYD-TDV in Puerto Rico
- ❑ CYD-TDV GRADE analysis

Dr. Atmar indicated that presentations would be provided on the following topics during this session:

- ❑ GRADE Analysis for DENGVAXIA®
- ❑ DENGVAXIA® Cost-Effectiveness in Puerto Rico
- ❑ Summary of WG Discussions and Next Steps

Future WG plans are to present information about DENGVAXIA® acceptability and feasibility in Puerto Rico and Evidence to Recommendations (EtR) during the February 2020 meeting. Topics for the June 2020 ACIP have not yet been determined.

GRADE Analyses for Dengue Vaccine CYD-TDV

Gabriela Paz-Bailey, MD, PhD, MSc
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Centers for Disease Control and Prevention

Dr. Paz-Bailey indicated that the objective of this talk would be to review dengue and why it is a public health problem, review CYD-TDV increased risk among younger and seronegative children, present the PICO (Population, Intervention, Comparison, Outcomes) and policy question, and review the GRADE analyses of the evidence on CYD-TDV.

Dengue virus is transmitted by *Aedes* species mosquitoes, primarily by *Aedes aegypti* and *Aedes albopictus*. It is the most important arbovirus in terms of worldwide morbidity and mortality. It is estimated that there are about 390 million infections annually, of which approximately 100 million infections are associated with clinical manifestations. In addition, there are about 500,000 hospitalizations and 20,000 deaths estimated per year. Epidemics

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typically have a cyclical pattern over years and seasonal incidence correlated with higher temperatures and rainfall months. Dengue virus (DENV) is a public health problem throughout the tropics and subtropics in 128 countries and is endemic in Asia, Latin America, the Caribbean, Africa, and the Pacific. With increasing travel and connectivity and rising world temperatures, more areas are becoming at risk. Dengue is caused by four antigenically closely related viruses (DENV-1, DENV-2, DENV-3, DENV-4). Clinical disease varies from a mild, undifferentiated fever to severe disease with shock, hemorrhage, and/or severe organ impairment such as hepatitis or encephalitis. The case-fatality ratio for severe dengue is 10% or higher when untreated, but can be reduced to <1% with good clinical management. A major risk factor for severe dengue is secondary infection with a different virus type.

Dr. Paz-Bailey reviewed the efficacy data among all age groups as background to the GRADE analyses, noting that the GRADE analysis would focus on children ages 9-16 years. CYD-TDV is a tetravalent, live-attenuated viral vaccine on a yellow fever (YF) backbone with precursor membrane and envelope genes isolated from each dengue serotype. The vaccine has four genetic constructs, one for each serotype. The main studies that evaluated efficacy were CYD14 and CYD15. These were Phase III randomized, observer-blind, placebo-controlled studies. CYD14 included 11 centers across Asia Pacific and a total sample size of 10,275 randomized 2:1. Only 2000 subjects had baseline samples to determine serostatus before vaccination. CYD15 included 22 centers across Latin America and a total sample size of 20,869. Again, only 2000 had known serostatus at baseline.

To summarize the vaccination schedule and trial follow-up time, 3 doses of the vaccine were administered at 0 months, 6 months, and 12 months. Vaccine efficacy (VE) against virologically confirmed dengue (VCD) is available up to 25 months when the active phase of the trial ended and the hospital phase started. The hospital phase of the study monitored the risk of hospitalization and severe dengue up to 6 years after the first dose of vaccine. VE against symptomatic VCD was lower among younger participants. In CYD14, it was 34% among children 2-5 years of age, 60% among children 6-11 years of age, and 74% among children 12-14 years of age. This efficacy data includes both seropositive and seronegative participants. No efficacy difference by age was seen in the study in Latin America which did not include children less than 9 years of age. CYD14 analysis identified a safety signal with increased hospitalization, relative risk of 7, during the third year of follow-up among the youngest children who were vaccinated compared to controls. This finding resulted in WHO recommending the vaccine for individuals 9 years of age and older.

Sanofi conducted a special study to further assess the increased risk of hospitalization and severe dengue. As mentioned earlier, the efficacy trials assessed baseline serostatus in a subset of participants. This limited subset, referred to as the immunogenicity subset, did not allow for precise estimates of the risk of hospitalization for dengue or the risk of severe dengue in seronegative vaccine recipients. In an effort to overcome this limitation, a case cohort study was conducted. Blood samples that had been collected after the third vaccination were used to retrospectively determine baseline serostatus using a new IgG assay that differentiates wild dengue from vaccine dengue past infection in this post hoc study. All cases of VCD, hospitalization, and severe dengue were included and 10% of participants were randomly selected after stratifying by age and site. In the supplemental study, Sanofi investigators used different analytical methods, including multiple imputation (MI), targeted minimum loss-based estimator (TMLE), and the NS1 test results from Month 13.

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This supplemental study showed that while the vaccine was effective against hospitalization and severe dengue among seropositives, efficacy was greater among older children. The hazard ratio was 0.50 for children 2-8 years of age for hospitalization and 0.21 for children 9-16 years of age for hospitalization. The findings was similar for severe VCD. The most important aspect in defining this vaccine only for seropositives is the increased risk of hospitalization and severe dengue among seronegatives. The increased risk was significant overall and among younger children, and a non-significant increased risk was seen for the older children. These data became available later, and after the first round of WHO recommendations on DENGVAXIA®, and resulted in revised recommendations by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) to vaccinate seropositive individuals only.

The FDA approved CYD-TDV in May 2019. The indication was for children 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Previous dengue infection can be assessed through a record of a previous positive laboratory test or through serological testing before vaccination. Established tests can diagnose acute symptomatic dengue infections, such as polymerase chain reaction (PCR) and immunoglobulin M (IgM) testing. However, a dengue seropositivity screening test would need to be able to identify with high accuracy true positive and true negative past infections that may have occurred several years in the past. The performance of the available IgG tests for this purpose Is uncertain. High sensitivity and specificity are needed, and positive and negative predictive values will be affected by the background seroprevalence.

SAGE has proposed that the target product profile of a dengue screening test would need to be a rapid diagnostic test that measures dengue-specific IgG that can be used from finger prick blood, provide a result in less than 30 minutes, have a specificity and sensitivity above 90%, and have high positive and negative predictive values. Tests with a given specificity and sensitivity are more likely to misclassify truly seronegative individuals in low transmission settings versus high transmission settings, because the pre-test probabilities are lower. To illustrate, Dr. Paz-Bailey shared two examples. In an example with 20% seroprevalence, with a test specificity of 90% and a test sensitivity of 70%, 36% of persons testing positive would be false-positives or actually negative for past dengue infection. In a higher prevalence setting of 80% seroprevalence, the positive predictive value is higher at 97% and only 3% of persons testing positive would be false positives. The problem here would be imperfect sensitivity, since more than half of those testing negative would be true seropositive who could benefit from the vaccine.

Turning to the review of the policy question and the results of the GRADE analyses, the target population for the policy question was persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in the endemic areas of Puerto Rico (PR), American Samoa (AS), US Virgin Islands (USVI), Palau, or the Federated States of Micronesia (FSM). The intervention was routine administration of three doses of CYD-TDV and the comparison was no vaccine. The outcomes of interest were symptomatic dengue illness, hospitalization, and severe dengue. The dengue risk definition was used from the *CDC Yellow Book* that provides health information for travelers. The *Yellow Book* defines areas with frequent or continuous risk as "those that report 10 or more dengue cases in at least 3 distinct years over the most recent 10-year period." These criteria then define endemic areas as including the US territories of AS, PR, and USVI, and the US-affiliated FSM and Palau [Jentes et al. Journal of Travel Medicine 2016; 23, 6, 1-5].

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To provide some context on the populations who would need to be vaccinated, here are the estimated children 9-16 years of age in Palau, AS, USVI, FSM, and PR. Of note, 90% of those who need to be vaccinated reside in Puerto Rico:

Territory	Population 9-16 Years
Palau	1,934
American Samoa	10,192
USVI	12,204
Federated States of Micronesia	19,000
Puerto Rico	296,696

Sources: USVI and AS 2010 Census, Palau and Micronesia 2015 UN Population Division; Puerto Rico 2018 American Community Survey

The policy question for this GRADE analysis was, “Should 3-doses of CYD-TDV be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas to prevent virologically confirmed dengue, hospitalizations, and severe dengue?” After discussion with the Dengue Vaccine WG, dengue fever, hospitalization of VCD, severe dengue, and death were considered critical. In terms of harms, injection site reactions and systemic reactions were considered important but not critical. Serious adverse events (SAEs), hospitalizations, severe dengue, and death were considered critical.

A systematic review was conducted of CYD-TDV vaccine trials in Medline, Embase, CINAHL, Cochrane Library, and Scopus published between 2009-2019. A search was done for trials of CYD-TDV in 9-16 year olds by serostatus. Efforts also were made to obtain unpublished or other relevant data, and the manufacturer was contacted for additional data on safety. Of 710 results, 351 were reviewed. Most were excluded because of a different dengue vaccine. Ultimately, there were 2 papers that included all data from the Phase 3 trials and a Phase 2b trial. Of the 30 papers found that described safety, 13 were included and Sanofi was contacted for the data on the 9-13 year old age group. As a reminder of the evidence types, evidence is ranked as 1 for randomized controlled trials (RCTs) or overwhelming evidence from observational studies. A 2 is given to RCTs with important limitations or strong evidence from observational studies, 3 is given to observational studies or RCTs with notable limitations, and 4 is given to clinical experience and observational studies with limitations.

Most of the outcomes data come from the two Phase 3 trials. Capeding et al was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam) among 2-14 year olds with a total sample size of 10,000 participants. Serostatus was only available for a subset that included 1340 seropositive and 643 seronegatives. Villar et al was conducted in 5 countries in Latin America (Colombia, Brazil, Mexico, Honduras, Puerto Rico) among 9-16 year olds with a sample size was 21,000. However, serostatus was known only for 1500 seropositive and 400 seronegative. The Sabchareon trial was a Phase 2b trial conducted in Thailand. These data were not used for efficacy, but were used to assess long-term hospitalization and severe dengue risk. Two studies, Handinegoro and Sridar, aggregate the data from the three trials. Handinegoro combines the two Phase 3 trials and Sridar is the supplemental study described above that used a case cohort analyses and includes the two Phase 3 studies and the Phase 2b for safety.

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In terms of the efficacy for the outcomes considered critical, Dr. Paz-Bailey limited the results to the population of the PICO question, children ages 9-16 years. However, she also presented the data on seronegatives to consider the risk of misclassifying a seronegative individual as seropositive and vaccinating them. [1]With regard to the efficacy results to prevent VCD fever at the end of the active phase of surveillance (25 months) among 9-16 year olds by serostatus in the study in Asia and Latin America and for both studies combined, efficacy was demonstrated for seropositive individuals. The results are consistent in the individual trial and combined results with efficacy of 79% in Asia, 84% in Latin America, and 82% of the two combined. For seronegative subjects, the efficacy estimates for each trial crossed 1 and the combined results showed significant protection. However, the confidence intervals were very wide (5.9-76.1). These results are for the immunogenicity subset; that is, the individuals for whom serostatus was known at baseline and are slightly different from the ones presented in the package insert. [2]With respect to the efficacy data by serostatus showing higher efficacy for serotype 4 and 3 and lower for 1 and 2 among seropositive, among seronegatives, protection was only significant for serotype 4 [[1]Hadinegoro SR et al. N Engl J Med 2015;373:1195-1206; [2]Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340].

Regarding the impact of the vaccine against hospitalization and severe dengue, Dr. Paz-Bailey presented the results on the longer-term follow-up 6 years after vaccine administration. The results by serostatus on vaccine protection against hospitalization and severe dengue were available only from the supplemental study and the longer-term follow-up during hospital-based surveillance. Dr. Paz-Bailey emphasized that she was presenting relative risks and not VE. The long-term follow-up data 5-6 years post-dose 1 for children ages 9-16 years of age showed reduced risk of hospitalization and severe dengue by all three analyses methods among seropositives, and a non-significant increased risk of hospitalization and severe dengue among seronegative vaccines compared to controls. Relative risk of hospitalization among seropositives was lower for serotype 4 (0.07), but with wide confidence intervals, and was similar for the other serotypes (0.22, 0.18, 0.38). No significant protection was observed for each serotype among seronegatives. Risk of severe dengue among seropositives was lowest for serotype 4, and protection was not significant for serotypes 1 and 3. [Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340].

In terms of the evidence for SAEs and deaths, there were no differences in SAEs at 28 days. At 6 months, there were fewer AEs in the vaccine group compared to the control group. An equal number of deaths occurred in the vaccine and placebo groups [Gustavo Dayan from Sanofi personal communication].

Moving to the evidence levels, for the outcome of VCD among seropositives, the initial evidence level was 1. Risk for bias, inconsistency, indirectness, and imprecision were considered not serious. The final evidence type was 1. For hospitalization and severe dengue, the initial evidence level was 3 since it comes from an observational study. It was upgraded for strong association. Risk of bias, inconsistency, indirectness, and imprecision were considered not serious. The final evidence type was 2. Among seronegatives, the outcome of VCD started at an initial evidence level of 1, but was downgraded for imprecision. The imprecision was due to the small sample sizes and wide confidence intervals. Among seronegatives, hospitalization and severe VCD started at 3 due to the study design and were downgraded due to imprecision for a final evidence type of 4. SAEs and deaths started and finished with an evidence type of 1.

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In summary, studies for VE included both RCTs and a case cohort study. The evidence levels for VCD, hospitalization, and severe dengue among seropositive were high at levels 1 and 2, with no evidence of harm. Among seronegatives, the evidence level was lower at 3 for all outcomes. A non-significant increased risk for hospitalization and severe dengue was present among those seronegative receiving the vaccine.

Discussion Points

Dr. Szilagyi asked what the prevalence of disease is in PR and the other US territories.

Dr. Paz-Bailey replied that unfortunately, not a lot of seroprevalence data is for PR and the other US territories. However, some information from mathematical modeling done with passive surveillance cases reported suggests that seroprevalence at age 9 is about 65% in PR. Also, some preliminary data from a cohort study CDC is conducting in Southern PR supports that finding.

Dr. Frey asked what the prospects are for the development of a good serological test, which needs to be done prior to giving this vaccine, and whether there was any evidence for the development of enhancing antibodies after receipt of vaccination and the worsening of AEs as a result of that.

