

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

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
February 26-27, 2020
Atlanta, Georgia**

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Final - February 19, 2020**MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)**

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium

Atlanta, Georgia 30329

February 26-27, 2020

<u>AGENDA ITEM</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Wednesday, February 26th</u>	
8:00 Welcome & Introductions	Dr. Jose Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
8:30 Ebola Vaccine	
Introduction	Dr. Sharon Frey (ACIP, WG Chair)
Review of Ebola virus disease and rVSVΔG-ZEBOV-GP vaccine	Dr. Mary Choi (CDC/NCEZID)
GRADE	Dr. Caitlin Cossaboom (CDC/NCEZID)
ETR and summary of WG considerations and proposed policy options	Dr. Mary Choi (CDC/NCEZID)
10:00 <i>Break</i>	
10:30 Ebola Vaccine, continued	
12:00 <i>Lunch</i>	
1:15 Public Comment	
2:15 <i>Break</i>	
2:30 <u>VOTE</u>	
Ebola Vaccine	Dr. Mary Choi (CDC/NCEZID)
2:45 2019 Novel Coronavirus (2019-nCov) Informational Session	TBD
3:30 <i>Break</i>	
3:45 Influenza Vaccines	
Introduction	Dr. Robert Atmar (ACIP, WG Chair)
Older Adult (65+) Adjuvanted Quadrivalent Influenza Vaccine (aIIV4)	Dr. Gregg Sylvester (Seqirus)
2019-20 U.S. Influenza Surveillance Update	Ms. Lynnette Brammer (CDC/NCIRD)
2019-20 U.S. Influenza Vaccine Effectiveness Update	Dr. Fatimah Dawood (CDC/NCIRD)
Safety of Adjuvanted vs. High-Dose Inactivated Influenza Vaccines in Older Adults	Dr. Ken Schmader (Duke University)
Summary and Work Group Considerations	Dr. Lisa Grohskopf (CDC/NCIRD)
5:00 Adjourn	
<u>Thursday, February 27th</u>	
8:30 Unfinished Business and Agency Updates	
CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	
9:00 Rabies Vaccine	
Introduction	Dr. Sharon Frey (ACIP, WG Chair)
Background to PrEP, Vaccine Safety, and Work Group Considerations	Dr. Agam Rao (CDC/NCEZID)
Rabies Vaccine Schedule & Duration of Immunity (Systematic Review Data)	Dr. Jesse Blanton (CDC/NCEZID)
Work Group Next Steps	Dr. Agam Rao (CDC/NCEZID)
10:00 <i>Break</i>	
10:30 Dengue Vaccine	
Introduction	Dr. Robert Atmar (ACIP, WG Chair)
Dengue Vaccine Acceptability in Puerto Rico	Dr. Ines Esquilin (University of Puerto Rico School of Medicine, Department of Pediatrics)
SAGE Perspective on Dengvaxia	Dr. Joachim Hombach (WHO)
Summary of Work Group Considerations	Dr. Steve Waterman (CDC/NCEZID)
12:00 <i>Lunch</i>	

Final - February 19, 2020

1:00	Polio Informational Session Polio and Polio Policy in the United States – The Oral Polio Vaccine to Inactivated Polio Vaccine Switch Global Polio Eradication: Progress and Prospects	Dr. Walt Orenstein (Emory University) Mr. John Salamone (Former ACIP Member) Dr. Stephen Cochi (CDC/CGH)
2:00	Hepatitis B Vaccine - Work Group Update	Dr. Sharon Frey (ACIP, WG Chair)
2:10	General Best Practices Introduction Update on Recent Postings	Dr. Paul Hunter (ACIP, WG Chair) Dr. Andrew Kroger (CDC/NCIRD)
2:20	Vaccine Supply Update	Dr. Jeanne Santoli (CDC/NCIRD)
2:30	Adjourn	

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
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]
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PrEP	Pre-exposure Prophylaxis
SAGE	Strategic Advisory Group of Experts
WG	Work Group
WHO	World Health Organization
VE	Vaccine Effectiveness

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACCV	Advisory Commission on Childhood Vaccines
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ACS	American Cancer Society
AE	Adverse Event
AECI	Adverse Events of Clinical Interest
AESI	Adverse Events of Special Interest
AFM	Acute Flaccid Myelitis
AFRO	Africa Regional Office
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
aIV	Adjuvanted Inactivated Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AMGA	American Medical Group Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APHL	Association of Public Health Laboratories
AS	American Samoa
ASH	Assistant Secretary for Health
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
BLA	Biologics License Application
BSC, DDID	Board of Scientific Counselors, Deputy Director for Infectious Diseases
BSL-4	Biosafety Level 4
CBER	Center for Biologics Evaluation and Research
cclIV	Cell Culture-Based Inactivated Influenza Vaccine
CDC	Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CHMP	Committee for Medicinal Products for Human Use
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment
CLD	Chronic Liver Disease
CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COPA	Communities Organized to Prevent Arboviruses
COVID-19	Coronavirus Disease 2019
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists

cVDPV2	Circulating Vaccine-Derived Poliovirus
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
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMP	Essential Medicine Department
EMR	Electronic Medical Record
EMRO	Eastern Mediterranean Region Office
EQ-5D-5L	EuroQOL-5 Dimensions-5 Levels
EQ-VAS	EuroQol-Visual Analogue Scale
ETC	Ebola Treatment Center
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
EURO	Europe Regional Office
EV	Enteroviruses
EVD	Ebola Virus Disease
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
FY	Fiscal Year
GAVI	Global Alliance for Vaccines and Immunisation; The Vaccine Alliance
GBS	Guillain-Barré Syndrome
GCC	Global Certification Commission
GCC	(Tom Harkin) Global Communications Center
GI	Gastrointestinal
GID	Global Immunization Division
GISRS	Global Influenza Surveillance and Response System
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GP	Glycoprotein
GPEI	Global Polio Eradication Initiative
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immune Globulin
HCoV	Human Coronaviruses

HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HDCV	Human Diploid Cell Vaccine
HD-IIV	High-Dose Inactivated Influenza Vaccine
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRQOL	Health-Related Quality of Life
HRSA	Health Resources and Services Administration
ICD	International Classification of Diseases
IDCRP	Infectious Disease Clinical Research Program
ICU	Intensive Care Unit
ID	Intradermal
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHD	Immunization Healthcare Division (DoD)
IHR	International Health Regulation
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IPV	Inactivated Polio Vaccine
ISD	Immunization Services Division
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
IVIG	Intravenous Immunoglobulin
KPSC	Kaiser Permanent Southern California
LAIV	Live Attenuated Influenza Vaccine
LRN	Laboratory Response Network
MASO	Management Analysis and Services Office
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHS	Military Health System
MMR	Measles, Mumps, and Rubella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
mOPV	Monovalent OPV
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
NAIS	National Adult and Influenza Immunization Summit

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
<i>NEJM</i>	<i>New England Journal of Medicine</i>
NFID	National Foundation for Infectious Diseases
NGO	Non-Governmental Organizations
NHANES	National Health and Nutrition Examination Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Immunization Conference
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIP	National Immunization Program
NIS	National Inpatient Sample
NIS	National Immunization Survey
NITAG	National Immunization Technical Advisory Group
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NOCD	New Onset of Chronic Diseases
NPAIHB	Northwest Portland Area Indian Health Board
NPI	Non-Pharmaceutical Intervention
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
OPV	Oral Polio Vaccine
OSHA	Occupational Safety and Health Administration
PAHO	Pan American Health Organization
PAIVED	Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD
PALM	Pamoja Tulinde Maisha
PCECV	Purified Chick Embryo Cell Vaccine
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PFU	Plaque-Forming Units

PHAC	Public Health Agency Canada
PHEIC	Public Health Emergency of International Concern
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PPV	Positive Predictive Value
PrEP	Pre-Exposure Prophylaxis
PREPARE	Pre-Exposure Prophylaxis in Individuals at Potential Occupational Risk for Ebola Virus Exposure
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)
PREVAIL	Partnership for Research on Ebola Virus in Liberia
PUI	Persons Under Investigation
PVRV	Purified Vero Rabies Vaccine
QIV	Quadrivalent Influenza Vaccine
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
RFFIT	Rapid Fluorescent Focus Inhibition Test
RIG	Rabies Immune Globulin
RIV	Recombinant Influenza Vaccine
RN	Registered Nurse
RNA	Ribonucleic Acid
ROA	Route of Administration
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
rVSV	Recombinant Vesicular Stomatitis Virus
RVV	Rabies Virus Variants
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SCR	Seroconversion Rate
SD-IIV3	Standard Dose Inactivated Influenza Vaccine
SEARO	South East Asia Regional Office
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SNS	Strategic National Stockpile
STI	Sexually Transmitted Infections
STRIVE	Sierra Leone Trial to Introduce a Vaccine Against Ebola
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TEC	Tribal Epidemiology Center

TCH Forecaster	Texas Children's Hospital Immunization Forecasting Software
TIV	Trivalent Influenza Vaccine
tOPV	Trivalent Oral Polio Vaccine
UK	United Kingdom
UNC	University of North Caroline
US	United States
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
US Flu VE	US Influenza Vaccine Effectiveness Network
USG	US Government
USPHS	US Public Health Service
USU	Uniformed Services University
UTD	Up-To-Date
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VAPP	Vaccine-Associated Paralytic Polio
VCD	Virologically Confirmed Dengue
VDPV	Vaccine-Derived Poliovirus
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VRC	Vaccine Research Center (NIAID)
VSD	Vaccine Safety Datalink
VSV	Vesicular Stomatitis Virus
WG	Work Group
WHO	World Health Organization
WPRO	Western Pacific Regional Office
WPV	Wild Polio Virus
YF	Yellow Fever
ZEBOV	Zaire Ebolavirus

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 February 2020 Advisory Committee on Immunization Practices (ACIP) and welcomed those present.

Dr. Cohn welcomed everyone to the February 2020 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 in the lobby 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 members of the public 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 4 weeks after the meeting. The live webcast videos 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 October 2019 meeting were scheduled to be posted shortly.

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, June 24-25, 2020. Registration for all meeting attendees is required and will open on the ACIP website when the *Federal Register* notice is published. Registration is not required for webcast viewing.

Dr. Cohn made the following announcements with regard to liaison organizations, member substitutions, and guest attendees for this meeting:

Liaison Organizations

- ❑ The International Society for Travel Medicine (ISTM) joins ACIP as a new liaison member. The ISTM Liaison Representative is Dr. Elizabeth Barnett, Professor of Pediatrics, Boston University School of Medicine.
- ❑ This will be the last meeting for Dr. David Weber, Liaison Representative for the Society for Healthcare Epidemiology of America (SHEA). Dr. Weber has served in this role for many years, and ACIP is very appreciative of his support throughout that time.
- ❑ This also will be the last meeting for Dr. Susan Even, the Liaison Representative for the American College Health Association (ACHA). She too has served in this role for many years, and ACIP is very grateful for her support throughout that time.

Ex Officio Representatives

- ❑ Kara M Elam, PhD, MPH, MS represents the Office of Infectious Disease Policy (OIDP).
- ❑ Barbara Mulach, PhD represents the National Institutes of Health (NIH).

Guest Attendees

- ❑ During the two days prior to this ACIP meeting, CDC was honored to host the Global National Immunization Technical Advisory Group (NITAG) Network meeting. ACIP is the NITAG for the United States (US). Representatives attended from over 50 countries to discuss how to build NITAGs across the world, and also were in attendance during this ACIP meeting.
- ❑ Students from The Walker School also attend ACIP each year, and were watching the ACIP meeting from a distance learning center within CDC.
- ❑ Students from the University of Alabama School of Public Health attended the second day of the ACIP meeting.
- ❑ In attendance representing the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) were Dr. Alejandro Cravioto, current SAGE Chair, and Dr. John Abrams, former ACIP Chair and former SAGE Chair.

Dr. Cohn emphasized 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 has 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. She announced that for this meeting, one oral public comment period would be held during the first afternoon at approximately 1:15 PM, after lunch, prior to the one anticipated vote of the day on Ebola vaccines.

To create a fair and 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. Written public comments may be made via [regulations.gov](https://www.regulations.gov) using the docket number ID CDC-2020-0002. Information on the written public comment process, including information about how to make a public comment, can be found on the [ACIP website](https://www.acip.hhs.gov). [Regulations.gov](https://www.regulations.gov) closes approximately 24 hours following the

[end of the ACIP meeting. Dr. Cohn pointed out that public comments could be made during and after the meeting as well.](#)

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. Cohn indicated that detailed instructions for submission of names of potential candidates to serve as ACIP members is now available on the ACIP website. Applications for ACIP membership are due no later than July 1, 2020 for the 4-year term beginning July 1, 2021. She invited everyone to encourage those they know to submit nominations for ACIP membership, and emphasized that they always appreciate both the number of applicants and the extraordinary level of expertise in the applicant pool.

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 February 2020 ACIP meeting.

Ebola Vaccine

Introduction

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

Dr. Frey reminded everyone that she introduced the new Ebola Vaccine WG during the October 2019 meeting and that the Ebola Vaccine WG's terms of reference are to: 1) review the available data on the rVSVΔG-ZEBOV-GP vaccine, which is a recombinant vesicular stomatitis virus (VSV) with a substituted envelope glycoprotein of the *Zaire ebolavirus* Kikwit 1995 strain, 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*). There have been several key events since October 2019.

The rVSVΔG-ZEBOV-GP vaccine (ERVEBO[®], Merck) was granted EU-wide conditional marketing authorization in November 2019. This vaccine is indicated for immunization of individuals 18 years of age and older to protect against Ebola virus disease (EVD) caused by Ebola virus species *Zaire ebolavirus*. The US Food and Drug Administration (FDA) approved rVSVΔG-ZEBOV-GP vaccine (ERVEBO[®], Merck) for individuals 18 years of age or older for the

prevention of EVD on December 19, 2019. On February 12, 2020, the World Health Organization (WHO) Emergency Committee unanimously agreed that the ongoing EVD outbreak in the Eastern Democratic Republic of Congo (DRC) still constitutes a Public Health Emergency of International Concern (PHEIC).