In terms of test development, Dr. Paz-Bailey indicated that a couple of dengue IgG tests are available in PR that are not FDA-cleared. However, they are being utilized under Clinical Laboratory Improvement Amendments (CLIA) by a couple of private laboratories. These tests were designed to diagnose acute and not past dengue infections. Independent evaluations apart from the manufacturer and a published Sanofi study have not been conducted. The possibility of lower specificity is higher now after the Zika epidemic in PR, since Zika and dengue are closely related flaviviruses. CDC is planning to conduct an independent evaluation of available tests including convalescent specimens of primary Zika infections to estimate sensitivity and specificity. Sanofi is working with a company in California to develop an IgG screening test, which is apparently in advanced phases of development. They anticipate that the test may be available some time in 2020. In response to Dr. Frey's second question, antibody enhancement after receiving the vaccine is the hypothesis for the increased risk of hospitalization and severe dengue among seronegative individuals. The presumption is the vaccine acts similar to a primary infection. Then with a second natural infection, seronegatives potentially experience antibody-dependent enhancement with a higher risk of severe dengue. The data showing an increase in the number of severe dengue cases and hospitalizations support this hypothesis. The number of severe dengue cases was small, but there was some evidence that the severe dengue cases among vaccinees were more likely to have severe plasma leakage, the clinical syndrome associated with secondary infections.

Based on the comment about 65% of children 9-16 years of age being seropositive, Dr. Poehling observed that the time of best benefit appeared to be between the first and second infection. She wondered whether they knew of the 65% how many had dengue once and how many had it more than once.

Dr. Paz-Bailey indicated that CDC Dengue Branch is collecting data that will shed light on that question. Some preliminary data suggest that a good number of children already have had two infections by age 9. Hopefully, they will have more solid data to present during a future ACIP meeting. She agreed that children with one prior dengue infection would be the group who would most benefit from Dengvaxia®.

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Dr. Sanchez asked what the currently available tests are measuring in terms of how the tests are being performed and the actual types of assays that are available.

Dr. Paz-Bailey indicated that in terms of diagnosis symptomatic acute dengue infection, there are well-established tests that detect virus by PCR or antigen and also IgM seroconversion. In PR, the health department and CDC have well-established capacity to perform those tests and are performing those tests. What one wants to measure for pre-vaccination screening is IgG from past infections, not necessarily acute infections. Two IgG tests are available in PR. These tests are not FDA-cleared and are being performed under CLIA. They are measuring a combination of antigen, IgM, and IgG. One is a rapid test, but because of the regulations in PR, it cannot be performed by the provider. It has to be performed in the laboratory. The other test is an ELISA test.

Dr. Messonnier pointed out that the 65% prevalence estimate, and most of the burden data to which Dr. Paz-Bailey referred, is from PR. The predictive probability and percentages of false negatives and false positives depends on population prevalence of dengue antibody. Dr. Messonnier suggested that during future meetings, ACIP consider any seroprevalence data from the other locations separately (e.g., US Virgin Islands, American Samoa, etc.). Such data could impact recommendations. Lower prevalence in other areas would impact the number of hospitalizations or AEs.

Dr. Paz-Bailey agreed that this was an important point. She noted that during the last ACIP meeting, she presented some of the data from the passive surveillance system. Symptomatic cases do not say much about seroprevalence. They have some recent estimates from mathematical modeling that suggest that for AS, seroprevalence is as high as in PR. Seroprevalence appears to be lower in the USVI. Of course, mathematical modeling has limitations and uncertainty. Some representative surveys have been conducted in the USVI recently for leptospirosis that provide an opportunity to conduct additional testing and have hard seroprevalence data for the USVI.

Dr. Hunter asked whether there is a policy option to vaccinate or not vaccinate or test or not test based on the estimated seroprevalence in a population.

Dr. Paz-Bailey indicated that the original recommendation from WHO had a consideration for areas with high seroprevalence, which was defined at 70% seropositivity at the age to start vaccination—9 years of age. With the new recommendation, the policy is screening before vaccination so it would be possible to determine serostatus before vaccination. However, it is still a relevant question since the background seroprevalence will affect performance of the test.

Dr. Frey asked whether there is any information on prevalence by serotype and how that should affect their thinking about this.

Dr. Paz-Bailey indicated that there is some variation in the efficacy level by serotype. The data CDC is collecting, at least in PR, includes plaque reduction neutralization test (PRNT) testing. Some data on serotype specific seroprevalence for those with a single previous dengue infection is possible with PRNTs. Still with PRNT, a cross-reactive antibody patterns are common once an individual has two or more infections so to determining the prior infecting serotypes is usually not possible. They also have data from the previous outbreaks coming from the surveillance system. The last large outbreak in PR was primarily DENV 1.

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Dr. Waterman added that looking at seroprevalence by serotype is extremely difficult because of the cross-reactivity of the antigens. The way serotype data are obtained is through PCR, which are incident cases not prevalent cases. While the vaccine has differences in the serotype-specific efficacy, he does not think this issue is critical for the indicated population of seropositive children.

Dr. Paz-Bailey pointed out that these trials were not really powered to determine serotype-specific seroprevalence. That is a secondary analysis.

Dr. Lee observed that understanding serostatus by country and by age seem important, since it seems quite age-dependent. She wondered whether any analyses had been done to determine whether there is any interaction in terms of age by serostatus. It actually may be a function of how many infections there were by serostatus, but it would be helpful to understand if there was any effect modification about which they should be concerned beyond serostatus data.

Dr. Paz-Bailey indicated that they are in the process of obtaining additional information. As Dr. Waterman noted, it is very complicated to know specific seroprevalence by serotype. There is an age cohort effect, and there was some variability in the historical outbreaks in terms of which serotype was more prevalent. That could be used to inform what type of serotype the younger age groups are more likely to be infected with, but it would be somewhat of an inference exercise.

Regarding SAEs in the proposed outcomes, Dr. Lee requested further information about appendicitis, gastroenteritis, and dengue fever as a consequence of the vaccine. She wondered whether this was a signal that had come up earlier, or what the rationale was behind the SAE cluster. She thought that being able to unpack those data more would be helpful.

Dr. Paz-Bailey indicated that the manifestations of severe dengue could include severe organ involvement. Infection of the liver is one possibility.

Dr. Waterman added that Sanofi would be the best to answer that question in terms of assessing AEs in the various pre-clinical trials and the Phase 3 trials. He said he thought these were AEs of any conceivable nature. The ones of concern that are most specific to dengue would have been encephalitis and hepatitis. Gastroenteritis not necessarily, but if there was an SAE, it was recorded.

Dr. Romero invited Sanofi Pasteur to comment.

Dr. Corey Robertson (Sanofi Pasteur) confirmed that Dr. Waterman’s assessment was correct. They captured any SAE as part of the trial and not necessarily related to the vaccination.

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Cost-Effectiveness

Alex Perkins, PhD
University of Notre Dame

Dr. Perkins noted that the work he was presenting during this session was done in conjunction with a Post-Doc in his laboratory, Dr. Guido España, and that they had one conflict of interest to declare. The authors have previously received research funding from GSK to support unrelated research on dengue vaccine development. This model completed the CDC economic review, following the *ACIP Guidance for Health Economic Studies*. Completion of the review does not confer any explicit implied endorsement of the model reviewed.

As Dr. Paz-Bailey reported earlier, dengue incidence has been increasing for decades. This year alone in the Americas, there have been over 2.5 million reported cases. Therefore, dengue continues to be a growing problem in PR and elsewhere in the US territories. One of the main things that stands out from the clinical trials is the difference in efficacy or the hazard ratio between seropositive and seronegative individuals, with significant protection detected in the seropositive group and a potentially elevated risk of hospitalized disease in particular in the seronegative group [Sridhar et al, 2018].

There are a number of possible hypotheses that could explain the mechanisms by which the vaccine works. Dr. Perkins described the assumptions that they have made in their modeling, which is consistent with a number of other modeling groups and leading thoughts in the field. There are two components assumed in terms of how this vaccine, DENGVAXIA®, might confer protection. One is a short-term protective effect similar to temporary cross-immunity experienced by natural infection. This is a broad protection against any dengue serotype that is assumed to last for approximately a year or less. The exact nature of that level of protection is estimated with a model based on data from the clinical trials.

The second component of protection is long-term and follows from the hypothesis that DENGVAXIA® acts somewhat like a silent natural infection. If someone is naïve and never been exposed, naturally they would experience their first infection and move on to the second infection and following the second infection, experience the higher chance of severe disease. The assumption is that upon vaccination, someone who has never experienced dengue before would have a rate of severe disease more similar to that of a secondary infection. They skip ahead from being a primary-like infection to being a secondary-like infection. An individual who has experienced one prior infection skips the secondary-like infection and goes on to experience a post-secondary-like infection, which is associated with a lower rate of symptomatic and severe disease.

These are two mechanisms that jointly affect how the vaccine confers protection in this model. It is important to emphasize that the first of these components, the short-term temporary immunity is where indirect protection or benefits are expected to come from in terms of eliciting herd immunity in a population. Whereas, the second effect acts like a natural infection and serves to reduce the probability of disease in a given individual and does not necessarily affect their chance of transmitting the pathogen.

The current recommendation from WHO is to perform pre-vaccination screening. This has been emphasized in this modeling work over the last couple of years. There are two possibilities. The idea is that individuals who have never experienced dengue would not be vaccinated in order to avoid setting them up for the secondary-like infection with a higher chance of severe disease.

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Seropositive individuals would be vaccinated. Conversely, there is the possibility of imperfect screening in which someone who has never experienced dengue would be vaccinated because they are a false positive. Likewise, someone who has experienced a prior dengue infection might come up as a false negative and not receive the vaccine though they could benefit from it.

To address questions regarding how sensitive and specific the vaccine needs to be in order to achieve a population- and individual-level benefit, an agency-based model of dengue transmission was used to protect the impact of pre-vaccination screening with DENGVAXIA®. This model is based on data that have been collected over 20 years in the City of Iquitos, Peru in the Amazon. This has a number of details about humans and mosquitos in terms of how they move around and how they transmit all 4 serotypes of the virus to each other. This was used in the initial exercise that informed the WHO's initial policy position in 2016, along with 7 other modeling groups, and generally showed good agreement in terms of its impact projects with the other groups. Four papers using this model have been published over the last few years looking at DENGVAXIA® impact. Dr. Perkins noted that the analysis he was presenting during this session was based primarily off of the paper by España et al published earlier in the year in *PLOS Neglected Tropical Diseases* [Flasche et al, 2016; España, Hogea et al 2019; Perkins et al, 2019; España, Yao et al, 2019].

Before getting into what this model projects about vaccination impact, Dr. Perkins first reviewed how their model comports with data from the vaccine trials. They compared their model predictions to results from the trials in terms of vaccine efficacy and the hazard ratio, broken down by seronegative and seropositive at baseline and by 2-8 and 9-16 age groups. Generally, their model predictions fall in line with confidence intervals of the trial data from Sridhar et al, 2018. Several model parameters were calibrated to the trial data, several of which related to the temporary protection that the vaccine affords. They found that they had to stratify that by seronegative or seropositive in order for the model to replicate the trial data. The level of protection in terms of per-exposure protection, they estimated 0.32 for seronegatives and 0.52 for seropositives, although there was quite a bit of uncertainty on that. Likewise, there is a lot of uncertainty on how quickly that temporary protection wanes. But in general, for both seronegatives and seropositives, it seems to be somewhere around the order of a year.

In addition to those parameters, they also calculated parameters related to the natural history of infection (e.g., is the probability of symptomatic disease upon first, second, or post-secondary infection) and likewise, the probability of hospitalization given that someone has experienced symptomatic disease for primary, secondary, and post-secondary infections. Symptomatic infection rates were found to be similar for primary and secondary infections, again with quite a bit of uncertainty in terms of which might be bigger than the other. Post-secondary infections were estimated to be substantially lower. More importantly, in the hospitalized cases, they estimated that the primary infections have around 0.07 chance of being hospitalized given that they were symptomatically presenting. For secondary infections, there was a substantial increase to 0.38 and then back down to 0.10 for post-secondary. The main way they are assuming the vaccine protects is by bypassing the 0.38 number and going straight from 0.07 to 0.10 in terms of risk of hospitalization upon having a symptomatic infection.

In terms of the scenarios they ran in this model, they assumed that the intervention worked as follows. They looked only at 9-year-olds in this case. Dr. Perkins indicated that he would comment at the end about how they might expect these results to apply to 9-16 year-olds. They just assumed a scenario of routine vaccination for 9-year-olds. They assumed for baseline that 80% of those individuals were covered by the intervention, meaning that they underwent serological screening and in the event that they were positive they were vaccinated and if

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negative they were not vaccinated. Dr. Perkins stressed that one important thing to distinguish here was that when he talked about coverage of the intervention, he was referring to how many people were screened; whereas the number vaccinated ends up being somewhat less than that depending upon the outcome of the screening process.

As mentioned earlier, they previously applied this model to PR for generic analyses. They sought to adapt this analysis to PR for the purposes of this exercise. They took two estimates from the literature for 9-year-olds, one from Sanofi and another from a separate paper that both suggested a seroprevalence in 9-year-olds in PR of around 50%. That was the baseline scenario upon which most of the analyses Dr. Perkins shared were based. They also considered a lower transmission scenario of 30% prior exposure. One of the main reasons they did that was to account for the possibility that there might have been less dengue transmission over the last few years in particular due to the Zika epidemic. These are sensitivity analyses to try to capture that range of uncertainty. Dr. Perkins again emphasized that they distinguished between previous exposure in 9-year-olds and seroprevalence in 9-year-olds, given that seroprevalence could be quite different depending upon how accurate the test is or is not. This table recaps the scenarios explored:

Age	9 years
Intervention coverage	80%
Transmission intensity (PE_9)	50%, 30%
Sensitivity	0.80 (0 - 1)
Specificity	0.95 (0 – 1)
Paired simulations	3,000
Burn-in period before intervention	40 years
Intervention timeline	10 years

The model is stochastic, meaning that there is a lot of randomness in the model. They had to perform replicate simulations to try to average over that randomness, so they performed 3000 paired simulations. One in the pair included vaccination and the other did not, and they tried to see what the average differences were between those. The burn-in period was to let transmission settle down to relatively stable equilibrium, and then explored that impact of vaccination 10 years after that.

One of the primary outcomes in terms of public health impact was the proportion of cases averted. In the 40-year burn-in period, the intervention and no intervention simulations were identical. But then after the vaccine was introduced, some differences are observed due to protection from the vaccine and to some degree of randomness. Dengue is a very heterogeneous disease, which is reflected in the model. There are benefits in terms of symptomatic and hospitalized dengue cases.

In terms of symptomatic disease, there are benefits in terms of the scenarios of sensitivity and specificity that are considered. Again, the baseline of sensitivity is 0.80 and specificity is 0.95. An increase is seen in the cases averted with an increase in sensitivity, mainly due to the fact that there is simply higher coverage when there is higher sensitivity because more people are vaccinated. Of course, there is a decrease in impact with a lower sensitivity and fewer individuals are being vaccinated. That was the primary driver of what happened in the symptomatic case, given that this model did not assume an increased risk of symptomatic disease upon secondary infections.

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Things are much different for the hospitalized cases where there was a dramatic increase in the risk of hospitalization upon secondary infection. There are some strong benefits of vaccination in terms of hospitalization seen under the different sensitivity and specificity scenarios. In the scenario in which 50% of 9-year-olds have prior exposure, relative to the baseline, the main place a dip is observed is when there is a decrease in the sensitivity. In a higher transmission setting, lower sensitivity equites to lower impact because fewer children are being vaccinated. The higher scenario about sensitivity is going to increase that. In contrast, at an assumption of 30% seroprevalence in 9-year-olds, something quite different is seen. When specificity is dropped from 0.95 to 0.76, there is a decrease in the proportion of hospitalizations averted. That is driven more by the negative outcomes occurring in the seronegative individuals who are at an increased risk of hospitalization.

Looking across a much broader range of possibilities for sensitivity and specificity to try to understand what minimums are necessary to achieve a positive impact in the first place regardless of a very positive impact, in the case of 30% prior exposure, at an absolute minimum specificity would need to be at least 0.6 in order to have any positive impact under this model. That also is assuming that sensitivity is very high. If sensitivity is lower than specificity, the minimum would need to be even higher at maybe around 90% in the case of a modestly sensitive test. In the case of the 50% previous exposure 9-year-old assumption, the conditions are relaxed somewhat, but again there is a strong tradeoff between sensitivity and specificity in terms of minimum requirements to achieve a positive impact.

The individual level of risk of hospitalizations is clearly a concern, especially for individuals who are false positives following serological screening. Looking at the 10-year timeframe following vaccination and looking at the risk of dengue at an individual level between the no intervention cohort and intervention cohort, the relative risk is below 1.0 across all of the different scenarios considered for the serological screening assay. In the scenario of 30% prior exposure, so lower transmission when specificity is sacrificed, there is somewhat of an increase in the relative risk. It still falls below 1.0, but is less than it would be under a higher specificity scenario.

Looking more specifically at the potential false positives in terms of hospitalizations in naïve children per 1000 vaccinees, depending upon a seroprevalence of 30% or 50%, that could be on the order of 2 to 3 hospitalizations that would not have been experienced without vaccination per 1000 vaccinees. That depends quite a bit on sensitivity and even more so on specificity. Specificity is sacrificed to increase sensitivity, going from 0.96 to 0.76. That number jumps by about 3-fold in both of those scenarios, so it is very important to have very high specificity to minimize those events. At a specificity of 99%, it is possible to keep those down potentially below 1.0 under the right seroprevalence settings. In terms of the number of hospitalizations that would be averted per individual who is seronegative who experiences a hospital event due to vaccination, about 5.5 hospitalizations would be averted per negative hospitalization under the 30% scenario and a higher number under the 50% seroprevalence scenario. When specificity is maximized at 0.99, both numbers are quite large in terms of averting a lot of hospitalizations per negative episode. A lot of that has to do with the fact that there are so many fewer hospitalizations occurring due to vaccination in this scenario.

Moving on to the economic part of the analysis, the focus was primarily on the incremental cost-effectiveness ratio (ICER) or the additional cost per gain in effectiveness of the intervention. The effect was assessed in three different ways. One was to estimate the quality-adjusted life years (QALYs) gained with pre-vaccination screening using disability weights and the duration of disability. Second, the ICER was used to determine the cost-effectiveness of pre-vaccination

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screening. Third, the hospitalizations and symptomatic cases averted were used in the denominator as additional measurements of the effects of the intervention.

To briefly review the assumptions that were made about the weights and QALYs are shown in the following table:

Event	Disability Weight	Time of Disability	Source
Dengue Fever	0.0158	4 Days	(Shim, 2017)
Hospitalization	0.545	14 Days	(Shim, 2017)
Deaths	1	Life Expectancy—Age of Death	

The costs of treatment used are shown in this table:

Type of Care	Cost (USD)	Cost (April 2019 USD)	Source
Ambulatory	$ 239 (2010)	$ 315	(Halsa, Shepard, & Zeng, 2012)
Hospitalization	$1,615 (2010)	$2,131	(Halsa et al, 2012)

Disease costs were projected to April 2019 using the Consumer Price Index (CPI) for Medical Care in PR. These are costs paid by the government, so there would be some additional costs depending upon the perspective being assessed). An annual discounting rate of 3% was assumed. The unit cost per fully vaccinated child was set to $70 USD based on pricing information from the Philippines [España, Yao, et al, 2019; (Appendix S4)]. The cost to screen an individual for previous exposure to DENV was set to $10 USD based on a seroprevalence study in school children in Vietnam [Turner et al, 2018].

In terms of the results, the ICER was higher for low-transmission scenarios at $42,750 USD at the 30% seroprevalence assumption and went down for high-transmission rates at $12,100 USD at the 50% seroprevalence assumption. Similarly, the incremental cost to avert a symptomatic case was around $1,000 USD at the 50% assumption and about $3,500 USD at the 30% assumption. The incremental cost to avert a hospitalized case was around $1,500 USD at the 50% assumption and about $5,000 USD at the 30% assumption.

A few sensitivity analyses were performed as well. The first pertained to lower coverage. The default assumption was 80% coverage of serological screening in 9-year-olds. A scenario of 50% coverage of serological screening to see if that 80% benchmark was not met. It turns out that had a fairly minimal impact on the ICERs. A lot of that has to do with the fact that the assumptions are that the vaccine primarily protects through direct protection of vaccinees rather than through herd immunity. There is some degree of herd immunity, but it is fairly modest, meaning that these ICERs change fairly literally with the changes in the assumed coverage.

Another sensitivity analysis looked at how the cost-effectiveness would vary as a function of the sensitivity and specificity of serological screening. Under the reference scenario of 0.95, baseline ICERs per QALY are $12,100 at 50% and $42, 750 at 30%. Patterns were similar for ICERs in terms of symptomatic cases and hospitalizations. The result to highlight is that when sensitivity was increased but specificity was decreased the 0.76, there was roughly a doubling of the ICER. This finding suggests that specificity is an important driver not only of public health impact and individual risk, but also cost-effectiveness.

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Sensitivity also was assessed in terms of assumptions about costs, given that there is plenty of uncertainty and variability in those. The two primary drivers of uncertainty in the ICERs as a function of these costs were the costs of hospitalization. A minimum of $1700 was compared to a maximum of $2500, with each type of cost (hospitalization, symptomatic, disability weight hospitalization, disability weight symptomatic) being plus or minus 20% relative to the baseline cost. With that 20% increase or decrease in the cost of hospitalization, there was quite a difference in the ICER ranging from $14,000 to $9,000 or $45,000 to $39,000. Likewise, the costs of serological screening can have quite an impact on cost-effectiveness because that range could be potentially much greater than 20% around the baseline scenario, with a range all the way from $1 per unit cost up to $20. The ICERs varied quite a bit as a function of that uncertainty.

Lastly, a scenario was explored in which there was 60% previous exposure in 9-year-olds. Again, there were roughly the same type of findings as seen at 50%. Basically, once above 50%, the results look better and better in terms of impact and cost-effectiveness. That is roughly what was seen with 60% previous exposure. Likewise, in terms of cost-effectiveness, there was a similar result in which there was a lower ICER per QALY for the 60% assumption going from about $12,000 down to about $7,400.

To summarize, specificity of the serological screening should be a high priority for a number of reasons, both for maximizing impact and also minimizing the events in the false positives. Likewise, that is important for cost-effectiveness based on this analysis. At the same time, in the event that coverage is lower than the baseline assumptions, the investigators do not feel that it would significantly affect cost-effectiveness. That could be similar under a range of different scenarios about coverage. There are some updates to various assumptions in this model, including previous exposure and different costs that could help improve or refine these analyses. Lastly, in the event that there was a catch-up campaign in 10-16 year-olds initially, over a 10-year timeframe based on prior work and some rough estimates, that is expected to roughly double the impact of vaccination relative to just doing routine vaccination at age 9.

Discussion Points

Dr. Szilagyi emphasized that this is complex. Regarding the assumption about duration of seroprotection, he asked whether only a year was correct and how that works when going out to the 10-year timeframe.

Dr. Perkins indicated that there are a variety of possible alternative ways to interpret that vaccine trial data in terms of how the vaccine works. Certainly, for the purposes of a model, some very specific assumptions have to be made that can be applied at an individual level. To do that, they had to appeal to the silent infection model in which one component ideally is skipping the secondary-like infection to reduce the probability of symptomatic disease. But, that does not have any impact on an individual's infectiousness. They still get infected. They just do not experience disease. For the component that protects against infection, the assumption was made that that would just last for around a year. That is similar to natural dengue infection where there is a temporary period of cross-immunity to all serotypes before having a longer lasting homotypic protection.

Dr. Maldonado (AAP) recalled that at one point, Dr. Perkins mentioned that the impact of the second hospitalization would not be any different than the impact of the third hospitalization.

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Dr. Perkins indicated that for symptomatic disease, they assumed that the probability of primary and secondary infection would be similar. For hospitalization, they assumed that it is for sure highest in the secondary infections.

Dr. Hunter said he was trying to put himself in the position of a parent of a 9-year-old in PR, looking at the data, and wanting a very specific test to ensure that the child does not experience the side-effects of getting the wrong result. He thinks it is going to be extremely important to have the support of the parents in this, and to be able to educate them clearly on it. Given how complicated this is, that is going to be quite a challenge.

Dr. Waterman indicated that they would be talking about acceptability and attitudes of parents in subsequent meetings.

Dr. Romero added that they are dealing with 5 US endemic areas in different parts of the world. This model is based on PR, but it does not address the issue of the FSM in terms of the incidence and costs there. He does not think that one model is going to fit all, which was what was going through his mind as he listened to all of these numbers. That adds an even further level of complexity because this means 5 different models.

Dr Frey agreed that this is very complicated, and said she was still trying to wrap her head around the silent infection model and what that really means. Related to efficacy, she wondered whether they were looking for a vaccine that eliminates symptoms of disease or one that eliminates the most severe disease, and in that context how cross-protective DENGVAXIA® is against the 4 serotypes.

Dr. Waterman responded that the silent infection phenomenon the model is assuming, and the vaccine probably works somewhat that way, is that it is not necessarily preventing infections but is preventing symptomatic disease. It prevents symptomatic disease to some extent. It prevents hospitalizations and severe disease to an even greater extent. But again, it only works in seropositive individuals. The silent infection skips the second infection with severe disease, which is how the vaccine appears to be working.

Dr. Talbot noted that the FDA licensed this vaccine for individuals 9 years of age and above; however, it sounded like a significant number of children in that age group may already have had two infections. Therefore, the benefit may not be gangbuster. She wondered whether they had any data on the seropositivity of individual younger than 9 years of age.

Dr. Waterman replied that they do not have great seroprevalence data. CDC is conducting a seroprevalence survey in PR that includes younger age groups. They may have some of that data. If it could be shown that there is high seropositivity in a younger children, the vaccine theoretically could be used in that population. However, it is not indicated for that population right now.

Dr. Cieslak (CSTE) asked for clarity regarding whether the assumption was that because the vaccine is simulating a second infection, and one can never have a second infection twice, the presumption was that the duration of immunity afforded thereby would be forever.

Dr. Perkins responded that this is the assumption for the longer-term aspect. He would say that there probably is not enough data from the trials to refine that estimate, but that is the current assumption.

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Dengue Virus Vaccines

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

Dr. Waterman summarized the Dengue Vaccines WG's considerations toward making a recommendation regarding CYD-TDV or DENGVAXIA®. As Dr. Atmar mentioned, the timing of recommendations depends on the pace of gathering and assimilating the EtR and further information on available screening laboratory tests. As a reminder, the policy question the WG is addressing is, "Should 3-doses of CYD-TDV be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas to prevent virologically confirmed dengue, hospitalizations, and severe dengue?"

As reported by Dr. Paz Bailey, the GRADE analysis indicates that the quality and certainty of the evidence for CYD-TDV is at a high level for vaccine efficacy and safety among seropositive children 9-16 years. The WG has discussed that ACIP and WHO recommend other partially effective vaccines (e.g., rotavirus vaccine can prevent a portion of disease in high burden settings). The WG considers that the major challenge regarding CYD-TDV is the availability of a good screening test with acceptable specificity and sensitivity, and cost-efficiency. Sanofi has a recently accepted article available online evaluating several commercial tests, including a commercial rapid diagnostic test (RDT) dengue IgG test used in American Samoa. A second Sanofi manuscript has recently been accepted on the two dengue IgG tests available in PR. The CDC Dengue Branch is in the process of obtaining 11 commercially available dengue IgG test kits for its own evaluation with well-characterized specimens from persons infected with DENV, both primary and secondary infections, or ZIKV. Sanofi has another test designed to be optimized for sensitivity and specificity in development through collaboration with a biotech firm. Another commercially available ELISA serologic test has been evaluated recently by Sanofi on which they plan to publish early next year. This test is among the tests CDC will be evaluating.

PR has a relatively strong immunization program with a well-established immunization registry that includes reminder/recall and 47% of children are VFC-eligible. Vaccine coverage in adolescents for mandated vaccines is relatively high at about 80% for the first dose of HPV and 50% for up-to-date HPV. The logistics of a dengue vaccine program involving laboratory screening in PR are challenging with the prospect of multiple visits, but potentially could be overcome with standing orders for the screening test, an RDT available in doctor's office, and phased roll out. The coverage of the cost of a laboratory test is an obvious issue for PR and elsewhere.