In terms of the WG's activities and discussions since October 2019, the WG identified 3 US populations at highest risk for potential occupational exposure to Ebola virus for whom potential policy options are most urgent, including the following:

- Individuals responding to an outbreak of EVD due to Ebola virus
- Individuals who work as laboratorians and support staff at Biosafety Level-4 (BSL-4) facilities that handle replication competent Ebola virus
- Healthcare personnel (HCP) at federally-designated Ebola Treatment Centers (ETCs) involved in the care and transport of confirmed EVD patients

Additional US populations with potential risk for occupational exposure include:

- Healthcare Personnel (HCP) at state or jurisdictionally-designated Ebola Treatment Centers
- HCP at Ebola Assessment Hospitals
- HCP at frontline facilities

It is important to note that HPC includes many people of various job descriptions. The formal definition utilized by the WG is adapted from the ACIP-approved definitions in the CDC [Infection Control in Healthcare Personnel](#) guidelines and is as follows:

Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).

Since October 2019, the WG has continued discussions on recommendations for additional populations at potential occupational risk. They developed a protocol for systematic review of vaccine data and selected critical outcomes to be considered. A systematic review was conducted of the vaccine literature for a GRADE (Grading of Recommendation Assessment, Development and Evaluation) analysis and for evidence to recommend (EtR). The WG has engaged in multiple discussions on proposed policy options.

This session included presentations focused on a review of Ebola virus disease and rVSVΔG-ZEBOV-GP vaccine, GRADE, EtR, and a summary of WG considerations and proposed policy options.

Ebola Virus Disease

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

Dr. Choi reviewed background material to set the stage for the subsequent sessions, including background on EVD, rVSVΔG-ZEBOV-GP vaccine, and the parameters for WG discussions over the past several months.

In terms of background, EVD in humans is a deadly disease caused by infection with one of 4 viruses within the genus *Ebolavirus* and family *Filoviridae* 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 remainder of this session focused on the Ebola virus species *Zaire ebolavirus*. This virus is responsible for the majority of reported EVD outbreaks, including the 2 largest outbreaks in history. The 2014-2016 West Africa outbreak resulted in a little over 28,000 cases and 11,000 deaths. The current Eastern DRC outbreak has infected over 31,000 persons and resulted in over 12,000 deaths in total. Untreated, mortality rates can be as high as 70% to 90%. Currently, there is no FDA-approved treatment.

The animal reservoir for Ebola virus is unknown. However, based on studies in similar viruses, the reservoir is believed to be fruit bats. A study was conducted in the early 2000s by Leroy and colleagues in which the investigators trapped bats, birds, and rodents in Gabon and the DRC in and around areas where there were known Ebola outbreaks in humans and/or animals. They were able to identify three species of bats in which Ebola virus was detected by both serology and polymerase chain reaction (PCR): *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*. It is important to note that none of these species exist in the US [E M Leroy et al., Fruit bats as reservoirs of Ebola virus *Nature* 438, 575-576 (December 2005)].

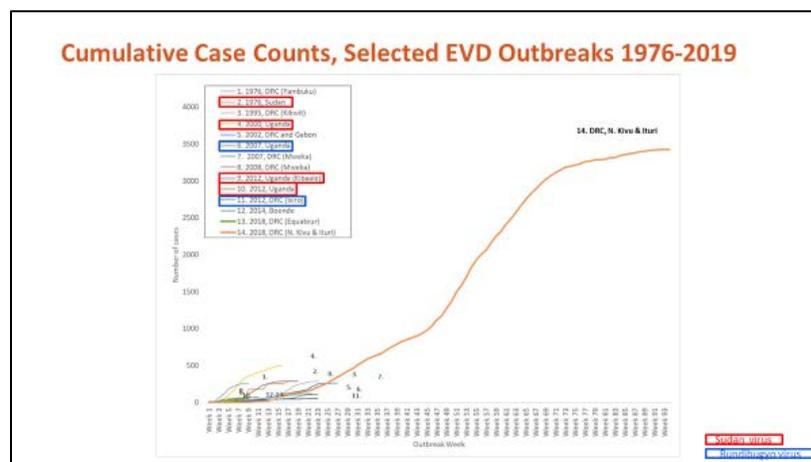
The signs and symptoms of EVD include: Abdominal Pain, Bleeding (epistaxis, injection sites), Diarrhea, Fatigue, Fever, Headache, Muscle Pain/Joint Pain, Rash, and/or Vomiting. Although bleeding can be seen in EVD, it is not universally present and is seen in about 40% of cases. When bleeding is observed, it usually is a late sign and pre-terminal. The signs and symptoms are non-specific and can be seen in many other diseases that are endemic in Africa. In an infected person, Ebola virus can be found in all body fluids, including: Amniotic Fluid, Blood, Breast Milk, Feces/Vomit, Saliva, Semen, Sweat, Tears, Urine, and Vaginal Secretions. Person-to-person transmission occurs through contact with broken or non-intact skin, and/or mucous membranes with the body fluids of a person that is sick or has died of EVD.

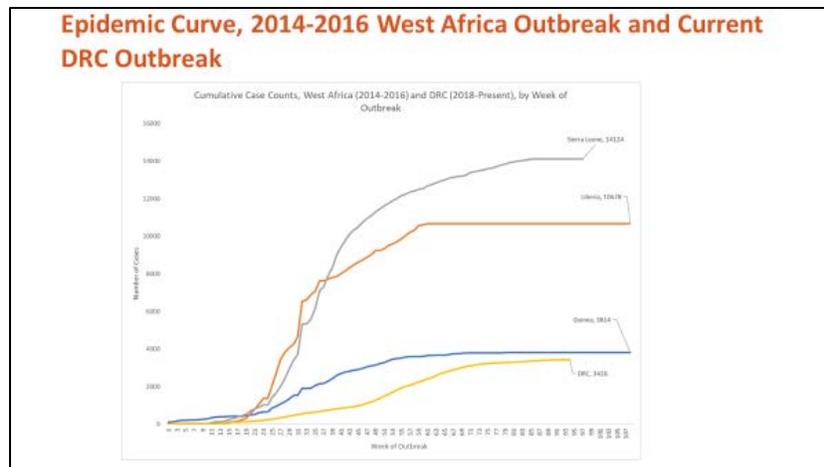
Those who survive the acute illness often suffer some sequelae. The true incidence of sequelae amongst EVD survivors is unknown primarily because these outbreaks occur in countries where there is limited access to healthcare or specialized services. Some studies have been conducted, particularly following West Africa. The most commonly reported symptoms were found to be arthralgia, uveitis, myalgia, abdominal pain, and fatigue^{1,2}. The uveitis can be quite

severe and lead to cataract formation and blindness. Following West Africa, a study was conducted that found that within one year of discharge, Ebola survivors had 5-fold greater mortality than the general population³. Looking into this further using verbal autopsy, renal disease was seen that may have been precipitated by the acute infection. It is also known that Ebola virus can persist in immune-privileged sites such as the testes, eyes, brain, and placenta. In some, this has resulted in continued disease transmission and disease recrudescence. For example, there was a man in Guinea who was 15 months recovered from his illness who then transmitted the virus sexually to his partners. This sparked a new cluster of disease that actually affected individuals in Guinea and Liberia. The incidence of disease recrudescence that has been described in the literature. A British nurse who was infected while working in Sierra Leone, fell ill while in the United Kingdom (UK), was treated successfully, and returned to the hospital about 9 months after her recovery with meningeal encephalitis, and Ebola virus was detected in the nurse's cerebrospinal fluid (CSF) and eventually the blood as well [1Rowe et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of Congo; 2Prevail III Study Group. A longitudinal study of Ebola sequelae in Liberia; 3Keita et al. Subsequent mortality in survivors of Ebola virus disease in Guinea: a nationwide retrospective cohort study Lancet Infect Dis. 2019].

On August 1, 2018, an EVD outbreak was declared in Eastern DRC. When the virus responsible for the outbreak was sequenced, it was found to be Ebola virus (species *Zaire ebolavirus*). The current outbreak is the 10th outbreak in the DRC and is the largest outbreak to have occurred there. In July 2019, the outbreak was declared a PHEIC because of cross-border travel-related cases that were detected in Uganda and cases detected in Goma, a very large city in the DRC. The PHEIC declaration was reaffirmed in February 2020. As of February 18, 2020, cases had been reported in 29 health zones and 3 provinces in the DRC. Case counts were at a little over 3000 cases and 2000 deaths.

In terms of how the current outbreak compares to other DRC outbreaks in the area from 1976-2019, the current DRC outbreak has been by far the largest and has lasted the longest. With the West Africa outbreak, particularly in Sierra Leone and Liberia, there was a period of time during which there was a very rapid increase in the number of cases in which the epidemic curve is almost a straight line. The current outbreak in the DRC has not followed that pattern and seems somewhat more gradual:





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, 9 were infected in West Africa and 2 (18%) died. There was one imported case of EVD that resulted in secondary transmission in 2014 in Dallas, Texas. In addition to these 11 EVD patients, additional individuals have been repatriated to the US following high-risk exposures to Ebola virus, but none of these individuals tested positive. This repatriation occurred during the 2014-2016 West Africa outbreak and the current DRC outbreak.

There is a live-attenuated vaccine recombinant (rVSV)-based Ebola virus vaccine (rVSVΔG-ZEBOV-GP). It is important to note that the vaccine cannot cause Ebola virus infection. This vaccine initially was developed by Public Health Agency Canada (PHAC) and NewLink Genetics. Merck currently holds the intellectual rights. The vaccine protects only against Ebola virus (species *Zaire ebolavirus*). In December 2019, the FDA licensed the vaccine for individuals 18 years of age or older for the prevention of EVD.

In terms of the vaccine construct, the glycoprotein (GP) was removed from the VSV and was replaced with the GP of the *Zaire ebolavirus* (Kikwit). The vaccine contains this recombinant virus. Once a person receives the vaccine, the virus will replicate and the person will develop antibodies toward the GP. The vaccine is administered as a one-time 1.0 mL dose by the intramuscular (IM) route. There are specific storage requirements for this vaccine. It must be stored between -80°C and -60°C . Once thawed, it can be stored at 2°C to 8°C for up to 2 weeks.

Animal studies were conducted on this vaccine to assess effectiveness in preventing Ebola virus. Cynomolgus macaques were vaccinated with various doses of the vaccine and then challenged with live virus 42 days later and examined survival. At 2×10^7 and up, protection 100%. At 3×10^6 , protection was 88%. Following the animal studies, multiple clinical studies were conducted throughout the world in the US, Canada, Africa, and Europe.

In regard to safety, there is generally a mild to moderate transient reactogenicity is commonly reported within 24-48 hours of vaccination that typically resolves within 7 days. Some of the common signs and symptoms during this period include injection site pain, swelling, erythema, fever/subjective fever, muscle aches, malaise, and headache. Arthralgia and arthritis reported in some vaccinees. Vaccine-related serious adverse events (SAEs) are rare.

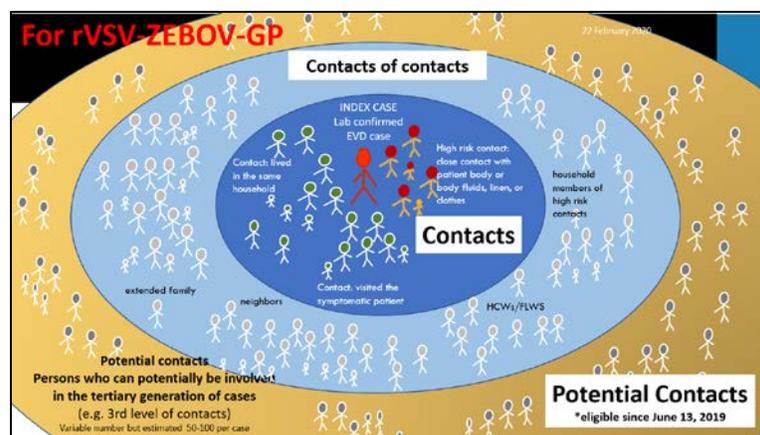
The rVSV has been detected in bodily fluids. Virus dissemination and replication can occur and persist for up to 2-3 weeks after vaccination. It has been detected in blood, which is expected because it is a live virus that replicates. It has been detected by PCR in blood as long as 14 days after vaccination. It also has been detected in urine for up to 7 days, saliva up to 14 days, synovial fluid up to 17 days, and skin vesicles up to 17 days post-vaccination.

With regard to immunogenicity, there is no known immune correlate for protection. A measure of the immune response that confers protection against EVD is unknown. It is thought that the protective effect of the vaccine conferred by vaccination is a combination of both innate and adaptive immune response activation. As measured by enzyme-linked immunosorbent assay (ELISA), the GP-specific IgG antibodies begin to rise at around Day 14 and can persist through 24 months post-vaccination.

This vaccine has been used in the outbreak setting in the *Ça Suffit* trial. The results of this trial were reported in 2 parts. It was a Phase 3, cluster-randomized, open-label ring vaccination trial. The trial took place in Guinea at a time when the 2014-2016 West Africa EVD outbreak was waning. A ring vaccination strategy was used to administer the vaccine, in part to generate robust data on vaccine efficacy (VE) in the setting of a waning outbreak. In this study, a cluster was defined around a confirmed case of EVD. The primary outcome was incidence of EVD with onset 10 days or more after randomization. This 10-day period was to account for the incubation period of EVD and the unknown time for the vaccine to develop protective immunity.

In terms of the interim results, clusters were randomized to immediate vaccination or delayed vaccination at 21 days after randomization. In this study, VE was found to be 100% (95%CI: 74.7-100, $p=0.0036$). Basically, the investigators identified the index case (confirmed case) and then defined contacts and contacts of contacts. This became the clusters, which were then randomized to immediate or delayed vaccination. In July 2015, randomization was discontinued at the recommendation of the Data and Safety Monitoring Board due to the interim findings of 100% VE. All subsequent clusters were offered immediate vaccination. The final results were reported on VE for randomized and non-randomized clusters, and again VE was reported to be 100% (95%CI: 68.9-100, $p=0.0045$) [Courtesy of Merck].

In the DRC, ring vaccination was started 1 week after the outbreak was declared and has evolved over time. The vaccine has now been administered to over 200,000 people using this strategy. The vaccine appears to be effective and SAEs have been rare. This graphic depicts the ring vaccination strategy being used in DRC:



Courtesy of Dr. Henao-Restrepo

In terms of the parameters of the WG discussions over the last several months, consideration was given to the fact that the suspected virus reservoir does not exist in the US, most of the individuals (9/11) treated for EVD in the US were responding to a foreign EVD outbreak, there is an ongoing EVD outbreak in Eastern DRC that is considered a PHEIC, and there is no EVD outbreak in the US. As such, the WG's deliberations focused on pre-exposure vaccination in US populations at immediate occupational risk.

As mentioned earlier, 3 US populations were identified as being at highest risk for potential occupational exposure to Ebola virus (species *Zaire ebolavirus*) for whom potential policy options are most urgent: 1) individuals responding to an outbreak of EVD due to Ebola virus; 2) individuals who work as laboratorians and support staff at Biosafety Level-4 (BSL-4) facilities that handle replication competent Ebola virus; and 3) HCP at a federally-designated ETCs involved in the care and transport of confirmed EVD patients. Additional US populations with potential risk for occupational exposure include: 1) HCP at state or jurisdictionally-designated ETCs; 2) HCP at Ebola Assessment Hospitals; and 3) HCP at frontline facilities. Discussions and recommendations of these groups are still ongoing.

Looking at the 3 additional populations more in-depth, the number of individual organizations responding to an outbreak will vary by size and location of the outbreak. There were over 4000 US government (USG) deployers to the 2014-2016 West Africa EVD outbreak, including the domestic EVD cases. US responders to the current eastern DRC outbreak include over 200 non-governmental organization (NGO) personnel and over 300 governmental personnel from CDC, NIH, and the United States Agency for International Development (USAID).

There are 10 BSL-4 laboratories in the US, with an estimated 350 to 400 laboratory and support staff, of which 8 currently handle replication-competent Ebola virus. There are 11 federally-designated Ebola Treatment Centers in the US that are specialized high-level isolation units equipped with infrastructure, laboratory capabilities, staff to care for patients with highly hazardous communicable diseases. These include the regional Special Pathogen Centers and NIH. These facilities are estimated to have approximately 500 HCP and support staff.

Discussion Points

Dr. Bernstein wondered about the clinical significance of the live attenuated vaccine not being able to cause disease, but being detected in certain bodily fluids up to 2 to 3 weeks.

Dr. Choi responded that the viremia is expected and most people clear it within a week or so. One study did find it as far as 14 days post-vaccination. It has been detected as shedding in saliva and urine, but no attempts were made to isolate it. When something is detected by PCR, it just means that it was possible to detect the nucleic acids and does not necessarily mean live virus. Some individuals developed a vesicular rash after vaccination, from which virus was isolated. There certainly is a concern about what that translates to in terms of transmission potential, particularly with rash that is shedding. This was one of the outcomes of interest in the GRADE analysis. After people are vaccinated in the Pre-Exposure Prophylaxis in Individuals at Potential Occupational Risk for Ebola Virus Exposure (PREPARE) clinical trial that is offering vaccination, precautions are given in terms of contact and what to do if a vesicular rash develops.

Dr. Hunter requested confirmation that Dr. Choi was talking about transmission of viral stomatitis, not of Ebola. He wondered what the worst clinical sequelae would be assuming that the viral strain would cause viral stomatitis if it were to transmit.

Dr. Choi clarified that it would be recombinant vaccine virus, not Ebola. VSV is found primarily in livestock. In situations where there have been outbreaks of VSV in livestock, there has been transmission into humans who handle livestock. There also has been transmission to humans because this virus backbone is a very popular one for other vaccines as well. There have been transmissions to laboratory personnel by accidental exposures. In humans, infection with VSV can be asymptomatic. If it becomes symptomatic, oftentimes it results in an influenza-like illness. The vesicular type of rash and oral ulcer has been observed in humans. Typically, arthritis and arthralgia have been seen with this virus but has not been seen in humans with VSV. In animals, it causes vesicular lesions in the oral mucosa and ulcers. Arthritis or arthralgia have not been seen in that population.

Regarding the definition of HCP and not specific to Ebola, Dr. Lee noticed that physician assistants (PA) and nurse practitioners (NP) were not included in the updated definition. She also noted that based on Slide 27 of Dr. Choi's presentation, it appeared that the ring vaccination strategy was now evolving in the DRC. She wondered if one way to think about the categories of people who might be at highest risk in terms of pre-exposure prophylaxis (PrEP) as that ring strategy continues to evolve would be more generalized to Ring 1 as the focus because additional subgroups might be identified who could benefit from vaccination.

Dr. Choi said she thought they probably try to make a distinction between what CDC is trying to make recommendations for and what is occurring in the DRC. CDC is trying to make recommendations for PrEP for people who have not been exposed in an attempt to protect them from a future exposure. In the DRC, this is different. Some pre-exposure vaccination is being done among HCP and frontline workers. For the most part, ring vaccination is done post-exposure. The ring is defined around a confirmed case where an outbreak occurring. Given that there is no outbreak or reservoir in the US, if there is an infection of EVD it is known to have come from either a foreign outbreak that was imported to the US or a BSL-4 laboratorian who was exposed while working with Ebola. They talk about the Ça Suffit trial and included it in the GRADE analysis because it showed efficacy, but many other clinical studies were conducted on this vaccine that attempted to show efficacy. By the time the studies were done, the outbreak was over and there were no other cases. While the Ça Suffit trial showed efficacy, it was in the setting of an outbreak and a post-exposure type of picture.

Dr. Lee clarified that she understood the difference between the pre- and post-exposure, but thought the group ACIP was interested in would be those with high-risk contacts with patients or their body fluids. She just wanted to harmonize the way they were thinking about the three groups to ensure that they are not exclusive of other people who potentially might be exposed.

Dr. Frey expressed appreciation for Dr. Lee's comments and emphasized that the WG would be assessing the groups in more detail moving forward. There is a PREPARE trial in which those working on the frontlines or are going to be deployed out can participate.

Thinking about the untreated mortality rate of 70% to 90% and the deaths of 2 of 11 subjects in the US, Dr. Bernstein inquired as to whether efforts for support have made a difference in Africa.

Dr. Choi indicated that mortality is 79% with no supportive treatment in Africa. With early supportive treatment alone, mortality is reduced to as low as 40%. In the current outbreak, the Pamoja Tulinde Maisha (PALM) trial was conducted in which experimental therapies were tested. These included ZMapp and remdesivir used in West Africa and 2 new monoclonal

antibodies, MAb114 and REGN-EB3. In this randomized clinical control trial (RCT), the control was ZMapp. This study found that there was a reduction in mortality in particular with the 2 monoclonal antibodies. The therapeutics are continuing to be given in-country, but this is limited to the 2 monoclonal antibodies.

GRADE: rVSVΔG-ZEBOV-GP Ebola Vaccine

Caitlin Cossaboom, DVM, PhD, MPH
LT US Public Health Service
Viral Special Pathogens Branch
Division of High-Consequence Pathogens and Pathology

Dr. Cossaboom presented the GRADE analysis of the newly licensed Ebola vaccine, which she referred to as rVSV moving forward in the presentation. The policy question for consideration is, “Should pre-exposure vaccination with the rVSV Ebola vaccine be recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older in the US population who are at potential occupational risk to exposure to Ebola virus (species *Zaire ebolavirus*) for prevention of Ebola virus infection?”

She then reviewed the population, intervention, comparison, and outcomes of interest (PICO) determined by the ACIP Ebola Vaccine WG. The population of interest is healthy, non-pregnant, non-lactating adults 18 years of age or older in the US population who are at risk of occupational exposure to Ebola virus within the following three subgroups: 1) Individuals responding to an outbreak of EVD due to Ebola virus; 2) healthcare personnel involved in the care and transport of confirmed EVD patients at federally-designated ETCs in the US; and 3) laboratorians and support staff working in BSL-4 laboratories that handle Ebola virus. The intervention of interest is pre-exposure intramuscular immunization with a single licensed dose of the rVSV Ebola vaccine, while the comparison was no vaccine. The outcomes the WG considered critical and that were subjected to analysis were: development of Ebola-related symptomatic illness; Ebola-related mortality which was not analyzed as there was no available data for this outcome; vaccine-related joint pain or swelling; vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within 2 months of vaccination; transmissibility of rVSV vaccine virus surrogate assessed with viral dissemination/shedding of the rVSV vaccine virus; and SAEs related to vaccination. There were two additional outcomes that the WG considered important, but not critical, that included the incidence and severity of oral or skin lesions and the interaction or cross-reactivity with monoclonal antibody-based therapeutics or other VSV-backed vaccines. However, data for these outcomes have not been analyzed to-date and were not included in this presentation.

Of the critical outcome measures that were included in the evidence profile for this presentation, the following five outcomes were included for meta-analyses: the benefit outcome of development of Ebola-related symptomatic illness; and the safety outcomes of incidence and severity of arthralgia, incidence of arthritis, and vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within 2 months of vaccination. The four remaining outcomes were included for descriptive analyses only: detection of rVSV vaccine virus in blood or plasma (viremia); detection of rVSV vaccine virus in saliva (viral shedding); detection of rVSV vaccine virus in urine (viral shedding); and SAEs related to vaccination.

On December 16, 2019, a literature search was executed in multiple biomedical and interdisciplinary bibliographic databases using a broad and rigorous search strategy that incorporated terms related to vaccination against Ebola virus using the rVSV Ebola vaccine, without date or language restrictions. Results were compiled in an EndNote library and duplicate records were removed. This search was updated on January 31, 2020 to screen recent records that were not captured in the original search. An attempt also was made to obtain unpublished or other relevant data not included in the search results from subject matter experts (SMEs) and the manufacturer and received one additional record for inclusion in the analysis.

Records were included for analysis if they presented data on the rVSV Ebola vaccine and involved immunocompetent adults 18 years of age or older regardless of pregnancy status, included data for the intervention of interest and data relevant to the outcome measures being assessed, and reported primary data from comparative or single-arm studies, RCTs, prospective or retrospective cohort, case-control, or cross-sectional studies. In total, 1818 records were identified through the database searches and the one unpublished record mentioned was identified through other sources. A total of 1742 of these records were excluded during title and abstract screening, leaving 77 full-text articles that were assessed for eligibility through full-text review. Of these, 59 full-text articles were excluded for these reasons: 41 were not relevant to the outcomes, 8 used the wrong study design, 7 were abstracts later published in full, 2 included the wrong intervention, and 1 had the wrong population. In total, 18 articles that presented data from 11 studies were included in qualitative synthesis while 9 articles that presented data from 8 studies were included in quantitative synthesis or meta-analysis. The references for the articles utilized in the analyses are shown here, with those included in the meta-analyses shown in black and those included in the descriptive analyses only shown in blue:

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Included in meta-analyses (RCT or NRS with comparator); Not included in meta-analyses (NRS, without comparator)

The GRADE approach for assessing the type or quality of evidence involves consideration of several criteria. Assessing the type or certainty level of the body of evidence for each outcome begins with the study design. RCTs are initially classified as Evidence Type 1 or high certainty and observational studies as Evidence Type 3 or low certainty. Following the identification of the initial evidence type, the body of evidence for each outcome is assessed and downgraded if there is uncertainty about any of the five following criteria: risk of bias, inconsistency which considers statistical heterogeneity and I^2 or the variation across studies due to heterogeneity greater than chance, indirectness or the generalizability of the body of evidence to the original PICO components, imprecision which considers the fragility of the relative and absolute effect measures as they relate to the 95% confidence intervals and optimal information size, and publication bias. The body of evidence from observational studies may be rated up due to dose-response gradient, large or very large magnitude of effect, or opposing residual confounding, considered under “other considerations.” After assessing on the described criteria, the body of evidence will be assigned an overall evidence type or certainty level as defined in the following table:

Type 1 (high certainty):	We are very confident that the true effect lies close to that of the estimate of the effect.
Type 2 (moderate certainty):	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Type 3 (low certainty):	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Type 4 (very low certainty):	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

As a reminder, these are not a measure of how well the individual studies were conducted, but rather how much confidence there is in the estimates of effect from the body of evidence across each outcome. For the purposes of the evidence assessment, RCT refers to a trial which randomizes participants to an active intervention or a placebo or unvaccinated comparator arm. Observational studies refer to one-arm studies, studies for whom participants were not randomized, or studies that did not provide disaggregated data to allow for the comparison between the randomized arms. Evidence also was considered observational if only data from the vaccinated study arms were included in analysis for a given outcome.

For Outcome 1 (development of Ebola-related symptomatic illness), there was one published study with an unvaccinated comparator that was included for the body of evidence for this outcome by Henao-Restrepo 2017. This is publication associated with the Ça Suffit Trial in Guinea. This was a 2-part Phase 3 cluster-randomized open-label ring vaccination trial. The initial study involved contacts and contacts of contacts of confirmed Ebola virus disease or EVD cases that were randomized to either immediate or delayed vaccination. Delayed vaccination was defined as vaccination that occurred 21 days after randomization. A follow-up study included immediate vaccination following cessation of the randomized trial. The primary outcome was the incidence of EVD with onset of 10 days or more following randomization. The 10 days accounts for the average incubation period of Ebola and unknown time for the vaccine to induce protective immunity.