Dr. Waterman highlighted some of the key points from the Notre Dame cost-effectiveness model and sensitivity analyses presented by Dr. Perkins, and which have been discussed by the WG. Using the base scenarios, vaccination can be beneficial from a public health payer and individual perspective as long as sero-screening is moderately sensitive and specific. Vaccination with CYD-TDV of 9 year olds with a 50% prevalence of prior infection can prevent about 6% of all dengue hospitalizations. Vaccinating a wider age range of the vaccine-eligible pediatric population would increase this proportion. While higher test sensitivity increases public health impact, the specificity of the screening laboratory test is more important, especially in lower transmission scenarios, to maximize cost-effectiveness and to minimize the number of hospitalizations in misclassified seronegatives. ACIP and dengue-endemic jurisdictions will need to decide what is an acceptable number of hospitalizations in vaccinated dengue naïves

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compared to hospitalizations averted in vaccinated seropositives. The model suggests at 50% seroprevalence and a specificity of 95% and 50% seroprevalence, 2 hospitalizations in dengue naïve individuals would occur per 1000 vaccines. At higher seroprevalence, cost-effectiveness increases and serologic misclassifications decrease. Preliminary data on seroprevalence of neutralizing antibodies for dengue from Ponce, PR show seroprevalence closer to 60% in 9 year olds.

The ICER obviously increases with the cost of the vaccine, with a slope of $300 at 50% seroprevalence per QALY gained for each dollar increment in vaccine cost. The ICER in the baseline 50% prevalence scenario was $1,500 per hospitalization prevented. Increases in the costs of hospitalization significantly decrease the ICER, and increases in the costs of the laboratory test significantly increase the ICER. The current costs of the commercial IgG laboratory tests in PR are at least three times higher than the $10 test cost used in the baseline scenario presented. Again, how screening laboratory test costs would be addressed in a vaccination program is an unsolved issue. The WG will review at least one additional cost-effectiveness study before making recommendations to ACIP.

The WG is gathering information regarding questions on safety details requested by ACIP last June. Sanofi recently has provided available answers to these questions from post-marketing data. The WG will discuss these data and share its assessment of these details with ACIP members. As always, the WG would appreciate feedback regarding whether there are other specific data ACIP would like to see and considerations ACIP would like the WG to cover.

Discussion Questions

With respect to the parents of a 9-year-old in PR, Dr. Hunter said he was not sure he understood the 2 hospitalizations in seronegatives out of 1000 vaccinees. He asked for clarity regarding whether that meant that a child who tested positive on a dengue test, but it was a false positive, this meant that there would be a 2 in 1000 chance that child could wind up going to the hospital no matter what the result of the test. In addition, he wondered what the child's chance would be of ending up in the hospital if he did not receive the vaccine.

Dr. Waterman indicated that could be considered from an individual perspective as the parent. If a child is seropositive, they are much more likely to have a hospitalization prevented. However, there is a 1 in 500 chance that they would be hospitalized because of the vaccine. The hospitalization hazard ratio point estimate the in case-cohort study for 9-16 year olds is 0.21, indicating a screened unvaccinated child would be close to 5 times more likely to be hospitalized. From a parent's scenario, if their child tests seronegative in various prevalence situations, it might be more logical for them to get vaccinated anyway. Explaining these benefits and risks to parents will be tricky, but preparing clear and understandable explanations for parents is important.

Dr. Atmar noted that one of the slides presented in the cost-effectiveness analysis addressed that. Depending upon the assumptions about sensitivity and specificity, one slide showed that somewhere between 10 and 40 children would likely benefit for every 1 child who was put at risk. This varies based upon how specific the test is and somewhat less so on how sensitivity it is. There is a population net benefit, but there is still a potential for individual harm.

Dr. Hunter said that he was reluctantly saying that they appeared to be going down the road toward shared decision-making on this one.

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Dr. Romero said he was not sure they could say that yet.

Dr. Talbot said that what would help her greatly would be overall worldwide estimates about number of infections, as well as estimates of how many children a year in PR are hospitalized with dengue and how many children in PR die in a year.

Thinking about this from a clinical perspective, Dr. Lee said she understood the model and how the sensitivity analyses played out. However, it would be helpful to have more concrete examples about what proportion of individuals would be true positives and what proportion would be false positives if she administers this test. This would help her better understand how to have that communication with a family about what the risk is to their child based on the accuracy of the test and pre-test probabilities. She thought all of the information was there, but the framing could be made simpler. She also requested additional information about whether there are any disparities in access to hospitalization. While reducing the risk of severe dengue infection is important, she also wants to make sure these children can get to a hospital if they need one. In addition, she wondered whether the outcome of a hospitalization or severity of illness is affected by vaccinating at an earlier age.

In the interest of time, Dr. Messonnier requested that the ACIP members make a list of what they would like to hear about during next meeting.

Rabies

Introduction

Sharon Frey, MD, FACP, FIDSA
Saint Louis University School of Medicine
Chair, ACIP Rabies Vaccines WG

Dr. Frey introduced the Rabies Vaccines WG members and session. The WG's terms of reference are to:

- Determine the epidemiology and burden of rabies exposures and pre-exposure prophylaxis (PreP) and post-exposure prophylaxis (PEP) administration in the US (The last overhaul of these recommendations was in 2008, and there were some PEP changes in 2010. The WG will be looking at all aspects as they related to vaccines during the WG meetings).

- Evaluate and revise recommendations as needed for vaccination schedules, route and site of PrEP and PEP, and cost-effectiveness

- Consider evidence generated to inform the rabies recommendations of other global organizations

- Review rabies exposure risk and risk assessment guidelines for the general population and by occupational and recreational groups

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- Evaluate serological and monitoring recommendations including whether recommendations should differ depending on the degree of rabies risk for a person and whether adequate antibody titers are needed to confirm immunization
- Consider whether recommendations should differ for healthy adults compared to immunocompromised persons and pregnant women
- Update recommendations with information about the 2 rabies immune globulin products approved by the US FDA during 2018
- Identify areas in need of further research for informing future vaccine and immune globulin recommendations

In terms the tentative timeline, Dr. Frey indicated that this session would focus on the background of and introduction to PrEP issues. The plan for the February 2020 meeting is to present detailed PrEP data, including the GRADE tables, and to introduce PEP issues. During the June 2020 meeting, the plan is to vote for PrEP topics and present more detailed information about PEP. The plan for the October 2020 meeting is to present more detailed information about PEP or vote on PEP issues.

There are current rabies vaccine and rabies immunoglobulin (RIG) shortages. However, these shortages are not significant enough to impact patient care. CDC has reported to the WG that vaccine and RIG are available for every patient who needs them, and no modification to current practices is anticipated. In terms of vaccine, RabAvert® by GSK is available directly from the manufacturer. IMOVAX® by Sanofi Pasteur is currently unavailable, but is expected to be available late October to early November. Regarding RIG, Imogam® by Sanofi Pasteur is available directly from the manufacturer. KEDRAB™ by Kedrion Biopharma and HyperRAB® by Grifols availability is unchanged and there are no difficulties filling the gap from Imogam®. GSK is divesting RabAvert® in the US to Bavarian Nordic. Vaccine will continue to be manufactured primarily at GSK's Marburg, Germany site until full production is transferred to Bavarian Nordic. No immediate impact to vaccine supply is anticipated.

Dr. Frey indicated that this session would include presentations on background information and WG plans, and introduction to the rabies PrEP schedule and serological monitoring by risk category in healthy, non-pregnant persons and special populations.

Background

Agam Rao, MD FIDSA
CDR, United States Public Health Service
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Rao explained that rabies is caused by viruses in the genus *Lyssavirus*. It is an acute, progressive encephalomyelitis that occurs worldwide and is nearly always fatal once clinical signs and symptoms begin. Rabies is transmitted from infected mammals by a bite, scratch, or exposure to saliva or neural tissue. It is not transmitted by exposures to blood, urine, or feces of infected animals.

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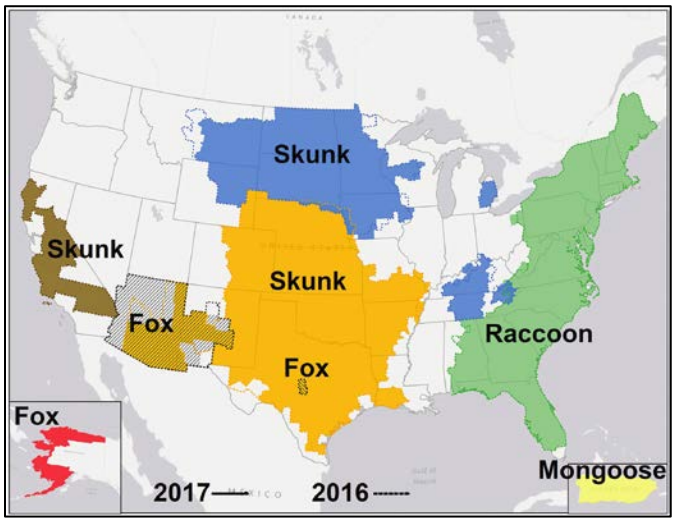
Rabies is a neurotropic virus. It enters peripheral nerves, travels centripetally to the central nervous system (CNS), and then flows centrifugally to innervated organs including salivary glands. The incubation period after an exposure is weeks to months, and death typically occurs within 2 weeks of illness onset. Few animal species are reservoirs for rabies. Rabies virus variants (RVV) are named for the animal reservoir species in which they circulate and are confined to geographically definable regions. Infection can be transmitted from the reservoir species to other species. For example, raccoon RVV can spread from a raccoon, to a cat, to a human. The take-home point is that a RVV does not denote the animal to which the human was exposed.

In the US, canine RVV has been successfully eradicated. That leaves terrestrial or wildlife rabies for which wildlife are reservoirs, and non-terrestrial rabies for which bats are reservoirs. This map shows confined areas for skunk, raccoon, and fox in the US and mongoose in Puerto Rico:



Skunk RVV: Orange = South central, Blue = North central,
Brown = California; Fox RVV: Red = Arctic fox, Hash = Gray fox;
Raccoon RVV: Green; Mongoose RVV: Yellow.

Non-terrestrial or bat rabies, on the other hand, is endemic in 49 of the 50 states. Hawaii is the only state without rabies. Approximately 5,000 animals test positive for rabies each year in the US.

Exposures that have led to confirmed human cases of rabies in the US can be broken down into domestic exposures and international exposures. Domestic exposures include: during recreational activities, during occupational exposures including veterinary and laboratory work, contacts during everyday life including if there are bats in a home or a residence is in a wooded area with increased opportunities for animal-human contact, and organ and tissue transplants.. International travel can be both leisure- and occupation-oriented. Dogs are the most important animal reservoir for rabies internationally.

During 2009-2019, there were 25 confirmed cases of human rabies in the US. Thus, there are approximately 5,000 positive animal cases each year and 2 to 4 human cases each year. Domestic exposures accounted for 17 of the 25 and the other 8 were international exposures. Most domestic exposures were due to bats, while most international exposures were due to dogs. It is important to note that none of these were due to occupational exposures.

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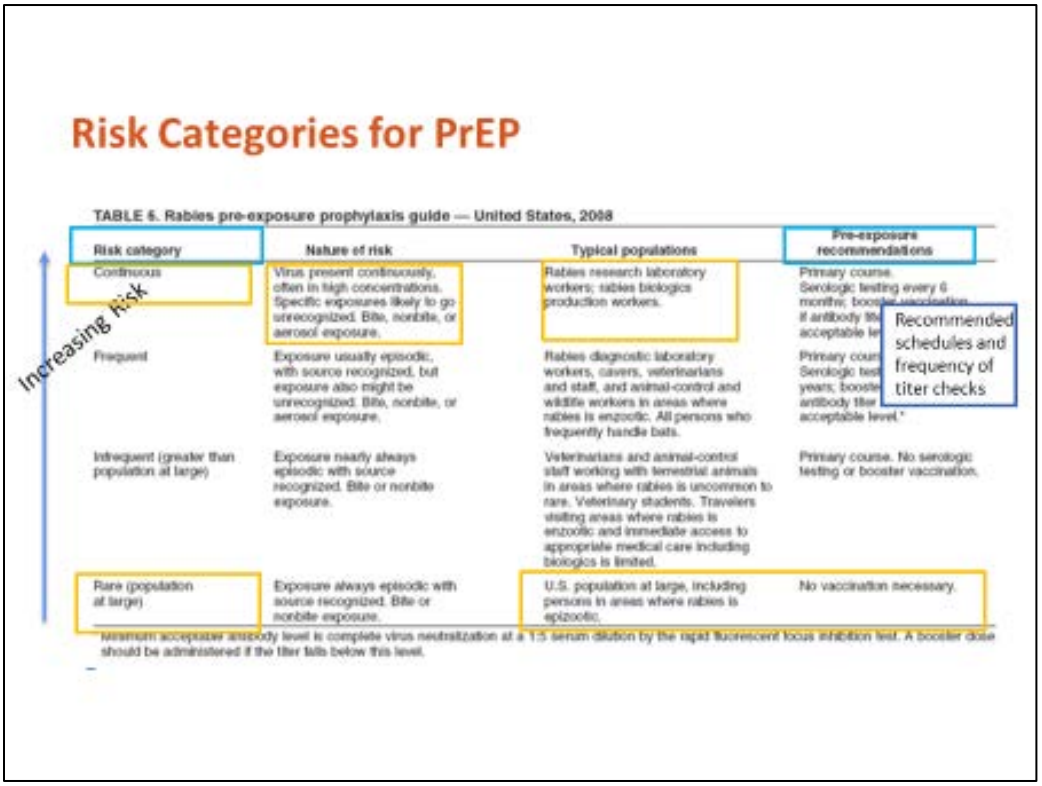
Primary prevention involves avoiding animal exposures and vaccinating domestic and wild animals. Secondary prevention is where rabies PrEP and PEP come in. PrEP involves a vaccine series. Over 15,000 people receive PrEP each year in the US. PEP involves thoroughly washing a wound with soap and water and administering RIG and a vaccine series. About 50,000 people receive rabies PEP each year in the US. While the number of human cases are very few, many people receive these preventive measures.