Walking through the table that presents the body of evidence for the outcome of development of Ebola related symptomatic illness from the one published study Henao-Restrepo 2017, Dr. Cossaboom focused on the development of EVD 10 days or longer after randomization (or for non-randomized participants, 10 days or longer after inclusion in the ring) because as explained earlier, these 10 days account for the incubation period and unknown duration to immunity. Out of 3775 participants within 70 clusters who received immediate vaccination between randomized and non-randomized, 0 participants developed EVD 10 days or longer after randomization. In contrast, of 4507 participants within 104 clusters who were delayed or never received the vaccine, 23 participants within 11 clusters developed EVD 10 days or longer after randomization. Focusing on only the participants within the randomized clusters, out of 2108 participants within 51 clusters who received immediate vaccination, 0 developed EVD greater than 10 days after randomization. In contrast, of 3075 participants within 47 clusters who were randomized to delayed vaccination, 16 participants within 7 clusters developed EVD greater than 10 days after randomization. These randomized data equate to a calculated vaccine efficacy of 100% (95% confidence interval 68.9 – 100).

Given that this was a cluster RCT in which the units of randomization were clusters, Dr. Cossaboom presented randomized cluster-level data. Using the randomized cluster level data presented on the previous slide (Slide 17) it equates to a risk ratio of 0.06. Because the population in this study consists of contacts and contacts of contacts of EVD cases and used a ring vaccination strategy that may include post-exposure vaccination, this was downgraded one level for indirectness to the US population and the intervention of interest, which is pre-exposure vaccination. For this cluster-level data, there were few events reported and the data do not meet the optimal information size and suggest fragility of the estimate, and the confidence interval crosses 1 and contains the potential for desirable as well as undesirable effects, so it was downgraded one level for imprecision. To provide some context, there were few events of confirmed Ebola reported even among the unvaccinated arm because this study was conducted at a time when the 2014-2015 West Africa outbreak was waning in Guinea. Taking into account this assessment, the overall assessment of this body of evidence at the randomized cluster level to address the outcome of development of Ebola-related symptomatic illness is Type 3 or low certainty evidence.

From the same study, Dr. Cossaboom presented participant level data from the randomized clusters that support there is a benefit of vaccination among those who are vaccinated, which was considered observational because the units of randomization within the study were clusters. Because a very precise decrease was seen in the non-randomized group, this was not rated down for imprecision at the participant level. This was rated down one level for indirectness for the same reason as the cluster-level data; however, the concerns with indirectness do not pose an inflationary effect and, therefore, the evidence could be rated up based on the very large magnitude of effect from the 96% relative risk reduction. Taken together, overall certainty was upgraded two levels to Type 2 or moderate certainty evidence for this participant level data.

Outcome 2 (incidence of arthralgia) was assessed with the incidence of arthralgia or joint pain that was solicited within 0-42 days, with the results of a meta-analysis of 6 studies that solicited arthralgia within 0-42 days presented in a forest plot. It is important to note that across these studies, variable definitions for arthralgia were used, including joint pain with or without joint swelling or effusion, and in some cases a definition was not provided. Additionally, length and time of follow-up varied between studies. An analysis was conducted that stratified by duration of follow-up and it did not have an impact on effect estimates for this analysis; however, there is a concern that pooling these data may under-estimate incidence because of this variability in

follow-up time. Additionally, the data presented are varying across doses or plaque forming units (PFUs) of vaccine. However, after conducting a separate analysis that stratified by dose, there does not seem to be a dose-response or effect on this outcome. Taken together, the calculated risk ratio from these 6 RCTs was 2.55. There were also two non-randomized studies with non-vaccinated comparators that were analyzed separately with a calculated risk ratio of 1.63. Additionally, across 7 studies that did not have a comparison group, 1546 out of 8329 (16%) of vaccinated participants reported arthralgia.

Looking at the body of evidence for the 6 randomized trials, overall, among 1874 vaccinated participants, 316 (16.9%) reported arthralgia compared with 42 out of 891 (4.7%) of non-vaccinated participants. This equates to a relative risk of 2.55 and an absolute risk of 73 more events of arthralgia out of 1000 people. This body of evidence was downgraded one level for a concern for risk of bias because of lack of blinding in participants, healthcare personnel, and outcome assessors in two studies that may have influenced events reported for this outcome. Additionally, there is a concern for underreporting in one study that only solicited arthralgia at one week and one month for the majority of participants, that may have led to underreporting of events. Due to concerns with heterogeneity with an I squared of 70%, this was downgraded one level for inconsistency. Because the 95% confidence interval crosses 1 and includes a potential for possible harms as well as benefits, a downgrade was made one level for imprecision. Overall, this body of evidence was assessed to be Type 4 very low certainty evidence. Looking at the body of evidence for the two observational studies, overall, among 469 vaccinated participants, 75 (16.0%) reported arthralgia compared with 8 out of 99 (8.1%) of non-vaccinated participants. This equates to a relative risk of 1.63 and an absolute risk of 51 more events of arthralgia out of 1000 people. Because there were few events reported suggesting fragility in the estimate, this was downgraded one level for imprecision. Overall, this body of evidence was assessed to be Type 4 or very low certainty evidence.

Outcome 3 (severity of arthralgia) was assessed with the incidence of severe (Grade 3) arthralgia solicited between 0-42 days and defined as significant joint pain or discomfort that prevents daily activity. For background, arthralgia is described on a Grade 1 to 4 scale:

- Grade 1: Mild; No interference with activity
- Grade 2: Moderate; Some interference with activity
- Grade 3: Significant; prevents daily activity
- Grade 4: Potentially life-threatening Medical consultation and/or hospitalization

In terms of the results of a meta-analysis of 4 studies with that reported on incidence of severe arthralgia within 0-42 days, it is important to note that similar to the previous outcome, across these studies, variable definitions for arthralgia were used. Additionally, time of follow-up and dose or PFU of vaccine used varied between studies. However, similar to the previous outcome, these did not have an impact on effect estimates. Taken together, the calculated risk ratio from these 4 RCTs was 6.4. There also were two non-randomized studies with non-vaccinated comparators that were analyzed separately and reported no events of Grade 3 arthralgia among 469 vaccinated and 99 non-vaccinated participants. Additionally, across 5 studies that did not have a comparison group, 7 out of 7209 (0.1%) of vaccinated participants reported Grade 3 arthralgia. There were no reports of Grade 4 arthralgia across the body of evidence.

Walking through the evidence table for assessment of the body of evidence for Outcome 3, looking at the body of evidence for the four randomized trials, overall, among 333 vaccinated participants, 2 (0.6%) reported severe arthralgia compared with 0 out of 264 non-vaccinated participants. This equates to a relative risk of 6.4 and an absolute risk of 0 more events of severe arthralgia out of 1000 people. This body of evidence was downgraded one level for a concern for risk of bias because of lack of blinding in participants, healthcare personnel, and outcome assessors in two studies that may have influenced events reported for this outcome. Because of a concern for fragility in the estimate due to the few number of events reported, this was downgraded one level for imprecision. Overall, this body of evidence was assessed to be Type 3 low certainty evidence. Looking at the body of evidence for the 2 observational studies, overall, no events of Grade 3 arthralgia were reported among 469 vaccinated and 99 non-vaccinated participants. Because there were no events reported among vaccinated and non-vaccinated participants, it suggests fragility in the estimate, this was downgraded one level for imprecision. Overall, this body of evidence was assessed to be Type 4 very low certainty evidence.

Outcome 4 (incidence of arthritis) was assessed with an event of arthritis reported within 5-56 days of follow-up. Based on the forest plot presenting the results of a meta-analysis of 4 studies that solicited arthritis within 5-56 days, it is important to note that each of these studies defined and diagnosed arthritis with considerable variability as follows:

- ❑ Kennedy 2017: Concern for underreporting because low % of female enrolled participants (37%); Kennedy only solicited at week 1 and at month 1
- ❑ Samai 2018: No capability of clinical diagnosis of arthritis, no rheumatology services available in Sierra Leone
- ❑ El Sherif 2017: Did not provide definition for arthritis
- ❑ Huttner 2015: first to encounter arthritis, so thoroughly clinically investigated arthritis (all participants with arthritis referred to rheumatologist, all but 2 participants with arthritis had an u/s done); this study is not included in the RCT analysis because arthritis was reported only in low dose participants and upon request de-aggregated data was unavailable

Additionally, time of follow-up and dose or PFU of vaccine used varied between studies. However, similar to the previous outcome, these did not have an impact on effect estimates. Taken together, the calculated risk ratio from these 4 RCTs was 1.8. There also were 2 non-randomized studies with non-vaccinated comparators that were analyzed separately and had a comparable effect size and lower precision. Additionally, across 2 studies that did not have a comparison group, 2 out of 50 (4%) of vaccinated participants reported arthritis. Additionally, three published studies reported on the detection of vaccine virus in synovial fluid. This data was not included in the evidence tables; however, the WG felt that it was directly applicable to this outcome and supports causality between vaccination and arthritis, so it was presented descriptively. Across this body of evidence, vaccine-virus has been detected by reverse transcriptase polymerase chain reaction (RT-PCR) in 4 out of 7 vaccinated participants who have had synovial fluid tested. Viral isolation was attempted on one synovial fluid specimen and was negative.

Looking at the body of evidence for the four randomized trials for Outcome 4, overall, among 1776 vaccinated participants, 39 (2.2%) reported severe arthralgia compared with 16 out of 868 (2.1%) non-vaccinated participants. This equates to a relative risk of 1.8 and an absolute risk of 23 more events of arthritis out of 1000 people. This body of evidence was downgraded one level for a concern for risk of bias because the studies used variable definitions and methods for diagnosing and reporting arthritis, and for lack of blinding in participants, healthcare personnel, and outcome assessors in two studies that may have influenced events reported for this outcome. Because the 95% confidence interval crosses 1 and includes a potential for possible harms as well as benefits, the evidence was downgraded one level for imprecision. Overall, this body of evidence was assessed to be Type 3 low certainty evidence. Looking at the body of evidence for the two observational studies, overall, 43 out of 520 vaccinated recipients reported arthritis compared to 3 out of 107 unvaccinated participants. This equates to a risk ratio of 2.06 and an absolute risk of 33 more events of arthritis out of 1000 people. Because of concern for fragility in the estimate due to the few number of events reported and that the 95% confidence interval crosses 1 and includes a potential for possible harms as well as benefits, the evidence was downgraded two levels for imprecision. Overall, this body of evidence was assessed to be Type 4 very low certainty evidence.

For Outcome 5 (vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within 2 months of vaccination that was assessed with incidence of pregnancy loss defined as spontaneous abortion and stillbirth), there was one study included in the body of evidence, Legardy-Williams 2020, which was a non-randomized sub-study of the Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE). In this study, 14 out of 31 (45%) pregnant women who received immediate vaccination experienced pregnancy loss compared to 11 out of 33 (33%) of unvaccinated pregnant women. Overall, the rate of pregnancy loss between these groups was not significantly different. Among live births, no external congenital anomalies were detected among either group. Further studies with larger sample sizes would be needed to rule out a meaningful difference in the percentage of pregnancy loss, pregnancy complications, or birth defects. There were 3 additional studies that reported on this outcome that did not have comparison groups. Among these 3 studies, there were 3 adverse pregnancy outcomes out of 20 pregnancies in 19 women; however, no conclusions can be made regarding the relationship between vaccination and adverse pregnancy outcomes based on these data.

In terms of the body of evidence for Outcome 5, in the one observational study with a comparator, 14 out of 31 (45%) pregnant women who received immediate vaccination experienced pregnancy loss compared to 11 out of 33 (33%) of unvaccinated pregnant women. This equates to a relative risk of 1.35 and an absolute risk of 117 more events of pregnancy loss out of 1000 people. This evidence was downgraded one level for indirectness because the study did not differentiate between spontaneous abortions, including induced abortion, and stillbirth and the outcome may not accurately distinguish between events due to the vaccine. Additionally, because of there being a concern for fragility in the estimate due to the few number of events reported and that the 95% confidence interval crosses 1 and includes a potential for possible harms as well as benefits, the evidence was downgraded two levels for imprecision. Overall, this body of evidence was assessed to be Type 4 very low certainty evidence.

For Outcome 6a (the transmissibility of vaccine virus, with a surrogate of vaccine virus dissemination assessed with detection of rVSV in blood/plasma by RT-PCR), data from 8 studies were included for the body of evidence for this outcome. Across these 8 studies, on day 7 post-vaccination, 32 out of 691 (4.6%) vaccinated participants were RT-PCR positive for vaccine virus. On day 14 post-vaccination, 1 out of 501 (0.2%) of vaccinated participants were RT-PCR positive for vaccine virus. Additionally, one study performed viral isolation on selected blood specimens and all were negative.

To summarize the body of evidence for the surrogate outcome of detection of rVSV in blood/plasma by RT-PCR, the longest recorded positive is 14 days post-vaccination. While these 8 studies include both RCT and non-randomized studies, for the purposes of this outcome, only data from the vaccinated arms were included for analysis. As discussed previously, the studies were considered observational for this outcome. This evidence was downgraded one level for risk of bias because of concern for incomplete outcome data as not all who received the vaccine were tested on a given day. It also was downgraded 2 levels for indirectness because the outcome of interest to the WG was transmissibility of the vaccine virus to humans or animals. There are no data that report on transmissibility, so viral dissemination and shedding is assessed as an indirect surrogate. Additionally, RT-PCR positivity is not synonymous with infectivity. Overall, this body of evidence was assessed to be Type 4 or very low certainty evidence.

For Outcome 6b (transmissibility of vaccine virus, with a surrogate of vaccine virus dissemination assessed with detection of rVSV in saliva and urine by RT-PCR), data were included from 4 studies for the body of evidence for this outcome. Across these 4 studies, on day 7 post-vaccination, 6 out of 257 (2.3%) vaccinated participants were RT-PCR positive for vaccine virus in saliva while 2 out of 246 (0.8%) were positive in urine. On day 14 post-vaccination, 1 out of 98 (1%) of vaccinated participants were positive in saliva while 0 out of 98 were positive in urine.

To summarize the body of evidence for the surrogate outcome of detection of rVSV in saliva and urine by RT-PCR, the longest recorded positive in saliva is 14 days post-vaccination and the longest recorded positive in urine is 7 days post-vaccination. Like the previous outcome, only data from the vaccinated arms were included for analysis, so the studies were considered observational for this outcome. This evidence was downgraded one level for risk of bias because of concern for incomplete outcome data as not all who received the vaccine were tested on a given day. The evidence also was downgraded 2 levels for indirectness because like the previous outcome, no data report on transmissibility, so viral dissemination and shedding is assessed as an indirect surrogate and RT-PCR positivity is not synonymous with infectivity. Overall, this body of evidence was assessed to be Type 4 very low certainty evidence.

Across the body of evidence for Outcome 7 (vaccine-related SAEs), 12 studies with unique populations reported on vaccine-related SAEs. Out of 19,184 people who received the vaccine across these 12 studies, 3 SAEs judged to be related or possibly related to the vaccine were reported. Two of these were related to vaccination and included a febrile reaction and anaphylaxis, both of which resolved without sequelae. One was judged to be possibly related to the vaccine, an influenza like illness, which also resolved without sequelae. In summary, the majority of studies did not report any vaccine related SAEs.

To summarize the body of evidence for outcome of vaccine-related SAEs, vaccine-related AEs are an uncommon occurrence. Across 12 studies, 3 of 19,184 (0.02%) vaccinees were judged to have an SAE related to or possibly related to vaccination. Like the previous outcome, only data from the vaccinated arms were included for analysis, so the studies were considered observational for this outcome and were not downgraded across any of the criteria. Overall, this body of evidence was assessed to be Type 3 low certainty evidence.

Evidence to Recommendations for Pre-Exposure Vaccination With rVSVΔG-ZEBOV-GP Vaccine for At-Risk Adults in the United States

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Dr. Choi reminded everyone of the policy question and PICO. The first EtR question is, “Is the problem of EVD due to Ebola virus (species *Zaire ebolavirus*) of public health importance?” For this question, the WG considered that Ebola virus (species *Zaire ebolavirus*) is the most lethal of the 4 viruses that cause EVD in humans. It is highly transmissible and in infected people, it can be found in all body fluids. The disease can be quite severe and death can be rapid, occurring as soon as 7-10 days after symptom onset. In survivors, the virus has been known to persist in immuno-privileged sites and in some instances, this has led to continued disease transmission and disease recrudescence. In addition, there is no FDA-approved treatment.

The virus is an international public health threat. It is responsible for the majority of reported EVD outbreaks (64%; 18/28) to include the largest EVD outbreak in history in 2014 in West Africa. The virus has infected over 31,000 persons and resulted in over 12,000 deaths. On August 1, 2018, an EVD outbreak due to Ebola virus (species *Zaire ebolavirus*) was declared in Eastern Democratic Republic of Congo. On July 17, 2019, the outbreak was declared to be a PHEIC. On February 12, 2020, the WHO Emergency Committee unanimously agreed that the outbreak still constitutes a PHEIC with over 3000 persons infected and over 2000 deaths. The current outbreak continues to be classified as a PHEIC. The virus also is a US public health threat. There were 11 individuals infected with Ebola virus (species *Zaire ebolavirus*) treated in the US, all of which were associated with 2014 West Africa outbreak. Of these, 9 were infected in West Africa and 2 were infected in the US while caring for a returned traveler. Additional persons were repatriated to the US following high-risk exposures to confirmed EVD patients during the 2014 West Africa outbreak and 2018 DRC outbreak, none of whom developed EVD. The WG would say “Yes” this virus is a public health threat.

The next question relates to benefits, “How substantial are the desirable anticipated effects of vaccination.” One study was evaluated using GRADE that provided data on vaccine efficacy. This study demonstrated protective effect from vaccination at the participant level with a 96% risk reduction (RR:0.04 [95%CI: 0.0001 – 0.74]). Therefore, the WG determined that the anticipated effects are “Large.”

With regard to harms, the question is, “How substantial are the undesirable anticipated effects?” From the GRADE analysis, it is known that arthralgia is more commonly reported among vaccinees (RR: 2.55). Severe arthralgia is more commonly reported among vaccine recipients, although it seems to be uncommon (RR: 6.40). Arthritis is also more commonly reported among vaccinees (RR: 1.80). Pregnancy loss in vaccinated women does not seem to be significantly higher than in non-vaccinated women (RR: 1.35). However, the data are limited for this outcome. It also is known that rVSV vaccine virus has been detected post-vaccination in blood,

saliva, urine, and synovial fluid and that vaccine-related SAEs are rare. The WG determined the undesirable anticipated effects to be “Moderate.”

The question regarding the balance of benefits and harms is, “Do the desirable effects outweigh the undesirable effects?” To make this determination, the WG considered the demonstrated efficacy of the vaccine, the high severity of illness in people who contract the disease, the high transmissibility of the virus in infected individuals, the issues of virus persistence demonstrated by instances of continued disease transmission and disease recrudescence, the lack of an FDA-approved treatment, and that vaccine-related SAEs are rare. Based on these considerations, the WG thinks that it “Favors Intervention.”

With regard to the overall certainty of effectiveness of the vaccine, one study evaluated using the GRADE process demonstrated protective effect from vaccination. At the participant level, the overall certainty in the evidence for effectiveness is “Moderate.”

Regarding the overall certainty for evidence of safety, several outcomes in the GRADE analysis were related to safety. The first was arthralgia (0-42 days). Arthralgia is more commonly reported among vaccine recipients compared to placebo. The certainty level for this evidence was “Very Low.” Low certainty may be due to the variability among the studies included in the evaluation in terms of the definition of arthralgia, evaluation of arthralgia, availability of specialized care/radiographic imaging, and timing at which arthralgia was ascertained.

In terms of the outcome of severe arthralgia, severe arthralgia is more commonly reported among vaccine recipients compared to placebo or unvaccinated, but overall appears to be uncommon. The certainty of evidence is “Low” or “Very Low” depending upon whether the studies were RCTs or observation. Again, low certainty may be due to variability between studies in the evaluation of arthralgia and timing at which arthralgia was ascertained.

With regard to post-vaccination arthritis (0-56 days), arthritis is more commonly reported among vaccine recipients compared to placebo. It also is known that the rVSV vaccine virus has been detected by RT-PCR in the synovial fluid of 4 vaccinated participants. The certainty of evidence is “Low” or “Very Low” depending upon whether the studies were RCTs or observation. Again, some of this may be due to variability between studies in the definition of arthritis, methodology used to diagnosis arthritis, availability of specialized care/radiographic imaging, and timing at which arthritis was ascertained.

Concerning vaccine-related adverse pregnancy outcomes, pregnancy loss among vaccinated pregnant women was not significantly higher than pregnancy loss among unvaccinated pregnant women. The certainty of this evidence is “Very Low.”

Regarding vaccine-related SAEs, across 12 studies and over 19,184 vaccinated individuals, there were 2 vaccine-related and 1 possibly vaccine-related SAEs (anaphylaxis, febrile reaction, influenza-like illness). All of these resolved without sequelae. The certainty of evidence is “Low” due to extraction of vaccinated-arm data only, which rendered the data observational, and that vaccine-related SAEs are rare.

Pertaining to transmissibility of vaccine virus, no data are available on vaccine virus transmissibility to non-vaccinated persons or animals. Viral dissemination and shedding were assessed as an indirect surrogate for this outcome. The certainty of evidence is “Very Low” as outcome data were collected only from the vaccinated study arms, thus rendering the data observational.

In summary, the overall certainty of the evidence in terms of the safety of the intervention was determined to be “Very Low.”

The next question relates to target population sentiment, “Does the target population feel that the desirable effects are large relative to undesirable effects?” No Knowledge, Attitudes, and Practices (KAP) surveys have been conducted amongst the 3 populations of interest for this subject. The WG had several discussions about this and the feeling was that persons responding to EVD outbreaks and HCP at federally-designated ETCs will likely think the desirable effects outweigh undesirable, given that several of them have enrolled in the PREPARE clinical trial that is offering the vaccine. In addition, the majority (10/11) of the EVD patients treated in the US were either responding to an EVD outbreak and/or were HCP.

Response to vaccination has been mixed among BSL-4 personnel. Some enrolled in the PREPARE clinical trial that is offering the vaccine, so there are people who are open to vaccination. Others have wanted to enroll in PREPARE, but have been unable to do so because of logistical challenges. There are currently only 3 clinical sites for the PREPARE trial in North America located at NIH, Emory University, and Winnipeg. However, people have expressed interest in accessing the licensed vaccine when it is available outside of the 3 PREPARE clinical trial sites. There are anecdotal reports of some people declining to be vaccinated because they felt that the additional level of protection afforded by vaccination, in the backdrop of strict biosafety measures already in place in BSL-4 laboratories, was considered to be minimal compared to the potential undesirable effects of vaccination. The WG determined that this “Varies” among the 3 different populations.

The second question regarding target population sentiments is, “Is there important uncertainty about or variability in how much people value the main outcomes?” Again, the WG feels that individuals responding to an EVD outbreak and HCP at federally-designated sites will likely think that the desirable effects are large relative to undesirable effects. Among the BSL-4 population, there was a mixed response to vaccination. However, the WG thinks that amongst BSL-4 laboratorians and support staff, most think the desirable effects are large relative to undesirable effects. For this question, the WG made the determination that there is “Probably no important uncertainty or variability.”

The question with regard to key stakeholder sentiments is, “Is the intervention acceptable to key stakeholders?” Again, no KAP survey data are available. The WG feels that for the majority of the 3 populations of interest, the vaccination is acceptable. NGOs, federally-designated ETCs, governmental organizations, and BSL-4 laboratories have been supportive of staff receiving the vaccine through the PREPARE clinical trial. Therefore, the WG answered “Yes” to this question.

The question regarding resource allocation is, “Is the intervention a reasonable and efficient allocation of resources?” A cost-effectiveness evaluation was not performed as this vaccine is intended for use in preparedness scenarios in limited populations and not as routine vaccination in the general population. At this time, the vaccine will be stored and made available through the US government. Therefore, the WG answered “Yes” to this question.

The question pertaining to feasibility is, “Is the intervention feasible to implement?” As it appears now, licensed vaccine will likely become available by the third or fourth quarter of 2020. The vaccine is currently available through the PREPARE clinical trial. There are ongoing discussions to identify mechanisms to allow for limited quantities of investigational-labeled vaccine to be made available for ACIP-recommended populations in the interim period between ACIP

recommendations and availability of licensed product outside the setting of a clinical trial. Therefore, the WG answered “Yes” to this question.

Regarding the balance of consequences, the WG made the determination that “desirable consequences probably outweigh undesirable consequences in most settings.”

The question related to the sufficiency of information is, “Is there sufficient information to move forward with a recommendation?” To make this determination, the WG considered that there are available efficacy data in an outbreak setting, as well as safety data for 19,184 persons vaccinated in the US, Europe, and Africa that has been evaluated using GRADE. Therefore, the WG answered “Yes” to this question.

Discussion Points

Dr. Romero requested additional information regarding the duration of the arthralgia or arthritis that presented in these patients.

Dr. Cossaboom responded that in general, most of the arthralgia events reported were mild and resolved over a short period of time. There were instances of arthralgia that persisted for more than a month, and also resolved then recurred.

Dr. Talbot observed that the studies were conducted in healthy populations, which she assumed meant immunocompetent. She wondered whether anything was known about other comorbid conditions such as whether the vaccine would be safe for someone who has severe heart disease, and what constitutes the definition of “healthy.” She emphasized the importance of having a standard definition for providers.

Dr. Frey did not think they had those data. The vaccine is being recommended for and presumably being given only to people who are otherwise healthy and not pregnant. She was not sure the WG had defined what “healthy” means. For clinical trials, the definition is usually pretty strict. They can look at the definition used in the PREPARE trial. The definition would likely differ in the US from international populations. In the US, “healthy” typically means without most comorbidities. Some studies allow issues such as hypertension if it is well-controlled. Certainly, non-pregnant and non-lactating women would be allowed.

Regarding Outcome 4 concerning arthritis, Dr. Szilagyi inquired as to whether patients were followed longer than 56 days, which would be an important measure. Also, the incidence rates for arthritis in Outcome 4 were 2.2% versus 2.1%. That does not calculate to a risk ratio of 1.8. He suggested checking those numbers. He wondered whether the vaccine supply would be large enough if there were to be a large outbreak, and if the WG planned to address this.

Dr. Cossaboom reiterated that there was considerable variability in the methods that were used to follow-up and clinically diagnose arthritis. Some of the references did follow-up patients for more than 56 days. There were few reports of recurrent arthritis and durations of longer than 56 days.

Dr. Romero asked whether individuals were screened for pre-existing arthralgia or arthritis conditions and, if so, whether those individuals were at greater risk.

Dr. Collier (Merck) indicated that long-term follow-up for arthritis and arthralgia was included in many of the studies during which the subjects continued to be followed out for at least 6 months in the US-based study. There were some recurrences as was alluded to for arthritis events, including issues such as trigger finger, that were observed out even 2 years in the Geneva cohort. Based on the limited sample size, she thinks they do have a reasonable view of the duration and recurrence of arthritis events.

Dr. Poehling inquired as to whether the data on transmissibility were based on the PCR studies. Since the backbone is a VSV, she also wondered what the incidence of stomatitis is in the vesicular outbreaks.

Dr. Cossaboom indicated that there were no data available on transmissibility of the vaccine virus, so the WG decided as a surrogate to assess the detection of vaccine virus by RT-PCR in blood, saliva, and urine. For the purpose of the presentation, the WG did not do a comprehensive systematic review on the outcomes of incidence of the oral and skin lesions because those were lower in importance to the WG. However, they do plan to address this in the future.

Dr. Cohn requested that Dr. Collier remind them of the overall incidence for arthralgias was and what proportions of the persons who had arthralgia had longer-term, greater than one week or recurring events.