PrEP and PEP are important and a lot of factors contribute to the ACIP recommendations for these. Dr. Rao walked through the important features of this table from the current ACIP rabies recommendations:



Pre-exposure recommendations, including schedules and frequency of titer checks, that are listed in the last column are derived from the other columns. These are different depending on risk level, which is in the first column. For example, at the bottom of the first column is the risk category with the least risk for rabies. Those are people in the general population. No PrEP is needed for the general population according to the current ACIP recommendations. Moving upwards in the table, risk increases. Infrequent, frequent, and continuous risk categories in the first column correspond to risks that are episodic with recognized exposures, episodic with some exposures that could be unrecognized, and all the way at the top continuous risk, which includes populations like research laboratory workers. Recommendations for PrEP in the last column can be different for different risk categories.

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The decision to administer PEP depends on different issues. Is the exposure a bite or non-bite (i.e., aerosol, organ / tissue transplant, contamination of wounds or mucous membranes with saliva or neural tissue)? Is the exposure to urine, feces, skin, or blood? What is the Bio-Geo-Behavioral Risk Assessment? Is the animal a reservoir species for rabies? What is the rabies epidemiology in the area? Was the animal showing signs of rabies? All of these weigh into whether a decision is made to administer PEP. Similarly, the recommendations for schedules and titer checks in the cases of PEP are different from PrEP. They depend on whether PrEP was administered to the patient before the exposure, whether there were deviations in PEP administration, and whether there are any special considerations for patients like immunocompromising conditions or pregnancy that could have an impact on schedules. That is, PrEP and PEP exposure recommendations will differ depending upon people's risks and other conditions.

With regard to national and global recommendations and products, ACIP and WHO recommendations have changed over the years. In the remote past, recommendations were based on the vaccine quality not being the best, decreased potency of the viruses, increased adverse events, intradermal (ID) and intramuscular (IM) licensed indications for rabies vaccine, and the large number of vaccines needed to complete a PEP series. Things have evolved quite a lot.

As recently as 2008, the ACIP PEP schedule was a 5-dose IM series. In 2010, the series was reduced to 4 doses. The impetus for that was a severe vaccine shortage that affected patient care, and the evidence available for a 4-dose series. In 2018, new data became available and WHO made new recommendations. ACIP is in the process of doing so as well.

The vaccines and RIGs currently licensed in the US are listed in this table and are the vaccines and RIGs that make up the PreP and PEP series:

Vaccines and human immunoglobulins licensed in U.S.

Biologic	Product name	Manufacturer	Licensed for Administration
Human diploid cell vaccine (HDCV)	Imovax®	Sanofi Pasteur	Intramuscularly
Purified chick embryo cell vaccine (PCECV)	RabAvert	GlaxoSmithKline (In future: Bavarian Nordic)	Intramuscularly
Human immune globulin	Imogam®	Sanofi Pasteur	Intramuscularly and Infiltrated around wound
	Kedrab™/ Kedrion	Biopharma and Kamada Ltd	Intramuscularly and infiltrated around Wound
	HyperRab™ S/D and HyperRab®	Grifols	Intramuscularly and Infiltrated around wound

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There are 2 vaccines manufactured by Sanofi Pasteur and GSK (in the future Bavarian Nordic). Both are licensed only for IM use. There are 3 human immune globulin products manufactured by Sanofi Pasteur, Biopharma and Kamada Ltd., and Grifols.

Discussion Points

Dr. Maldonado (AAP) wondered whether there are plans to address the global eradication work from WHO and how that might be phased in or out.

Dr. Rao indicated that ACIP recommendations are focused on the US population. ACIP has different considerations from WHO, so ACIP's considerations may differ. Global eradication is not part of the scope.

Dr. Messonnier requested clarity about one of the points Dr. Rao made about the large number of people who are receiving PrEP and PEP. She wondered if the interpretation was that the large number of people are receiving this, none of whom have had disease, a sign that the intervention is thought to be so effective that this is the right number. Or, if the implication was that a lot more people are receiving these than actually need it.

Dr. Rao clarified that it is probably both. As far as the cases that she showed from the last 10 years of the confirmed cases, none of those patients received PrEP or PEP. A lot of PrEP and PEP are being administered, but it is not known whether any of that could be inappropriate. The ACIP recommendations exist, but it is not 100% clear whether people are following them. If they are, the assumption would be that people are having exposures that fall into the risk categories and people are following the different steps and determining that those are risky situations that deserve PEP. Veterinary students and laboratorians all receive PrEP. The 10,000 to 15,000 who receive PrEP are probably all appropriate. Perhaps some of the travelers do not need it, but that pool is probably more representative of the need overall than the PEP population.

Dr. Hunter commented that when he receives a call from an ED about a bite regarding whether they should administer PEP, he refers them to the Wisconsin Division of Public Health algorithm. That type of aid is probably something that should be reviewed to ensure that they are correct, given that these are what people are using.

Rabies Pre-Exposure Prophylaxis Schedules and Serological Monitoring of High-Risk Exposure Populations

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Dr. Blanton reported that in general, the WG has been considering the current classical vaccination schedule recommended by ACIP. That is a 3-dose vaccination series given on Days 0, 7, 21 or 28 with subsequent recommendations around serological monitoring and boosters based on risk category. Given the amount of evidence that has been generated over the past couple of decades and the recent changes by WHO to recognize accelerated vaccination series, the WG also wanted to consider other potential series. Particularly, the 2-dose, 1-week schedule given at Days 0 and 7, for rabies PrEP. In addition, consideration would be given to routes of administration and how this would affect the various risk categories and

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immunocompromised populations. This would be a shift away from the FDA-approved 3-dose series for licensed vaccines in the US.

More than 100 years passed between the advent of rabies vaccination by Pasteur to the modern biologics and schedules used today. After more than 40 years' experience with the current recommendations, recent studies have begun to recognize the potential for accelerated PreEP schedules. However, despite the relatively good amount of information on the humoral response to rabies vaccines, particularly rabies neutralizing antibody responses, there continues to be limited studies and information regarding the cellular response [Sudarshan et al. (2005 and 2010). Hum Vaccin].

This is why it is good to have a discussion about neutralizing antibodies as a surrogate of protection for rabies vaccination. The 0.5 IU/mL rabies virus neutralizing antibody (RVNA) level has been classically used as the cutoff limit of detection throughout studies over the past several decades. It is important to point out that this is not a measure of protection despite it being presented that way in some studies. It is actually just a measure of adequate response, and in laboratory studies has been recognized largely as being the limit of detection to reliably report RVNA. While there is definitely a strong correlation between antibody titer and survival, it also is known from largely animal studies that there is considerable variability in survival of animals above and below this cutoff. Quite a few animals have survived below this level, and animals that do succumb to severe rabies challenge above it. The only thing that can definitely be pointed toward is that individuals who have an adequate antibody response, generally recognized above this level, after primary vaccination and anamnestic response to challenge or booster dose of vaccination are the best surrogates to indicate that they will survive rabies challenge [Rabies Virus Antibodies from Oral Vaccination as Correlate of Protection against Lethal Infection in Wildlife; Moore S, et al. (2017). Trop Med Infect Dis].

Another issue that there has been quite a bit of discussion about in the WG is the route of vaccination. It is important to point out that ID vaccination against rabies has been recommended globally since the 1980s. It was recommended in the US by ACIP between 1984-2008. One licensed product was available for ID vaccination during that time period. Intradermal vaccination was no longer recommended by ACIP after the ID product was removed from the market. However, the ID route has been found to be cost-effective in all of the modeling studies and studies that have been conducted in dose-sparing in supply-limited settings, which largely represents the rest of the world. That said, there continues to be no licensed single use ID packaging or multi-draw vials for rabies vaccination anywhere in the world. Injection safety around large-scale ID administration of rabies vaccine has not been well-studied. The cost-effectiveness of ID versus IM becomes somewhat moot with lower and lower patient volumes to the point where in very low-volume clinics, no additional cost-effectiveness is gained by using ID versus IM. However, studies that utilized ID administration still provide valid data for consideration because it is known from the many studies that have been compared ID and IM administration in terms of neutralizing antibody kinetics that a full 1.0 mL dose IM generally produces only slightly higher equivalent responses to the ID dose of 0.1 mL. Therefore, some of these studies can be considered to get an idea of what the response may be over different schedules [Fishbein et al. (1987). JID, Hampson et al. (2011). PLoS NTD].

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Although many schedules have been evaluated in the literature, the WG is focusing on the 0, 7 schedule. Part of that is because there is a wealth of information on the primary response to this vaccine in addition to the WHO recommendations. Because this runs in parallel to the 0, 7, 21 or 28 classical schedule, and many of the studies in the literature have evaluated serology at Days 14 and 21 before that third dose. For many of these, there is typically equivalent response among persons 1 to 2 weeks after a 2-dose schedule as there is a 1 to 2 weeks after the 3-dose schedule. It is certainly not just about the pre-exposure or just about the issue of the primary response. There have been some large-scale clinical studies, such as a study by Soentjens et al using the ID route. This study found a 100% adequate response and no difference between the classical accelerated schedules at Day 35. They also found that the 2-dose group had significantly higher GMTs at 1 year compared to the 3-dose group. When a booster was given as a surrogate of rabies exposure, no difference was found between the two different groups [Soentjens et al. (2018) CID].

The issue of duration of immunogenicity is one that came up and was largely one that the WG felt was not discussed as much by the WHO in making their recommendations. Typically, there are very few studies that have followed up further than 1 year. A few long studies of 2 to 3 years and out to 10 years have focused mostly on the classical schedule. A few studies have used the 2-dose schedule, but a 0, 28 schedule was used historically in some countries. However, on general trend that did come out is that looking at the titer as the primary response 1 to 2 weeks after vaccination was not a very good predictor of what the long-term immunogenicity would be in these individuals. It was found to be much better to look at the titer at 1 year, and even better to look at the response after a booster dose was given at 1 year as a predictor of 2 to 7 or even out to 10 years.

The potential of adding a booster led to quite a bit of discussion amongst the group, with a considerable amount of evidence of even the limited studies that have examined long-term response and relied on a booster at 1 year to achieve these long-term responses. Even with the current classical schedule, there is drop-off in 20% to 25% of people not having an adequate titer greater than 0.5 at 2 years compared to those who received a booster at one year who maintained very high level, with very few persons who dropped below that cutoff again over multiple years. This is the same not only with the classical schedule, but also with other schedules looking at different dosages as well [Pengsaa et al (2009) Ped Infect Dis Jrnl].

The one thing that has been clear in the studies evaluated is that anamnestic response does appear to be essentially universal. In the 60 studies being assess as part of a systematic review, only a single report has been identified of an individual who did not respond to a booster dose of vaccine. That individual was later diagnosed with B-cell lymphoma. It is not just about reacting to booster doses of vaccine. There are many cases and case reports of individuals who respond to natural infection, have an anamnestic response to vaccination, and survive exposure to rabies. For example, mass vaccination of children in the Amazon who are being predated upon by vampire bats has resulted in a complete reduction in the rate of rabies in these communities [Sabchareon et al. (1998) Ped Inf Dis Journal, Maier et al (2010) CID].

That is not to say that there are not pre-exposure failures in the literature. There is one classical example of this. In 1982, a Peace Corp volunteer who was vaccinated ID in Kenya was bitten by dog about 6 months later and died of rabies 3 months after the bite. This is the case that classically has been attributed to concerns about co-administration of chloroquine while receiving the PrEP series, specifically ID. While the study suggested that multiple factors were involved in this person having a lower titer and at risk, the general literature and surveillance have continued to not find any additional cases of failure of pre-exposure vaccination since this

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time. That being said, there are reports in studies that have identified inadequate response to primary vaccination reported in immunocompromised persons, particularly amongst HIV+ cohorts.

What this means from the WG's perspectives and the discussions that they have had about the potential use of an accelerated vaccination schedule, there is some concern about the risk populations Dr. Rao identified earlier in the high risk Continuous and Frequent categories in endemic and zoonotic areas. These are people who have a high rate of exposure events. Animal health care workers have a 300% to 500% higher rates of animal bites than the general population. The persons in these areas also have much higher risk that the exposure will involve a rapid animal. In the areas shown on the map that Dr. Rao showed earlier of skunk, raccoon, and fox in the US and mongoose in Puerto Rico, 14% to 17% of the wildlife submitted for testing typically are rabies-positive. Approximately 1% of domestic animals also test positive for rabies. This is a population for which there is interest in maintaining higher titers, with the sense that a higher titer is better correlation with protection. This also involves populations that have unrecognized exposure, such as laboratorians working with high titer viruses. These are situations in which the evidence would suggest maintaining higher titers in these populations over long time periods, and for whom consideration might be given to recommending a booster at 6-12 months after primary vaccination to improve the likelihood of maintaining an adequate titer. If this is done, the recommendations pertaining to the frequency of serological monitoring might be reduced for these populations as well.

Those in the Moderate category still have a very high rate of exposure events to animals in their occupational setting, but there is a low risk of rabies from these exposures. In comparison to 14% of the population in endemic areas, only about half a percent of samples from other areas submitted for rabies testing are positive. There have been no reports of domestic animals being positive in some number of years in these areas. Similar to the current recommendations, this is an area in which a routine booster at 6-12 months and routine serological monitoring are not critical.

Data are scarce for immunocompromised populations. In line with the current ACIP recommendations, risk reduction is thought to be the most critical action with an increased focus on providing advice about exposure avoidance, appropriate PPE, and prompt health-seeking behavior. Even if an accelerated vaccination schedule is used, it would not necessarily be necessary to recommend a larger dosage to this group as opposed to recommending required serological confirmation of an adequate immune response. This aligns with the current ACIP recommendation for the classical schedule and the WHO recommendation for the accelerated schedule.

For pregnant women, as a healthy population, there is a very good response to the vaccine. As far as the WG is aware, no safety concerns have been reported. Again, there are relatively scarce data in this regard. The focus would be on risk reduction with an increased focus on exposure avoidance, appropriate PPE, and prompt health-seeking behavior. In situations where occupational risk could be avoided or risk reduced and PEP is readily available, it might be considered to defer vaccination amongst pregnant women. In situations where there is any kind of ongoing concern, the recommendation would be to go forward with pre-exposure vaccination.