Dr. Collier (Merck) indicated that the overall incidence of arthralgia across the program, specific from the US prescribing information, is that approximately 10% to 15% of individuals develop arthralgia. Typically, that resolves within the first 7 days or so. She will look up and report back to ACIP the proportion of persons among whom arthritis or arthralgias resolves and the proportion in which they are long-term.

Dr. Sanchez asked whether arthritis or arthralgia had occurred in the other vaccines for which the VSV has been used.

Dr. Choi said that she read other papers on this, which did not seem to find that. In a review paper that examined other VSV-based vaccines, arthritis was not seen. Arthritis was not seen in humans affected by the VSV vaccine, so the initial paper that assessed arthritis and the synovial fluid issue in vaccinated individuals postulated that this may be something that is specific to this combination of the VSV plus the glycoprotein of the Zaire behaving somewhat differently than would have been expected because it was not seen with the VSV in humans or animals.

Dr. Bernstein noted that the patients who had arthralgia did not evolve into arthritis, and wondered whether those were the same or different patients.

Dr. Cossaboom replied that in many of the reports, there were individual-level data. There were reports of arthralgia and arthritis, but in some cases it was not clear whether they were the same people.

Dr. Collier (Merck) added that in many of the cases, it was the same individuals who experienced some joint pain and then had evidence of joint swelling. Recalling an earlier question about whether there was evidence that a prior joint injury led to an increased risk of arthritis and arthralgia, she reported that they conducted an analysis in the large Phase 3 study conducted in the US and did find that prior damage to joints and/or being female led to an increased risk of arthritis.

Dr. Fink (FDA) mentioned that in the data that the FDA evaluated in the Biologics License Application (BLA) submission, they looked at events of arthritis and arthralgia and found that arthritis specifically occurred at a range of 0% to 24% of subjects. In most studies they evaluated, the arthritis rate was less than 5%. There was one outlier in a study from Switzerland where arthritis occurred at a rate of 24%. That outlier study also had the highest proportion of subjects who had prolonged arthritis, which was 6 subjects out of 24.

Dr. Messonnier asked whether the FDA considered pre-existing conditions and if there are any that should be contraindications, and if they considered pregnancy categories.

Dr. Fink (FDA) indicated that the FDA did not consider there to be any pre-existing conditions for which the vaccine would be contraindicated based on the available data, and considering the severity of Ebola disease and the benefit/risk considerations. There were individuals in the safety database who had some pre-existing conditions, including human immunodeficiency virus (HIV) infection and other immunocompromising states. It is also worth noting that in the Ebola Ça Suffit trial, there were no exclusion criteria related to pre-existing conditions other than having a medically significant condition that resulted in hospitalization or required treatment for Ebola disease. In terms of pregnancy, the FDA labels no longer have pregnancy categories. Instead, there are descriptions of data and risk considerations related to human and animal data regarding pregnancy. The non-clinical or animal studies that were done to assess for reproductive toxicity did not raise any concerns with regard to use in pregnancy. As mentioned during the presentation on the GRADE analysis, there are limited data on pregnancy outcomes in humans who have been vaccinated. There are not enough data to make any firm conclusions about risks from exposure to the vaccine during pregnancy. That being said, considering the overall risk and benefit balance, the vaccine indication does include women who are pregnant who are at risk of Ebola exposure.

Dr. Schaffner (NFID) pointed out that the emphasis had been on PrEP, but he wondered about post-exposure prophylaxis (PEP) If there were to be another episode such as the one in Dallas, he imagined there would be great interest in using this vaccine in a PEP circumstance. He asked whether the WG had considered PEP.

Dr. Choi indicated that the WG discussions have focused on PrEP and identifying the populations at highest risk. In the DRC, the vaccine is used essentially in a post-exposure method with the rings and clusters. The WG will continue to address the issue of post-exposure and other populations for whom they potentially would suggest recommendations.

Dr. Frey emphasized that the WG still has a lot to discuss, but concentrated this session on the 3 most urgent groups who needed to be addressed. They will have a lot more to present in the coming months.

Dr. Bernstein observed that since pregnancy loss was higher in vaccinees versus non-vaccinees, although not statistically significant and there were limited data, perhaps there would be value in objectively identifying that women are not pregnant before receiving this vaccine.

Dr. Choi indicated that in some of the clinical trials conducted, pregnancy was an exclusion criterion. Certainly, there would have to be some precautionary language on that issue.

Dr. Frey emphasized that the WG is just concentrating on the 3 major populations of interest in the US, and that there are limited data available. There is a lot of uncertainty about the evidence to recommend, so they want to be cautious. They are moving forward with these first 3 groups in terms of vaccinating adults 18 years of age and older who are relatively healthy and not pregnant. They hope to review more information as more vaccine is administered, particularly from the trials that are ongoing. She used the correlate of smallpox and giving Dryvax® or ACAM2000® live attenuated viruses, which would be used to vaccinate pregnant women and otherwise compromised hosts in an outbreak setting. While the WG was not yet at that point in their deliberations, those discussions will be forthcoming.

Ms. McNally asked whether there was any specific information about what concerns the BSL-4 personnel had who anecdotally indicated that they were concerned about the potential undesirable effects of the vaccines.

Dr. Choi responded that some of the BSL-4 laboratory personnel felt that there are other precautionary measures in place in BSL-4 laboratories and as such, some of them did not feel that vaccination would add that much to the existing protection. At the same time, there are people in that population who have been vaccinated through PREPARE and are supportive of others being vaccinated. They also heard that there are groups within that population who wanted to take part in PREPARE, but could not do so because of their location. Because it is a clinical trial, there is a lot of follow-up that has to be done at the clinical trial site. Some people were not able to take the time off for that and still be paid, so there were a lot of logistical and financial concerns that impeded them from enrolling.

Dr. Frey reminded everyone that the information the WG has from these populations and their desire to receive or not receive vaccine is anecdotal. They spoke to some of the supervisors and administrators in those areas, who shared anecdotal information. Some people wanted to see more safety data after the vaccine had been tested further. A variety of other reasons were given as well, but the overall sense from the people who the WG spoke with was that the majority of those populations would be interested in having the vaccine available to them. Those who had not already received the vaccine or were hesitant about taking it cited that they already were doing a good job with existing personal protective equipment (PPE) and preferred to wait for additional safety data.

Dr. Cohn requested clarification on what the risk is to BSL-4 laboratory workers in terms of whether there ever has been a case of Ebola related to an exposure, or if there have been exposures in this population.

Dr. Choi responded that there has never been a case of EVD diagnosed in a BSL-4 worker in the US. There was one individual in Russia, who she believes died.

Circling back to the comment about the HCP definition, Ms. Stinchfield (NAPNAP) emphasized that hospitals and healthcare settings take that definition very literally. As they saw earlier, it is not complete. She cautioned that as they get into lists and policies, they may find themselves in trouble. For example, in the Children's Minnesota policy for proof of immunity to work at the hospital, they basically put in the link to the CDC healthcare vaccination schedule. At that site, there is a very abbreviated part of the definition that was shown during this session that does not include the sentence about "including, but not limited to." It looks like the professionals

listed there are the professionals to whom that refers, which she did not think was the intent. She called everyone's attention to the National Foundation for Infectious Diseases (NFID) [Call-to-Action: Improving Healthcare Personnel Immunization Rates](#) written in March 2018. Many of the ACIP liaisons participated in the development of that publication and developed a much simpler definition, which is, "All healthcare personnel who work directly with patients, or who work in any capacity in a healthcare setting, should be vaccinated in accordance with CDC recommendations." The CDC recommendations include the details for specific vaccines. She suggested that they work on improving the definition.

Dr. Lee asked whether the groups queried for acceptability were frontline workers handling replication competent Ebola virus, or if it was generally anecdotal reports from supervisors. She is more concerned about the frontline workers specific to this recommendation category.

Dr. Damon, Director of the Division of High Consequence Pathogens and Pathology (DHCPP) where BSL laboratory work occurs at the agency, reported that in the history of the BSL-4 laboratory work at CDC, there have been no breeches in the use of PPE that would have required some sort of PEP or treatment. Most other institutions that have BSL-4 laboratories track this very closely and to her knowledge, there is one example in Eastern Europe of an exposure in which treatment with an investigational antivirals and post-exposure vaccination were used. Dr. Choi described the one episode on Russia where there was exposure. In terms of work in a field laboratory setting, CDC ran and operated a laboratory that tested and processed tens of thousands of suspect and confirmed Ebola samples and had no breeches in exposure and no infections. Several of CDC's personnel had been vaccinated prior to going to work in that laboratory through one of the investigational protocols.

Dr. Frey asked Dr. Damon to explain to ACIP if it is the policy to vaccinate workers, if a vaccine is available, prior to them working in BSL-4 laboratories.

Dr. Damon responded that this decisions would be made with occupational health with the scientific program to understand the level of risk and the additional benefit versus risk that would be associated with any individual vaccine. There is not a requirement for anthrax vaccination in CDC's laboratories as it is BSL-3, but there is a requirement for smallpox vaccination among BSL-4 laboratory workers. The smallpox decision was made because there is no disease anywhere in the world, so the potential risk for an undiagnosed exposure led to that recommendation. With the additional barriers available to prevent infectious exposure with Ebola within the BSL-4 laboratory and training of the personnel, this would likely be an individual decision that should be made in concert with the scientific program and occupational health to judge the level of risk. Certainly, people handling animals and infected animals are likely at higher potential risk than others. Understanding people's level of risk in terms of the potential for an arthritis is important, given that it could be debilitating for a number of days. BSL-4 personnel carry around an additional 5 to 10 pounds of weight in terms of the suit and breathing apparatus, so mobility is already less than what it is like to walk around in in a normal environment.

Ms. McNally emphasized that as reported during this session, no KAB surveys have been conducted among the 3 populations of interest and the anecdotal reports indicated concern regarding the arthritis/arthritis or the potential vaccine-related events from pregnancy outcome. She requested that someone flesh that out further.

Dr. Choi recalled that the concerns were mostly related to arthritis/arthralgia and reactogenicity associated with the vaccine. She did not recall a WG discussion specifically about concerns with pregnancy.

Dr. Hunter thought they had discussed 2 fairly well-defined population thus far, the BSL-4 laboratory personnel and people who work in a federally-defined Ebola Treatment Center. However, the other groups is somewhat less well-defined and could include volunteers in NGOs and others who are deploying in various capacities who will have various levels of risk. Consideration should be given to the level of risk, where someone is on the ring, and how much risk there is of death depending upon whether someone is out in the bush in West Africa and cannot get a medivac because transportation is breaking down, someone is in a regional center away from the outbreak and may not have direct contact with patients based on the assignment, or someone is on their way and may or may not have exposure depending upon length of stay. There is going to be a lot of interesting conversation about risk for dying versus risk for arthralgia. He assumed that the simple policy statement that "it is recommended" is going to have a lot of information in the guidance for various levels of risk upon which ACIP is not going to vote.

Dr. Choi said that the WG agrees. They kept the definition somewhat broad. Initially, it was "persons deploying to an outbreak." However, they felt that on some level that was limiting. As mentioned, someone was repatriated during the current outbreak because of a high-risk exposure. That is a US personnel who is in the DRC and normally works at a hospital in the DRC. He had contact because a pregnant Ebola patient presented to his facility whom he took care of. That is why they left out the word "deployed." There are oftentimes NGOs and other organizations working in places where the Ebola outbreak hits. If the language is limited to "deployed," it potentially puts them out of the box though they could be at risk depending upon transmission in the community.

Dr. Cohn pointed out that they would be voting on the language in the recommendation in terms of these groups. However, there will be additional guidance in the Policy Note that is being written about how to assess persons at risk and guidance for these organizations. This is going to be a very risk-based assessment not only for laboratory personnel, but also for all of these groups. There also will be guidance about groups who should not be vaccinated.

Dr. Bell indicated there are a number of consultants on the WG, some of whom in Europe are already vaccinating their responders and have developed some clear vaccination guidelines targeted to the types of settings their workers may encounter. The WG anticipates something similar that would appear in the Policy Note as Dr. Cohn indicated. The point is every well-taken in that there are all sorts of exposures that may be particular to specific types of organizations and they will have to work through that very carefully.

Dr. Frey noted that if ACIP decided to recommend this vaccine, an ACIP recommendation would not make it mandatory for people to be vaccinated. She appreciated the fact that when particular organizations read that ACIP recommends a vaccine, that automatically translates to a mandate to be vaccinated. That is not the case, and a lot of guidance would be given for how those decisions should be made. It would be up to organizations to determine the risk for their particular employees. There are so many different individual situations that could occur, the decision-making needs to occur at the level of employment.

Dr. Cohn asked whether there has been any discussion about an upper age limit in terms of a recommendation or information about use of this vaccine in older adults.

Dr. Choi indicated that when the WG reviewed the clinical trials, some of them did have an upper age restriction that she believed was 65 years. However, the WG has not talked specifically about setting an upper limit.

Dr. Frey added that this relates back to the definition of what constitutes “healthy.” As people age, they do have a tendency to have morbidity or comorbidities.

Dr. Fryhofer (AMA) said that as a practicing physician and member of this WG, she conveyed how much she appreciated the questions that came from ACIP regarding this decision and what a fabulous job the two CDC leads have done in looking at this. She said she did not think they had slept over the last two months, and expressed gratitude for their hard work.

Dr. Frey reminded everyone that this is a live-attenuated vaccine vector, VSV, in its recombinant state. With live-attenuated vaccines come more side effects (fever, myalgias, arthralgias) than occur with subunit vaccines, for example. These are frequently not unexpected. In addition, there is limited information about transmissibility in terms of this vaccine. While people have concerns about transmissibility, this has not been well-studied. There is no evidence for it, but there is evidence for skin lesions that have virus in them and other fluids that test positive through PCR. The WG recommendations are population-based for this particular vaccine, given the mortality related to infection should someone become infected. They are not being presented in the sense of shared decision-making. The decision-making processes will be at the level of the institution.

Dr. Collier (Merck) reported back on some of the questions for which she looked up specific responses. In terms of arthritis, data from Merck’s largest double-blind, placebo-controlled, US-based Phase 3 study, approximately 3.7% of subjects developed arthritis who received the target dose. The median onset for that was 11 days post-vaccination. The median duration of the arthritis was 6 days, with a range from 0.5 to 44 days for the target dose and 0.5 to 156 days for the high-dose group included in that study. Nearly all of the arthritis events had resolved prior to the 6 months and there were no recurrences out to 2 years. A subset of about 500 subjects were followed for 2 years out of the total of 1200. For arthralgia, there was a lot of variability. It was assessed across all of the trials. In the Phase 1 blinded trials, it ranged from 10% to 50% versus 22% in placebo. On the US-approved label, that number is 18%. Median onset tended to occur quite early, within days, and was generally resolved by Day 14. Some went longer than that, but generally resolved by Day 14. As Merck talk about it, the arthralgia was generally days to weeks and the arthritis was more weeks extending out to months in some cases.

Dr. Cossaboom added more information with regard to background. The Geneva trial was the first to identify arthritis and they provided extensive investigation into the cases. To add on to the information Dr. Collier provided, there were 24 cases of temporally associated arthritis in this trial out of 102 subjects. The median duration of the arthritis was 34.5 days. The median time of onset was 10.5 days. Of the 24 subjects with arthritis, 5 reported recurrent arthritis or arthralgia. That had a duration ranging from 3 to 222 days, with a median duration when taken together with those recurrent reports of arthritis of 81.5 days. Regarding the question of the risk ratio that was reported for Outcome 4, she discovered that there was a small arithmetic error that will be updated for the final slides, but it was not significant.

Dr. Damon recalled that there had been discussion at some point about the potential for people with cardiac risk factors. She invited their colleagues from the Strategic Advisory Group of Experts on Immunization (SAGE) who have been following the WHO efforts to assess safety, and from the FDA to discuss what they have seen in terms of any cardiac risk factors or AEs.

Dr. Cravioto (WHO/SAGE) indicated that they have not received any information regarding any cardiovascular effects. The main AEs that have been reported in the use of the vaccine have been arthralgias. Probably because of the way the vaccination has been done and the follow-up difficulties, they have not seen the arthritis problems in that sense. He noted that the Global Advisory Committee on Vaccine Safety (GACVS) recently published its newest bulleting that includes the entire analysis of safety data for the VSV and Ad26.ZEBOV Ebola vaccines, which is available on the WHO webpage.

Dr. Fink (FDA) indicated that in the safety data the FDA reviewed for the licensure application that included approximately 16,000 adult subjects who received the vaccine, there were no reported cases of myocarditis or pericarditis specifically. More generally, there was no signal to suggest any cardiac toxicity related to the vaccine.

Work Group Considerations: Proposed Recommendation Text for Policy Options

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Dr. Choi indicated that all of the policy considerations to be presented would be limited to vaccination of healthy, non-pregnant, non-lactating adults ≥ 18 years of age.

The first vaccination policy issue for posed for ACIP consideration pertained to individuals responding to an outbreak:

Should pre-exposure vaccination with the rVSV Δ G-ZEBOV-GP vaccine be recommended for individuals in the U.S. population responding to an outbreak of Ebola virus disease due to Ebola virus (species *Zaire ebolavirus*)?

Amongst the WG members, the proposal by strong majority was to recommend. The rationale is that there is a documented history of infections in outbreak responders, the benefits of vaccination outweigh the risk in terms of severe disease and the lack of an FDA-approved treatment, and that there is a risk of exposure even with appropriate use of PPE. It is not always what someone wears, but how someone wears it and takes it off. The proposed text for the population of individuals responding to an outbreak of EVD was:

Pre-exposure vaccination with rVSV Δ G-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older in the US population who are responding to an outbreak of Ebola virus disease due to Ebola virus (species *Zaire ebolavirus*).

The second vaccination policy for ACIP consideration involved HCP:

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for healthcare personnel* involved in the care and transport of confirmed Ebola virus disease patients at federally-designated Ebola Treatment Centers in the United States?

The WG proposal by strong majority again was to “recommend.” The rationale is that operational ETCs with trained and vaccinated personnel is a part of public health preparedness. This population is at high-risk of occupational exposure to the virus. Vaccination provides an added layer of protection, in addition to other biosafety measures (e.g., personal protective equipment, engineering controls, et cetera). The proposed text for HCP vaccination was:

Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older who work as healthcare personnel¹ at a federally-designated Ebola Treatment Center in the United States.

The third vaccination policy for ACIP consideration pertained to laboratorians and support staff working in BSL-4 facilities:

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for laboratorians and support staff at biosafety-level 4 facilities that handle replication-competent Ebola virus (species *Zaire ebolavirus*) in the United States?

The WG proposal by strong majority was to recommend. The rationale is that BSL-4 laboratorians and support staff are at high risk for occupational exposure. Also, the vaccine provides an added layer of protection in addition to other biosafety measures (e.g., personal protective equipment, engineering controls, et cetera). The proposed text for this consideration was:

Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older who work as laboratorians and support staff at biosafety-level 4 facilities in the U.S. who are at potential risk for occupational exposure to Ebola virus (species *Zaire ebolavirus*).

Discussion Points

1st Vaccination Policy Issue for Consideration: Individuals Responding to an Outbreak

Dr. Bernstein pointed out that a strong majority is not unanimous.

Dr. Choi confirmed that a strong majority is not unanimous and explained that for each of the 3 groups, 1 person voted for shared clinical decision-making. All of the rest voted to recommend and there were no votes not to recommend.

Dr. Romero clarified that ACIP voted and makes recommendations, while the WG may move to submit proposed language to be presented to ACIP.

Dr. Bell further clarified that it would be accurate to say that there were no WG members who were opposed to some sort of recommendation for each of these groups.

Dr. Bernstein said he was still questioning whether there was value in documenting someone not being pregnant before they receive this vaccine. He requested that Dr. Ault comment on this as an obstetrician.

Dr. Ault said he thought it would be the same issue as whether someone is healthy or not. There is a general principle that live viruses should not be given to pregnant women, so that probably would fall under implementation. In terms of implementation, there is an accurate urine test to detect pregnancy.

Dr. Messonnier noted that when the language was discussed in preparation for this policy consideration, it clearly had a tenor of being risk-based. Yet, the way the language was articulated did not exactly have that same sense of being risk-based.

Dr. Hunter agreed in context that avoiding clinical decision-making for this would be appropriate, because the decision is on more of an institutional level. However, occupational health recognizes that there are risks and goes through categories of risk. For just the first of the 3 groups, he suggested inserting a phrase that states “are at high risk for Ebola infection due to responding.”

Dr. Lee emphasized the importance of conveying consistently that this recommendation would pertain to certain individuals who are at high risk of exposure not only to confirmed infected patients, but also their associated infectious materials. This is important from an access standpoint for individuals and from a public health standpoint.

Dr. Cohn suggested that to capture the idea of there being a risk-based assessment, perhaps the statement could include the language about all of these recommendations applying to “healthy, non-pregnant, non-lactating adults \geq 18 years of age based on a risk-based assessment” and then include parentheses in the 3 different groups to attach the risk-based assessment and capture all 3 recommendations.

Dr. Eckert (ACOG) expressed concern with excluding pregnant women, because a woman may be working in a laboratory or deployed and happen to find herself pregnant in a high-risk situation. The data were not compelling that there is an increased risk to safety in pregnant women. This is an opportunity to consider language that might be somewhat less exclusionary toward pregnant women for this vaccine and in general. It is known if a pregnant woman gets Ebola how bad that is.

Dr. Sanchez agreed that the disease is so severe, they should not completely exclude pregnant women. It should be left up to the individual to decide, because nothing is done for the fetus either in a pregnant woman who develops Ebola.

Dr. Atmar reminded everyone that this is PrEP, so the vaccine would be given electively. Due to the relative lack of data in pregnant women, though the available data do not suggest an increased risk, because it is elective and in practically in every circumstance can be withheld until the woman is no longer pregnant, the WG decided to suggest the recommendation not to use it in pregnant women. This adheres to the concept that live virus vaccines are not given to pregnant women, and there are not a lot of data. There may be more data from PEP where it is administered in pregnant women to try to prevent them from getting a disease to which they

may have been exposed. That may be a mechanism by which eventually this could be recommended for pregnant women. The WG thought at this time, it would be prudent not to include pregnant women. There was some discussion about whether pregnancy tests should be done or not. He deferred to his obstetric colleagues on that question. Regarding the question about risk, the WG certainly included “at risk” for the BSL-4 laboratorians and other personnel. There also was some discussion about people being deployed who would never come in contact with patients. But it also was recognized that many times, people who were deployed to an area in response to an Ebola outbreak with the original intent not for them to have patient contact, things are fluid and they might end up having a higher risk than initially anticipated. This is why the WG thought that those responding might be sufficient, and the risk language could be couched in the text rather than in this statement. He did not think anyone was necessarily wed to the statement, but the discussion was that risk changes or can change once a person is on the ground after responding.

Dr. Frey pointed out that if they took out pregnancy, it would follow to take out non-lactating women.

Dr. Romero emphasized that it is known that certain antibiotics should not be used in pregnant women due to the theoretical risk of joint damage in animal models. This vaccine definitely shows evidence of arthritis, so this raises a concern about whether that also would occur in the developing fetus.

Dr. Bell noted that it sounded like people were interested in potentially reflecting the concept of risk in the language, and that they wanted to balance that with the kind of implementation considerations that would be more appropriate in a Policy Note. For example, agencies deploying people would have their own occupational health policies. It seemed that there was a fair amount of sentiment to add some wording to the language reflecting the fact that this is based on potential risk of exposure to infect patients or materials.

Dr. Messonnier said she thought it may just be in the framing. In other recommendations, it is not the recommendation language that is meant to be precise. It is the paragraph before in which there is an explanation about why the decision was made that would provide more context. It seemed that it would be helpful in the paragraph before this language to articulate that this is a risk-based decisions. That is not clinical decision-making exactly. It is a risk-based decision, and many of the recommendations include that kind of language.

Dr. Cohn reminded the ACIP members that they would receive a draft of the Policy Note for review, comment, and feedback. If they voted to approve the recommendation, there still would be plenty of opportunity to provide feedback in how it is framed.

Dr. Frey emphasized that they would be recommending this vaccine only for people who are at risk. Because the risk factor makes the decision-making difficult, the WG anticipated providing that kind of guidance in the framing to help people make decisions regarding whether someone should be vaccinated.

Dr. Hunter appreciated that and was reassured by the commitment to incorporate risk into the guidance that goes along with this outside of the actual vote ACIP makes. He remained concerned about how recommendations are implemented in institutions in that the main thing, and sometimes the only thing, that is focused on it what ACIP actually votes on and the verbiage of that. While he was not wedded to having the word “risk” in the recommendation, but stressed that point that if the word “risk” did not appear directly in the statement, it could go both

ways. An institution may over-interpret or under-interpret and not necessarily take the risk into account and just make an administrative decision, which has happened sometimes.

Dr. Wharton asked whether the Countermeasures Injury Compensation Program (CICP) would be applicable if the proposed use of this vaccine resulted in significant AEs.

Dr. Rubin (HRSA) indicated that she was awaiting a response to that question and would get back to ACIP.

Dr. Cohn suggested that they go through each of the recommendations and then take a short break to incorporate the suggestions and language of risk prior to any motions.

Dr. Talbot pointed out that if an occupational health program requires an employee to receive the vaccine who then develops an arthritis/arthralgia, that could be problematic for a nurse at the bedside, a surgeon, or someone who works in a BSL-4 space suited up. The risk of contracting Ebola may be increased further for someone working in a laboratory who develops arthritis. It would be very helpful to know that these people who have stepped forward to take care of patients and do this research are protected if they do develop an arthritis.

Dr. Romero added that this raised a very good question pertaining to whether the arthritis or arthralgia affects large or small joints. It would be helpful to have this information.

Dr. Cohn asked whether anyone from Merck was present who could speak to the type of arthritis that was developed.

Dr. Collier (Merck) thought there was both small and large joint involvement, such as trigger finger and knee issues. She said she would verify and report back to ACIP.

The language was revised to read as follows, subsequent to which the discussion continued:

Vote #1 Revised Proposed Language: Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older in the U.S. population who are responding to an outbreak of Ebola virus disease and are at potential risk for exposure to Ebola virus (species *Zaire ebolavirus*).

Dr. Sanchez said he still would prefer that “non-pregnant” be removed because the way it was written, it was almost like the non-pregnant woman would not receive the vaccine under any circumstances. However, it is a risk and if a woman is at high risk for whatever reason this should be an option.

Dr. Frey reminded everyone that they were talking about pre-exposure and that she understood that there was concern about the difference between pre- and post-exposure. Typically, post-exposure is a higher risk. She said if she understood the FDA comment earlier, pregnant women or people with comorbidities potentially could be vaccinated. She emphasized that the WG’s recommendation was only for pre-exposure. Given the limited data available, the WG feels more confident making this particular recommendation. Certainly, if there are major outbreaks or overwhelming cases and people are exposed who are pregnant or potentially pregnant, that consideration would be swept away perhaps.

Dr. Cohn asked whether everyone would be more comfortable if they paralleled this recommendation to other immunization recommendations in which they do not include non-pregnant, non-lactating adults, vote on the recommendation, and then have a contraindication to state that it is not recommended for pregnant or lactating women.

Dr. Sanchez said that was his point. He thought in the discussion it could be stated that ACIP does not recommend it, but it can be a personal choice so that if someone is at high risk enough, they could receive the vaccine. The way it was worded suggested that a pregnant or lactating woman could not get the vaccine even if she wanted it.

Dr. Bell thought there was an argument to be made for making the language parallel to other relatively new live virus vaccines.