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To wrap up, the WG will go into more detail during the February 2020 meeting with the presentation of the system review and the GRADE analysis for a 2-dose PrEP schedule. During future ACIP meetings, the plan is to vote on the PrEP schedule and provide additional data for consideration of and alternate PEP schedule.

Discussion Points

Julian Ritchey (Sanofi Pasteur) provided a supply update. It was noted earlier that IMOVAX® vaccine has been on supply restrictions. Beginning October 5, 2019, it will be back in supply and will be shipping the following week without restriction for direct orders.

Dr. Talbot observed that it sounded like the goal was to reduce the number of PrEP doses from 3 to 2, and she wondered whether there was a reason for doing this other than WHO doing it.

Dr. Blanton indicated that there is evidence to suggest that this is an acceptable schedule moving forward. The WHO recommendations is a consideration, but the WG is looking at this from the evidence that has become available over the past 20 years. There are other advantages to moving to a 2-dose schedule, particularly in populations such as travelers and volunteers that are more time-limited in receiving the vaccine and issues pertaining to reduced cost.

In terms of special populations, Dr. Poehling did not see bats listed. However, the data on the people who actually were exposed showed that it was predominantly to bats in the US.

Dr. Blanton indicated that the WG would further describe this during the February meeting. Based on the current ACIP recommendations, any persons working directly with bats would fall into the Frequent category and either would go through additional serological monitoring or be recommended to have a booster.

Dr. Hunter asked whether other countries recommend a booster or if ACIP recommending a booster would be totally new.

Dr. Blanton indicated that currently there is no ACIP recommendation for a booster dose. Some countries informally recommend a booster to veterinarians. There is probably not as much adherence to PrEP in most of the world. By default, a lot of these individuals do wind up getting a booster if occupational monitoring of serology is occurring, certainly by Year 2 based on current ACIP recommendations. That is probably where most of the low responder individuals are being caught up and are in fact, getting a booster 2 years later.

Dr. Kimberlin (AAP) asked what percentage of bats are infected with rabies.

Dr. Blanton indicated that in the general population of bats, the estimate is about 1%. However, among bats that are having some kind of interaction or contact with humans, the ones that are being submitted for rabies diagnosis, that increases to 6% to 12% depending upon the region.

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Measles Update

National Measles Overview

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Dr. Gastañaduy provided an update on measles activity in the US. From January 2018 through October 16, 2019 there were 1637 measles cases reported in the US. An increase in cases began in October 2018 corresponding to the outbreaks in New York City (NYC) and New York State (NYS). Cases peaked in March and April of 2018, and there has been a steady decrease in cases in recent months. This table shows the characteristics of 2019 cases compared with earlier measles post-elimination years (2001-2018):

Characteristic	2019	2001-2018
Annual number of imported cases	83	28 (18, 83)
Annual number of cases	1255	79 (37, 667)
Annual number of outbreaks	22	4 (2, 23)
Number of cases per outbreak	6 (3, 646)	5 (3, 383)
Outbreak duration in days	27 (5, 230)	21 (3, 121)

Notably, there have been over 1200 cases this year. This has been the largest number of cases reported in a single year since 1992 and since measles was eliminated. The number of outbreaks also has been at the high end, with 22 outbreaks this year. Except for a couple of outliers, there has been no notable difference in the number of cases per outbreak or duration of the outbreaks.

As in previous years, 89% of all cases were unvaccinated or have an unknown vaccination status. A minority of cases were vaccinated. The burden has been concentrated in children 16 months to 17 years of age. This is somewhat on the younger side compared to prior years. This has been driven primarily by the outbreaks in NYC and NYS, which primarily affected pre-school children. Incidence has been highest among infants and babies 6 months and 15 months of age, which is similar to previous years.

Cases related to outbreaks in New York accounted for 75% of the almost 1500 cases reported in the US since the outbreaks began in late September 2018. There was sustained transmission related to these outbreaks for close to 11 months. These outbreaks threatened the measles elimination status of the US. However, there has been no transmission since the last cases in those outbreaks and elimination has been maintained. The New York outbreaks occurred in under-immunized orthodox Jewish communities. In fact, the most sizeable outbreaks reported post-immunization have occurred in specific close-knit under-immunized communities in the US. This table describes the 5 largest outbreaks in the US post-elimination (2001-2019), which account for almost half of all cases reported after elimination:

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Year	State	Source (Genotype)	Community	Cases	Duration (Months)
2018/2019	NY + 4 states	Israel/Ukraine (D8)	Orthodox Jewish	1,114	10
2014	OH	Philippines (D9)	Amish	383	4
2014/2015	CA + 7 states	Unknown (B3)	Various	147	2.3
2018/2019	WA + 2 states	Ukraine (D8)	Ukrainian Russian Moldova	78	2.5
2017	MN	Unknown (B3)	Somali	75	3.8

In summary, the highest annual number of internationally imported cases since measles was eliminated and the highest annual number of measles cases since 1992 was reported in the US in 2019. Most cases (75%) were related to the New York outbreaks and transmission was driven by delays in or lack of vaccination. The reasons for increases in measles cases in the US include global increase (WHO is reporting a 300% increase in their case estimate in 2019 compared to 2018), continued importations, and pockets of under-vaccination.

Discussion Points

Dr. Hunter said that as he understood it, there used to be a seasonal fluctuation in the number of cases per month of measles when it was endemic in the US that peaked in late winter to early spring. He was assuming that this was not necessarily going to apply to the upcoming several months because there is now elimination, and instead what would be more likely to cause a problem in the next several months would be importations.

Dr. Gastañaduy indicated that this is correct. Basically, seasonality has gone away since measles was eliminated and everything is related to importations. There is some tendency to have importations in early months of the year (correlating with measles activity globally) and in the summer season (when people travel the most).

Dr. Maldonado (AAP) asked whether the genotypes were known for the circulating viruses this year.

Dr. Gastañaduy responded that almost 95% of the circulating viruses have been D8. This is a common genotype that has been circulating across the world and is not specific to one area.

Dr. Patel added that with vaccination increasing globally, there has been decreased heterogeneity in genotypes. One of the steps that the CDC measles laboratory is going to be taking is to understand more discriminatory genetic analyses among the various genotypes, and those data are forthcoming.

Ms. Stinchfield (NAPNAP) commented that now is the time to have the attention and urgency around this. Despite hearing from WHO that there has been a 300% increase from 2018 to 2019 and having worked on the Somali measles outbreak, she emphasized that there is a misperception that 1000 cases in the US is a small outbreak and people think there is no reason to worry. However, this is exactly the time to worry because of how infectious and

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contagious this disease is. It is imperative to keep getting the message out that prior to vaccine, there were 4 million cases and 500 deaths per year. These large numbers of cases, percentages, and deaths are occurring around the world and that will happen here if the sense of urgency is not conveyed. It is not about the small numbers of outbreaks. It is about the potential if vaccination is not continued.

Dr. Messonnier pointed out that there seems to be some misunderstanding about the 300% increase that WHO has reported. Some of the countries that are having outbreaks are conflict countries like Venezuela. There also is ongoing measles transmission occurring in other countries in places where people do not think about the importance of getting the measles vaccination. The top countries for importations this year include Ukraine, Israel, Philippines, and the United Kingdom. People might think about getting vaccinations and checking the *CDC Yellow Pages* when going to countries they consider to be less industrialized, but there have been importations from London this year. CDC tries to emphasize the global threat and the need for people to check their immunization status before they travel overseas, but are repeatedly surprised that Americans seem unaware of that risk.

Measles Outbreak in New York State, 2018–2019

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Dr. Blog described the NYS measles outbreak, excluding NYC, that took place from October 1, 2018 to September 30, 2019. While this presentation excluded NYC and concentrated on the Lower Hudson Valley, the characteristics of both outbreaks were similar. The overwhelming majority of measles cases that occurred in NYS were in under-vaccinated, close-knit Orthodox Jewish communities. The total number of confirmed cases in the Lower Hudson Valley was 407. There were 10 cases imported from Israel. These consisted of 7 cases imported in the first month of the outbreak alone and 3 further importations, 1 in December 2018 and 2 in April 2019.

Cases occurred in 5 counties. Rockland County had 312 cases, Orange County had 57, Sullivan had 19, Westchester Counties had 18, and Green County had 1 case. All of these counties have Orthodox Jewish communities, with Rockland being the largest and the most diverse. While the outbreak took place in 5 different counties, it was concentrated in several Zip Codes. The widely dispersed geography of this outbreak was a challenge when working to control it. The county health departments ranged from small to large in terms of size and the population served. This made assisting with case investigations, contact tracing, and monitoring the contacts difficult. It also was hard to get specimens to public health laboratories, and it was necessary to set up a relay system to get that done.

This is the epidemic curve showing the number of cases over time by rash onset. The colors reflect the different counties, with Rockland County in gray, Orange County in dark blue, Sullivan County in yellow, Westchester County in turquois, and Green County in Black:

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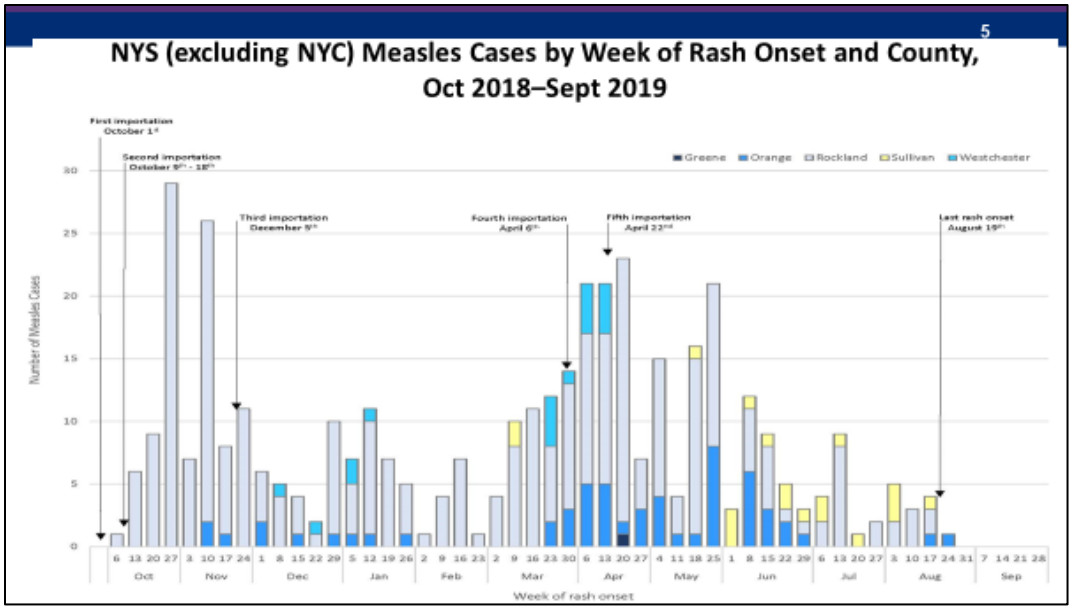

The arrows show the importation of cases. The last arrow on the far right shows that the last date of rash onset was August 19, 2019. The epidemic curve has two main peaks, which could reflect unreported cases that occurred in the middle or increased travel that occurred before and during the Passover holiday in the spring. It also may be due to the outbreak affecting different orthodox communities. For example, transmission in one area was very active in the beginning but virtually ceased later on before other areas took off.

In terms of cases by vaccination status, 82% of cases had zero MMR doses, 5% had 1 dose, 4% 2 doses, and 9% had an unknown vaccination status. Among those with zero MMRs, 274 were 12 months of age and older and could have received MMR vaccine. An additional 35 children 6 months to 11 months of age could have received an MMR in the outbreak setting.

In terms of complications, 28 (7%) patients were diagnosed with pneumonia, 28 (7%) patients were hospitalized, and 20 (71%) were children. However, not everyone who was hospitalized had pneumonia and vice versa. Among the 20 hospitalized children, 6 (30%) were admitted to the intensive care unit (ICU). All of the children admitted to an ICU were 7 years of age and younger. Two preterm infants were born at 34 and 25 weeks gestation to women who had measles while pregnant. Both infants were born with congenital measles infection that was confirmed by measles PCR testing. There were no deaths or cases of encephalitis.

The causes of this outbreak were multifactorial. However, the key factor was under-vaccination due to vaccine hesitancy. This community was targeted by anti-vaccine advocates who are skillful at disseminating misinformation in ways that resonated with this community. This, combined with multiple importations from a large outbreak in Israel during holidays when there were large gatherings of family celebrations, allowed for transmission of disease. Other factors included large families where measles could spread to all unvaccinated children, and families who were unwilling to report cases or seek medical care, allowing unidentified transmission to occur. In addition, positive IgM results were reported through laboratory reporting that was usually done because parents wanted their children to return to school. By the time the labs were drawn or were received, it was difficult to confirm if they were cases and too late for control measures.

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Communicating fact-based information about measles was a priority during the outbreak. Because electronic media was not a useful way to reach these groups, materials were developed in the form of flyers, posters, advertisements at malls and highway rest stops, and articles in local publications. Materials were developed in both English and Yiddish and 55,000 door hangers with information about measles were distributed to all homes in affected zip codes. Conference calls were held with women from the community, and many meetings were held with community members and religious and educational leaders. In recent years, the increase of vaccine hesitancy in orthodox communities was recognized. After dissemination of an antivaccine pamphlet called *PEACH (Parents Teaching and Advocating for Children's Health*), the Hudson Valley Health Coalition was formed to address this problem. A booklet on vaccination and measles was created to combat misinformation *Tzim Gezint*. In addition, the Orthodox Jewish Nurses Association (OJNA) wrote a booklet titled *A Slice of PIE (Parents Informed and Educated): Making PIEs Out of PEACH*, which addressed all of the points made in *PEACH*. 90,000 copies of both pamphlets were printed and mailed to households and made available to provider offices.

Outreach and communication with all types of HCP were also a priority. This took the form of advisories, conference calls, and forums. More than 30 detailing visits took place with practices, urgent cares, and hospitals. NYSDOH provided additional MMR vaccine to practices that requested it, and also offered materials for patients and families that could be used in offices. Collaboration with a large Federally Qualified Health Center (FQHC), Refuah-FQHC, was particularly noteworthy. They implemented screening procedures at the door, honed their infection control procedures, administered thousands of doses of MMR, and were a constant source of reliable information to the community they serve. They continue to work hard to address vaccine hesitancy among their patients.

From October 1, 2018 to September 30, 2019, providers in outbreak counties vaccinated over 84,000 individuals with MMR, a 77% increase from the same period during the prior year. Rates in the 4 most affected zip codes for children aged 1-18 years was 87.3% before the start of the outbreak. By August 1, 2019 increased to 98.3%. Vaccine was given primarily in private practices and FQHCs, though state and local public health departments held clinics as well. Rockland County issued orders to exclude unvaccinated children not only from schools with cases, but also schools in proximity to cases. Weekly attestations were required from each school that affirmed continued compliance with the order. Audits of most schools in the outbreak areas were conducted and several schools were fined for non-compliance. At the peak, Rockland County alone had 6,000 unvaccinated children excluded from 60 schools. Most counties with outbreaks excluded unvaccinated children from summer camps and conducted some form of camp audits. However, Sullivan County was at particular risk since in the summer the population there increases to about 300,000 from their year round base of 67,000. The increase is due primarily to Orthodox families from New York City who come to the county to spend summer in groups of bungalows and to attend camps. All 300 camps in Sullivan County were audited in a joint effort between the county, NYS, and CDC.

There were many lessons learned during this outbreak. One primary lesson was the ongoing need to address vaccine hesitancy and misinformation and to find ways to do this with close-knit, culturally diverse communities. The second major lesson was the importance of partnerships between communities, healthcare, and public health and also between local, state, and federal public health. Finally, they learned that religious exemptions had to go. NYS passed legislation in June 2019 removing non-medical exemptions from school vaccination requirements for children for school entry.

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Discussion Points

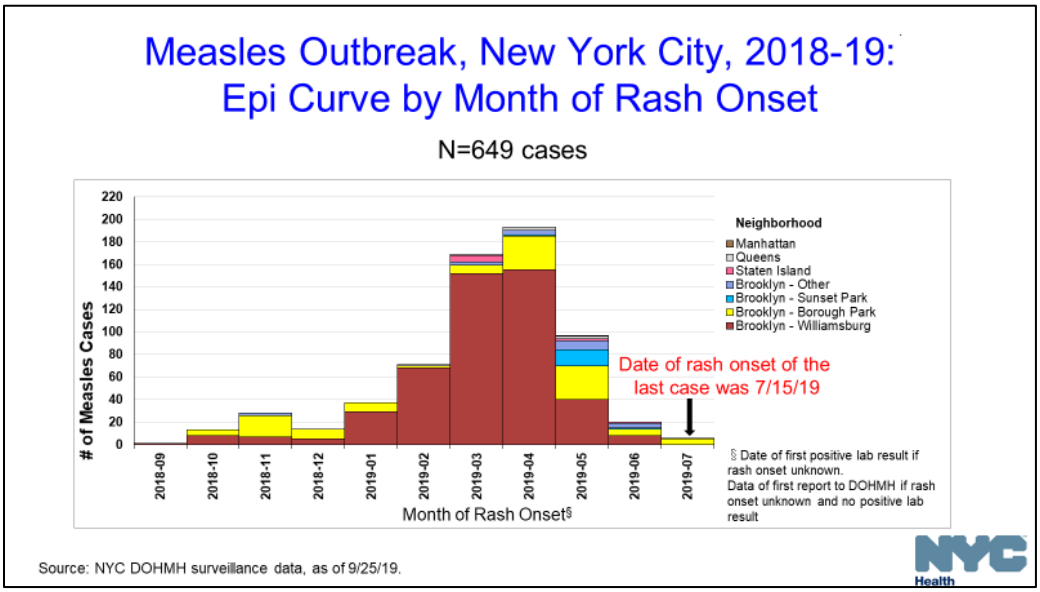
Dr. Bell asked about whether there was any heterogeneity among the various communities in terms of their acceptance. She knew that in some other situations, the position of the Rabbi was important in helping to direct the community in terms of their perspective about vaccination and wondered whether the Rabbis were on board, or if people were just not listening to them as they might have in the past.

In terms of the community where the outbreak was very active for a number of weeks and then virtually ceased, Dr. Blog said that the information she heard was that the Rabbi there implored the community to end this. Orange County is basically one large group, but in Rockland there are many groups. It is obviously more challenge to reach out to many groups. Several statements were made by prominent Rabbis locally and in Israel.

Current Status of Measles in the United States: New York City Outbreak, 2018-2019

Jane R. Zucker, MD, MSc, FIDSA
Assistant Commissioner
Bureau of Immunization
New York City Department of Health and Mental Hygiene (NYC DOHMH)

Dr. Zucker reported that NYC DOHMH's first case of measles that was part of this outbreak had rash onset on September 30, 2018. This was in an unvaccinated child who returned from Israel. The outbreak was centered in two Orthodox Jewish neighborhoods in Brooklyn, Williamsburg and Borough Park. This is the epidemic curve for the NYC outbreak with number of measles cases by month of rash onset:



Williamsburg represented 73% of all cases, while Borough Park represented 19% of all cases. The NYC outbreak lasted 9.5 months and the last rash onset occurred on July 15, 2019. NYC declared the outbreak over two incubation periods later on September 3, 2019. Of NYC's cases, 81% of were under 19 years of age and 19% of cases were adults. In terms of vaccination status, 74% of cases had no MMR doses, 7% had 1 dose, 5% had 2 doses, 14% had an

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unknown vaccination status. Most (92 out of 94) of those with unknown vaccination status were adults. The median age of cases was 3 years and the range was 1 month to 70 years of age.

Regarding the context of the outbreak, NYC DOHMH has a long history of working with the community, providers, community-based organizations (CBOs), and other partners. This goes back to the 1990s when there were hepatitis A outbreaks in the community. That kind of longstanding relationship was very important. Because of several other health issues in the community, NYC DOHMH had hired an Orthodox Jewish community liaison to help further strengthen those relationships. They also had established the Haredi Health Coalition for this community before the outbreak started.

NYC has a Citywide Immunization Registry (CIR) Immunization Information System (IIS), which is population-based. NYC is very proud of this well-functioning registry. There is high compliance with mandatory reporting of childhood vaccines, as well as high data quality and completeness. This has been a sentinel site for over 10 years.

In terms of the outbreak response, a lot of work went into all of the activities. There was a major focus on notification of exposed contacts, PEP with MMR or immune globulin (IG) within 72 hours for those who were unvaccinated, and home isolation as needed. There was a lot of citywide and targeted outreach to providers, community engagement, press release and media interviews and articles, print ads and social media talking about the importance of vaccination and vaccine safety, daycare and school exclusions, an emergency order requiring vaccination, and MMR vaccination. All of this was meant to increase vaccination coverage in the community. The Jewish Press were fantastic partners as part of this response.

Noting that the NYS and NYC outbreaks were very similar, Dr. Zucker indicated that her comments would focus on some additional response efforts other than what was presented by Dr. Blog. In terms of contact information, NYC had over 20,000 names contacts that went into the surveillance database. These were the ones that they knew about rather than more casual exposures, and many of these exposures occurred in healthcare facilities. One thing that was really important for NYC was that their surveillance database is connected to the CIR ISS, so they are able to kick off a query out of the database into the registry to pull the vaccination history back into the surveillance. This was enormously helpful and let them focus on people who did not have documented vaccination and not worry about people who were known to be immune by vaccination. Because of this large number of contacts, they had to set up a dedicated call center because they attempted to reach everybody, whether it was by phone or by sending a letter. They also had to implement a new structure within the response to address the large number of contacts. The new structure focused on exposures in households, daycares and schools, and medical facilities. They assigned Health Liaisons to individual medical facilities to help them manage the exposure list, and to try to put in place mechanisms to prevent additional exposures. DOHMH staff were stationed at a high-volume facility at the epicenter of the outbreak to assist with potential exposures and set up screening outside of facilities to help prevent more exposures.

As of December 7, 2018, NYC required exclusion of unvaccinated students with medical and religious exemptions in impacted communities, as well as those who were not in compliance with the immunization requirements. That was due to increasing transmission in the community and targeted those in the affected zip codes. DOHMH conducted audits to ensure that there was compliance with immunization requirements and these exclusions. At the height of the outbreak, they were auditing 101 facilities in Williamsburg every week to ensure that there was compliance. The programs that were not in compliance were subject to Commissioner's Orders,

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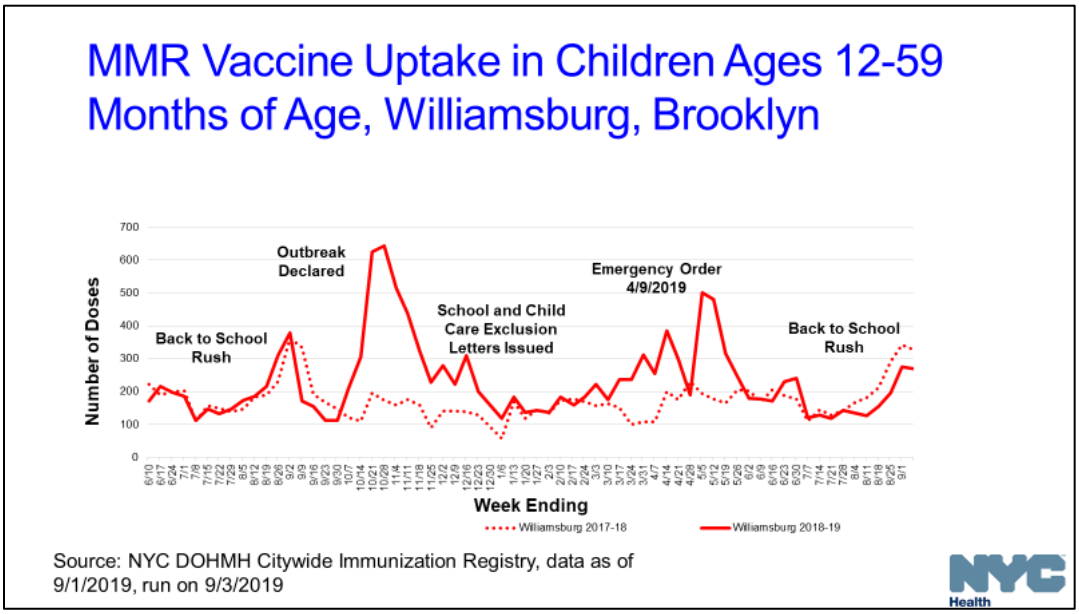
Notices of Violation, and fines. With follow-up in terms of non-compliance, 12 schools and daycares were closed either for failing to provide access to medical and attendance records or for having students without the required documentation of MMR in attendance.

There was a large increase in cases in March and April, so a public health emergency was declared through a Commissioner's Order. It required that every adult and child who lived, worked, or resided in Williamsburg and had not received the MMR vaccine to be vaccinated. There were exceptions for people who had a valid medical exemption or who could demonstrate that they were immune from measles. The Board of Health met the following week and approved this resolution. Overall, 232 individual summonses were issued in relation to this order. The good news is that many of those were cancelled because the person submitted proof of vaccination or proof of immunity.

In terms of whether these strategies were effective, these data from the CIR focus on Williamsburg and the youngest children since that was where most transmission was observed:



The solid line is the current time period compared to the dotted line, which was the 12 months before that. Looking left to right, there was the back-to-school rush with the increase in vaccination that occurs every year. The outbreak was declared and as hoped, many children were vaccinated. Some peaks in vaccination occurred when the school and childcare exclusion letters were issued. Again, these are the younger children. In the same graph for school-aged children, those peaks would be much higher. Vaccination declined until the Emergency Order was issued in April 2019, and a full year later there was an increase in vaccination for back-to-school.

Overall in NYC, over 188,635 MMR doses were administered during the outbreak period. This represents a 14% increase overall compared to the same period last year. Close to 12,000 MMR doses were administered in Williamsburg, the epicenter of the outbreak. This represents a 54% increase compared to the same period last year. Most of these vaccinations were administered by providers. The health department did not hold any clinics. Based on the registry, it was estimated that coverage for children 12 through 59 months of age in Williamsburg increased during the course of the outbreak from 80% to 91%.

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As might be imagined, an outbreak of this scale had tremendous impact on the health department. Over 559 NYC DOHMH staff were activated at some point and were deployed to the outbreak. This represents about 7% of the staff. At the peak of the outbreak, over 260 staff were working on measles. NYC DOHMH conduced almost 2300 case investigations. Of these, there were 649 cases and none of the others met the clinical case definition or were PCR negative. A preliminary estimate of the cost of the outbreak to NYC DOHMH is approximately $8.4 million. NYC DOHMH implemented labor allocation codes to be able to count the hours and dollar amount, though this was not complete in terms of everyone filling out the codes, and this figure also includes costs for vaccine purchase and advertisements.
Going forward, NYC DOHMH remains vigilant.

There is a continued risk of future importations. This year alone, there have been 12 measles cases that were not related to the outbreak. In addition to the outbreak, they have to address additional importations. They also are working to implement the new legislation to remove religious exemptions, conducting school and childcare audits, and reviewing medical exemptions. There has been a tremendous number of requests to review medical exemptions, given that there were children who previously had religious exemptions for whom medical exemptions are now being requested. Those are being reviewed by NYC DOHMH when requested. They continue to track vaccine uptake and address vaccine misinformation. They have launched a campaign in this city to talk about the importance of vaccination, saving lives, and vaccine safety. They are in the process of developing new targeted materials as well. They know that they are in it for the long game. The outbreak may be over, but continued work is necessary to maintain high vaccination coverage.

Discussion Points

Dr. Messonnier pointed out that overall immunization coverage in NYS is 97% plus and in NYC is probably higher. She asked how it happened that there are communities with such low vaccination coverage without NYS and NYC knowing, given that being aware of the issue they have outreach into these communities. She wondered whether it was just bad luck or if there was a knowledge gap that occurred from not looking closely enough at these communities at a level that would have resulted in them being identified in advance.

Dr. Blog replied that they were aware that there was vaccine hesitancy in these communities; however, she thinks they did not understand the extent of it. The result is that they want to look closer at other communities as well.

Dr. Zucker indicated that the last measles outbreak was in 2013. They have had varicella and pertussis. They had been mailing out documents to address vaccine hesitancy well before the outbreak, and they were working with individual providers. After the measles outbreak, they did a lot of work and there was a lot of frustration among providers about the challenges with getting children vaccinated. The truth is, they cannot force vaccination. They have focused heavily on daycare and school compliance with the idea that when children could be captured in the system, they could make sure that they are vaccinated. They were aware of and working on the problem, but she thinks that in part it was that this was an incredibly complex outbreak. This was not one outbreak. It was multiple outbreaks that occurred simultaneously. Over 90 chains of transmission were identified. Bad luck and the impact of what is occurring in Europe with multiple importations were also part of it.

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Dr. Blog added that religious exemptions were okay. A lot of children in schools had religious exemptions. Even though the schools were audited, they were not necessarily doing anything wrong or illegal.

Dr. Zucker added that 28% of children in some schools had religious exemptions, but they were in compliance. That is a challenge. Once measles got into the school setting, that fueled transmission.

Dr. Sanchez said he was intrigued by the number of cases among those less than 6 months of age, whether other risk factors were associated with that, and whether their cases were more severe. The recommendations are for children 6 months of age and older to be vaccinated. He recalled that some of the cases were congenital and wondered whether the mothers were not immune or had not been vaccinated.

Dr. Blog responded that she did not think they had explicitly assessed this, though they did know maternal status. The children under 6 months of age often were in families in which the children were not vaccinated, and the older children all got measles and transmitted it to them as well. Some were just exposed in the community. For the congenital cases, the mothers were tested and had measles. The infants were tested after birth with PCR and serum and then were followed over time.

Dr. Zucker added that they could look at the cases in children under 6 months of age to see if they were more severe. Some children were admitted to the hospital, but not all of them and hospitalization was not concentrated in that group. Here were children who were known to be exposed whose parents refused IG, so a certain portion of those could have been prevented.

Dr. Frey thanked Drs. Blog and Zucker for two nice presentations and complimented them on an incredible amount of well done work.

Ms. McNally requested information about how vaccination was handled in the age range of 6 months to 11 months. She also wondered whether it would be appropriate to include a note in the schedule regarding an outbreak occurrence.

Dr. Blog indicated that they primarily targeted the practices that see these children and getting them to offer it, and they targeted that information to the parents of these children as well.

Dr. Zucker added that NYC issued recommendations that children 6 to 11 months of age in the affected communities should receive an early MMR. Because they have the registry, they were able to track that to know that it was being implemented and to determine the vaccination rate in that younger age group. There already is a note in the ACIP guidance for outbreaks. The other part of that was the travel recommendations, because there was still a lot of travel back and forth during the outbreak and even now, especially with the Jewish holidays. So, they have been heavily messaging the importance of vaccination for the younger age group as well.

Dr. Kimberlin (AAP) requested clarity about whether he heard that one of the challenges was getting physician practices to offer MMR as part of the response.

Dr. Blog clarified that it was a challenge to get practices to offer MMR to children 6 to 11 months of age.

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Dr. Cieslak (CSTE) asked to what degree vaccine hesitation in this Orthodox Jewish community was a heart-felt religious conviction as opposed to other reasons people more typically choose exemptions.

Dr. Zucker said that consistently from the Rabbinical community that there are no religious prohibitions to vaccination in this community. In fact, there is a sense of importance of vaccination to protect people who are more vulnerable. The religious exemptions really were philosophic exemptions that were couched in religious language.

Dr. Tyler-Hill (NMA) emphasized that as a practicing pediatrician, the supply chain is a major issue in terms of getting vaccines. She wondered whether there have been any problems with children receiving the second doses children need at 12 months of age or older in terms of supply and being able to appropriately immunize the children who received the vaccine between 6 to 11 months of age.

Dr. Zucker indicated that there were no supply issues in NYC in terms of making sure that practices had as much MMR vaccine as needed. They made every effort to ensure that practices that may not normally stock MMR, such as urgent care facilities. For example, NYC DOHMH provided urgent cares with MMR to be able to vaccinate adults presenting there. While a lot of the doses administered were first doses, they also administered a lot of second doses because they also recommended that children under 5 years of age who received 1 dose got their second dose early. They know that this was occurring. The children who got a dose at under 12 months of age, as long as they were 12 months of age and older and it was 4 weeks later, would have a recommendation in the registry. That was part of the guidance that was given as well.

Dr. Blog indicated that it was the same for NYS. They made a big effort to get vaccine in a regular flow to all of the key practices in the communities that were affected. It was very successful. All they had to do was call to ask for more.

Dr. Bernstein expressed interest in knowing whether the state legislation applied to home schools and private schools.

Dr. Blog responded that it did apply to private schools. While there is some disagreement about home schools from the legal community, it basically does not apply to home schools and would be very difficult to enforce.

Dr. Zucker added that if home-schooled children are entering the school setting for exams or school programs, they are required to be vaccinated.

Vaccinate With Confidence

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

Dr. Mbaeyi began by acknowledging their colleagues from New York and expressing gratitude for their efforts. Although the US narrowly maintained measles elimination status, the country is not “out of the woods yet.” These measles outbreaks highlight the continued threat of vaccine-preventable diseases in the US and have led to rethinking of the approach to protecting the public from outbreaks. The first measles case is too late. Confidence must be built in the

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immunization program to ensure that all US communities are protected through vaccination. During this session, Dr. Mbaeyi talked about CDC's strategic framework to strengthen public trust in vaccines and prevent outbreaks of vaccine-preventable diseases.

The good news is that overall vaccine coverage is high in the US. Most parents are confident in vaccines and choose to vaccinate their children according to the recommended schedule. Over 94% of kindergarteners have received 2 doses of MMR vaccine. While school entry requirements provide a safety net for ensuring school-age children are vaccinated, some younger children are left unprotected. National coverage of at least 1 dose of MMR is 90% by 24 months of age, but there is geographic variation in coverage rates. Twenty states have less than 90% coverage.

As seen in the previous presentations, lower rates of vaccination in some communities can create a foothold for diseases to spread. In particular, close-knit, under-vaccinated communities are a key vulnerability. Each of these communities is unique, with distinct factors affecting vaccination including isolation or insularity, access issues, distrust of public authorities, or localized misinformation. Myths and misinformation have always been part of the vaccine landscape. However, rapid dissemination and sophistication of misinformation present new challenges. While its impact nationally is unclear, misinformation plays a clear role in eroding vaccine confidence and reducing vaccination rates in some local communities.

To address these challenges, CDC launched *Vaccinate with Confidence: CDC's strategic framework for strengthening vaccine confidence and preventing outbreaks of vaccine-preventable diseases in the United States.* This strategy responds to the dynamics shared by recent outbreaks, including pockets of low vaccination in close-knit communities, the spread of compelling vaccine misinformation targeted at these communities, and the perennial issue of ensuring that vaccines are accessible and easy to obtain. *Vaccinate with Confidence* advances three key priorities:

- ❑ Protecting communities: Using every tool available to find and protect communities at risk using tailored, targeted approaches;
- ❑ Empowering families: Ensuring parents are confident in their decision to vaccinate by strengthening provider-parent vaccine conversations; and
- ❑ Stopping myths: Using local partners and trusted messengers, establishing new partnerships to contain the spread of misinformation, and educating critical stakeholders about vaccines

Vaccinate with Confidence combines CDC's existing work with new investments and activities. To protect communities from outbreaks, the communities that are most vulnerable must be found first. To do this, CDC will: 1) leverage the *2019 Immunization and Vaccines for Children* cooperative agreement to support awardee efforts to find and respond to pockets of low vaccine coverage in their jurisdictions; 2) use immunization information system data and small area analyses to pinpoint areas of low vaccination coverage and identify barriers to vaccination; and 3) build immunization program capacity to effectively respond to outbreaks.

Every parent wants to make the best decision for their child's health. To help empower families and ensure that parents are confident in the decision to vaccinate, health care professionals must be equipped with resources to have effective vaccine conversations. CDC's new investments and activities will: 1) support partners to help vaccine conversations start earlier

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with parents of very young infants and pregnant women; 2) reduce hesitancy and improve vaccine access at the nation's community health centers; and 3) develop provider toolkits to address parents' vaccine questions during outbreaks of vaccine-preventable diseases.

To stop myths, it is imperative to ensure that reliable information is not drowned out by misinformation, educate key stakeholders about vaccines, and engage trusted local messengers to provide accurate and reliable information about vaccines. CDC is working with social media companies to promote trustworthy vaccine information, educating state policy makers on vaccine safety and effectiveness, and engaging state and local health officials to advance effective local responses and community-based initiatives to counter misinformation and hesitancy.

Progress has been made. So far, CDC has assisted states and cities to respond to the worst year for measles since 1992; developed state and local health departments, healthcare provider, and camp toolkits; worked with key partners to get their perspectives on vaccine hesitancy challenges; developed a strategic framework to strengthen vaccine confidence; and funded new work by key partners to implement immediate efforts. But, there is still more work to do. CDC's priorities are to: 1) leverage diverse data sources to find and protect communities at risk; 2) expand resources for working with communities; 3) build and foster a culture of immunization in healthcare practices; 4) provide technical assistance to funded partners; 5) strengthen communication messages; and 6) further invest in vital partners.

Partners are key. Advancing CDC's strategy requires a cohesive approach with state and local governments, as well as partnerships with stakeholders and providers. Dr. Mbaeyi noted that the pictures in her slides were a great example of the partnership between the American Academy of Pediatrics (AAP) and *SELF Magazine* designed to accurately and responsibly portray vaccination. Creative efforts such as these are needed to promote the positive and vital role vaccines play in protecting children and encouraging confidence in the decision to vaccinate. Together, we can protect our communities, empower families, and stop myths.

In conclusion, she acknowledged all of those who helped developed CDC's *Vaccinate with Confidence* strategy and all who work tirelessly to promote vaccination in their communities.

Discussion Points

Dr. Tyler-Hill (NMA) commented that the African American population is at high risk for the Anti-Vax Movement, and she wondered what culturally competent, community-based efforts are being made to target that population and if surveying is being done. She hears on social media from closed physician groups that include African American pediatricians that they are seeing increased levels of vaccine hesitancy. There is already a disparity in vaccine uptake in that population, so she wondered if anything is being done to survey how much of that is getting into the community as a preventive measure and then once that is done, what the tactic would be using these kinds of opportunities.

Dr. Mbaeyi indicated that CDC has been doing a lot of work to try to help remove disparities in healthcare and vaccination access. In terms of vaccine hesitancy, one of the key cornerstones of this strategic framework is to help identify communities at risk and then implement tailored, targeted interventions. CDC really wants to work with its state and local health departments and other partners, to help them find communities at risk such as the African American population, other cultural groups, religious groups, and other language groups and then implement tailored

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approaches. They know that there is no one-size-fits-all approach, so they want to try to help develop tools to tailor approaches.

Dr. Cohn added that when they talk about “community” it may mean a community that may not be geographically close-knit, but it may be a community that shares similar values. The African American community is a group that CDC has identified as being at risk for increased hesitancy. The agency would love to work with NMA and other groups more, including partnerships with religious organizations.

Dr. Tyler-Hill thought this would be excellent and suggested that one thing that would help would be data and tools to illustrate how this is growing within the population. After practicing for 35 years, this is something she never heard of previously. Now she is hearing about this, it is growing, and it needs to be monitored to determine what needs to be targeted to prevent this from happening. NMA would love to work with CDC on this.

Dr. Hunter asked as an ACIP member, especially as a member of WGs, that CDC evaluate *Vaccinate with Confidence* in order to provide data to be incorporated in the EtR process so that the way ACIP crafts policy options will reflect what will actually work.

Dr. Zahn (NACCHO) pointing out that investing in infrastructure to support the local level means enough money will have to be spent in the budget at state and local health departments in order to have ample people in their immunization and communicable disease programs to respond to events and to make sure that immunization efforts are kept in schools. At some point there is a capacity need. Certainly, at the local health department level, the loss of thousands of positions around the country in the last 10 years is not a small issue.

Dr. Messonnier indicated that one thing CDC has tried to emphasize this year, and that NACCHO should hear them saying all of the time, is that while national activities are important, this issue is going to be fought locally. Local public health, local AAP, local AAFP, and all of CDC’s partners such as NMA are the front lines. There are some things CDC can do centrally, but in the end, every community is so different, very local public health will have to help them in this situation.

Vaccine Supply

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

During this session, Dr. Santoli presented an update on the pediatric and adult HepB vaccine supply. She reported that Merck anticipates continuing to have a limited supply of pediatric HepB vaccines throughout mid-2020 and will continue to direct its limited supply to CDC to support utilization consistent with current clinical guidance. GSK is able to continue to cover the supply gap during this time period, using a combination of monovalent and combination vaccine. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time. The expected monovalent supply remains sufficient to cover the birth dose for all children, as well as some second and third doses.

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With the exception of a limited release of vaccine available in the fall of 2019, Merck will not be distributing its adult HepB vaccine or the dialysis formulation through 2020. Dynavax and GSK have sufficient supplies of adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply during this period. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time.

As a reminder, CDC has a vaccine supply page that is kept updated in sync with all of the updates made during ACIP meetings. The Vaccine Supply/Shortage Webpage can be found at: https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html.

Discussion Points

Dr. Frey noted that the supply updates are always interesting and worrisome. She wondered whether in the future, ACIP also could be apprised of the reason behind any shortages.

Dr. Santoli indicated that they defer to the manufacturers to provide any additional information about the causes for supply issues. Generally, CDC manages these issues by serving as an honest information broker between manufacturers, sharing limited information about anticipated supply gaps with other manufacturers who may be able to mitigate the situation. Information CDC receives from impacted manufacturers is confidential and CDC requests confidentiality about the information they share when they reach out to manufacturers of alternative vaccines. That is the level at which CDC operates. In terms of the vaccine supply presentations to ACIP, CDC wants the ACIP members to understand the status of vaccine supply, including any gaps in supply and what is known about the timing of resolution. CDC is are not at liberty to report any other details about the reasons behind vaccine supply shortages.

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Certification

Upon reviewing the foregoing version of the October 23-24, 2019 ACIP meeting minutes, Dr. José Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACIP Membership Roster

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2019 – June 30, 2020

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