Dr. Eckert (ACOG) encouraged consideration of taking out “non-pregnant, non-lactating” and placing it below simply because this is not the same risk consideration as if someone contracts the disease as some of the other live virus vaccines, given that it is so much more harmful to a pregnant woman and her fetus. She agreed that it would be good to give the pregnant woman a choice. If she finds herself pregnant in a situation where she is at risk of contracting Ebola, the fear is that she would lose a choice of whether she could receive this vaccine if the language remained as presented.

Dr. Cohn reminded everyone that on the adult schedule, live virus vaccines for pregnant women are “do not give” but it is not in the language of the recommendation exactly.

Dr. Frey asked whether they also wanted to remove “healthy.”

Dr. Poehling agreed that they should mimic the other live vaccines in whatever way that has been done previously.

Dr. Cohn did not recall that the word “healthy” had been used in prior language, though the word “immunocompetent” is used in the zoster recommendations.

Dr. Bahta emphasized that if they were going to use the word “healthy” it needed to be put into context to clarify what they mean.

Dr. Frey recalled that Dr. Talbot mentioned that earlier and the WG would look into what a good definition would be. Typically, that would refer to people who do not have much in the way of comorbidities. Usually, having a slight cold would not necessarily preclude someone from receiving a vaccination.

Dr. Hayes (ACNM) suggested that perhaps instead of “healthy” the word “immunocompetent” should be used.

Dr. Atmar thought that would be consistent with the way some of the other adult vaccines are recommended to different groups, so he was going to propose something similar.

Dr. Sanchez agreed that “healthy” should be removed, given that they had no definition for it. Someone with diabetes could be healthy.

Dr. Frey said she thought there was a special chart for immunocompetent patients, so they could handle it the same way as is done for pregnant women.

Ms. McNally emphasized that from a consumer perspective, consistency in the recommendations is important to lead to a clear understanding of how these recommendations work.

Dr. Romero indicated that the WG would continue to work on the wording during the lunch break before making a motion and taking a vote.

2nd Vaccination Policy Issue for Consideration: Healthcare Personnel

Dr. Lee noted a discrepancy in the wording in that the handouts provided to ACIP differed from the language presented in that it no longer stated, “care and transport of confirmed Ebola virus.”

Drs. Choi and Romero clarified that correct language was in the handout, which would be corrected during the break.

Dr. Cohn clarified that this would be persons identified at a treatment facility identified to be at risk, not every individual who worked there.

Dr. Hunter observed that perhaps “in the care and transport confirmed Ebola virus” was too specific of a risk to mention. Just HCP is not specific enough, but there might be more than care and transport that could pose a risk.

Dr. Atmar pointed out that it would be laboratory personnel who would work in there. Whether they are considered to be involved in the care directly could be misinterpreted. The intent was HCP at risk, which would include all individuals surrounding that patient and his or her clinical specimens (those involved in the direct care, those involved in handling samples, those who clean the patient’s room, et cetera).

Dr. Choi added that the initial HCP definition had to do with people involved in direct and indirect patient care, including support personnel as well.

Dr. Frey added that the patient transport staff would be included in the HCP definition provided that includes examples, so “in the care and transport of confirmed Ebola virus” could be removed.

The language was revised to read as follows, subsequent to which the discussion continued:

Vote #2 Revised Proposed Language: Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older who work as healthcare personnel¹ at a federally-designated Ebola Treatment Center in the United States who are at potential risk for exposure to Ebola virus (species *Zaire ebolavirus*).

Dr. Romero suggested that the same language changes be made for this recommendation as made in the first recommendation.

Dr. Atmar suggested adding “and” before “who are at potential risk.”

Dr. Duchin (IDSA) noted that a question arose during the break pertaining to revaccination for people who have ongoing exposures—not the first responders but the laboratory workers for example.

Dr. Frey indicated that there is not enough information to recommend to not recommend revaccination. That question and the available data are being studied by the WG and there will be a recommendation forthcoming.

Dr. Romero reminded the voting members and audience that the ACIP the right to revisit any recommendation as new information becomes available, so they can bring this back again.

Dr. Lee requested clarification that for the federally-designated Ebola Treatment Centers, they were speaking specifically about anyone attached to the unit, including environmental services and so forth. Looking at the names of the centers, she thinks of the entire institution versus the specific unit caring for Ebola patients.

Dr. Choi clarified that this does not mean everyone who works at a facility, given that the facilities treat patients other than Ebola patients. It is intended for people specifically working with confirmed patients.

3rd Vaccination Policy Issue for Consideration: BSL-4 Laboratorians and Support Staff

Dr. Szilagyi said he liked the wording and thought the phrase “who are at potential risk” should be included in the other two recommendations as well—not just in the framing.

Dr. Frey agreed that this would be a nice solution.

The language was revised to read as follows, subsequent to which the discussion continued:

Vote #3 Revised Proposed Language: Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older who work as laboratorians and support staff at biosafety-level 4 facilities in the US and who are at potential risk for occupational exposure to Ebola virus (species *Zaire ebolavirus*).

Dr. Romero suggested that the same language changes be made for this recommendation as made in the first and second recommendations.

Dr. Sanchez pointed out that the wording “laboratorians and support staff” may be confusing since support staff are a different group of people.

Dr. Frey indicated that “support staff” is a catch phrase that specifically would be for people who would be at risk of contracting infection. Those types of decisions would be made at the level of the institution, which would define who would and would not be at risk.

Dr. Choi explained that it is not just laboratorians who work with viruses. The laboratories must be maintained, so there are people involved in the maintenance of the laboratories who are not necessarily laboratorians. If they have to enter a BSL-4 laboratory that at some point contained Ebola virus, they certainly could be at potential risk. Therefore, the WG identified them as support staff.

Ms. McNally suggested referring to the HCP definition that gives the examples of clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel.

Dr. Frey clarified that the third recommendation focused on BSL-4 laboratories, so this pertained to laboratorians and their associated personnel not HCP per se. It was not clear to her how to fit HCP in this definition.

Ms. McNally said she understood that, but some of the people identified as support staff in the HCP definition were the same and she would like to see consistency in language to the greatest extent possible.

Dr. Bahta suggested saying “laboratorians and the associated staff” rather than “support staff.” Support to her is someone who is entering data and did not make her think of someone doing the housekeeping in that area.

Dr. Atmar suggested “other staff at risk.”

Combined Language for All 3 Populations

Dr. Romero indicated that during the lunch break, the language for the Ebola vaccine recommendation was combined into a single recommendation. He indicated that they could vote on the language this way, or vote on each recommendation separately.

Dr. Choi explained that the WG looked back at previous language for other live vaccines, and found that the terminology used in the recommendation language varied. Therefore, the decision was made to defer to the FDA indications that state, “adults 17 years of age or older” with the idea of then discussing pregnancy, immunocompromising conditions, and other concerns separately in the Policy Note. She presented the following combined option as revised for ACIP’s consideration:

Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older in the US population who are at potential risk of exposure to Ebola virus (species *Zaire ebolavirus*) and:

- Are responding to an outbreak of Ebola virus disease; or
- Work as healthcare personnel¹ at federally-designated Ebola Treatment Centers in the United States; or
- Work as laboratorians or other staff at biosafety-level 4 facilities in the United States

Dr. Bernstein suggested changing “and” at the end of the first sentence to “because they.”

Dr. Frey made a motion to approve the language with the idea that it will be corrected for grammar and punctuation. Dr. Ault second the motion.

Motion/Vote: Ebola Vaccine

Dr. Frey made a motion to approve the language for the proposed policy as presented, with the idea that the verbiage would be made grammatically correct prior to publication. Dr. Ault seconded the motion. No COIs were declared. The motion carried unanimously with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

For the public record, Dr. Ault reported briefly on the discussion that occurred during the lunch break. There was a Task Force 10 to 15 years ago to address language around vaccine and pregnancy as a lead up to the Tdap vaccine and the pandemic occurring at that time. The Task Force decided to state the data available and tell people what was known and what was not known. That will apply to the Ebola vaccine as well.

CDC's Response to Coronavirus Disease 2019 (COVID-19)

Nancy Messonnier, MD
Center Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Messonnier presented an update on CDC's Response to Coronavirus Disease 2019 (COVID-19). She emphasized that over 800 people at CDC are working on this response, and that she was pleased to be able to be the person they could spare for a little while to update ACIP on what is occurring and respond to questions.

As a backdrop to what is occurring with COVID-19, coronaviruses (CoV) are a large family of viruses that cause respiratory illness. They are named for the crown-like spikes on the surface of the virus. In general, coronaviruses are a zoonotic disease that is typically spread among animals and can sometimes jump to people. There are 7 human coronaviruses (HCoVs). The 4 more common HCoVs (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) are associated with a disease spectrum like the common cold. There are 2 other HCoVs (SARS-CoV and MERS-CoV) with which everyone may be familiar. The newly identified virus is SARS-CoV-2, which causes coronavirus disease (COVID-19).

The more common HCoVs usually cause mild to moderate upper-respiratory tract infections like the common cold, but can cause more severe disease such as pneumonia and bronchitis. The symptoms are the same as would be expected with a viral upper-respiratory tract infection (runny nose, headache, cough, sore throat, fever, general unwell feeling). Laboratory tests can be used to diagnose these common HCoVs, but people generally do not test, so they do not identify it.

and there are additional American patients in Wuhan, China who were associated with exposures in Wuhan.

A major topic of consideration regards how COVID-19 is spread. Investigations are ongoing to better understand spread. What is thought at this time is largely based on what is known from other coronaviruses, as well as the epidemiological data being gathered. In general, the presumption is that it is spread primarily through close person-to-person contact with respiratory droplets. There are some data to suggest that at least some minority of cases are exposed by touching a surface or object that has the virus on it and then touching the mouth, nose, or eyes.

The data available suggest that the early symptoms of COVID-19 are fever, cough, and shortness of breath as would be expected from other viral respiratory diseases. However, a wide range of illness severity has been reported from mild to severe disease. As seen from the numbers, this can result in death. The estimated incubation period is believed to be 2 to 14 days. In the rush to make sure that everyone throughout the world knows information as quickly as possible, there have been some unpublished reports in the lay literature suggesting longer incubation periods. The published literature still focuses on 2 to 14 days. Complications can include pneumonia, respiratory failure, and multisystem organ failure. Certainly, the deaths that have been reported are more common in people with underlying illnesses and on the older age spectrum.

In terms of prevention and treatment, there is no specific antiviral treatment licensed for COVID-19. A variety of products that are licensed for other reasons are being investigated for their potential role in COVID-19 treatment. In general, the same everyday preventive actions are recommended that would be utilized for any respiratory disease:

- Wash your hands often with soap and water for at least 20 seconds; use an alcohol-based hand sanitizer with at least 60% alcohol if soap and water are not readily available
- Avoid touching your eyes, nose, and mouth with unwashed hands
- Avoid close contact with people who are sick
- Stay home when you are sick
- Cover your cough or sneeze with a tissue, then throw it away
- Clean and disinfect frequently touched objects and surfaces

Because there is no specific antiviral treatment, general treatment for patients has been supportive care to relieve symptoms and manage pneumonia and respiratory failure. As of that morning, the US cases have been/are generally doing well. They are on the less severe end of the spectrum and are recovering. However, several have required oxygen.

CDC has a lot of information online about COVID-19. The website is the place where CDC tries every day to ensure that the information, guidance, and communication materials are as up-to-date as possible. The agency has tried to include information that is helpful to every sector of the community, including public facing materials, materials for providers, and materials for public health. Information can be located at the following URLs:

- Latest COVID-19 information for the public (www.cdc.gov/COVID19)
- CDC's travel health notices (wwwnc.cdc.gov/travel/notices)

CDC is recommending seeking medical care if one feels sick with fever, cough, or difficulty breathing and have a travel history to China or were in close contact with someone with COVID-19 in the 14 days before beginning to feel sick. This is the current definition. It is useful to know that of the 12 patients in the US who had travel-associated COVID-19, many returned to the US and were asymptomatic upon return. They received information somewhere along their route that told them this exact information, they followed it, and were diagnosed with minimal exposure to other people. As the disease continues to spread globally, CDC is certainly reviewing these case definitions. This is an outbreak for which day-by-day and sometimes many times a day, there is new information that CDC is synthesizing and incorporating into the recommendations.

In terms of what CDC is doing, a major part of the early strategy is travel recommendations. CDC recognizes that any border control strategies are not absolute. The reason for these strategies is to try to slow entry of this disease in the US, knowing that the borders cannot be sealed off. There was a Presidential Proclamation suspending entry of foreign nationals who visited China within the past 14 days into US, exempting immediate family members of US citizens and legal permanent residents. Enhanced entry screening is being done for anyone coming in from China through 11 airports.

There are a variety of travel alerts, which include the following:

Level 3 (Avoid Non-Essential Travel)	Level 2	Level 1
China	Iran	Hong Kong
South Korea	Italy	
	Japan	

State and local readiness is a key part of any strategy in terms of preparedness and response, as it is for everything that CDC does. CDC is dependent upon states for their active monitoring of health of travelers from China. It is also very important that the state and local health departments are pivoting to assess state and local readiness to implement community mitigation measures if these become necessary. They are working to identify and mitigate gaps in readiness to reduce disease spread while protecting workers, infrastructure, and institutions. They are also linking public health agencies and healthcare systems to identify and mitigate stressors to the health system. Even if not in a COVID-19 outbreak, these are still activities that state and local health departments are already doing. Everything that CDC is doing with states is built on eons of preparedness work that has been ongoing in states, as well as at CDC.

Engagement with public health and the healthcare sector is important. CDC engages in calls every day with at least some portion of core public health partners, such as the National Association of County and City Health Officials (NACCHO), the Council of State and Territorial Epidemiologists (CSTE), the Association of Public Health Laboratories (APHL), and the Association of State and Territorial Health Officers (ASTHO). They also are speaking with multiple subsets of these organizations. There are bi-weekly private sector calls as well. CDC is also engaged in governmental outreach including Attorneys General, Mayors, and Governors, all of whom have a stake in this effort. In addition, there are multiple conversations with public health associations including webinars, podcasts, and conference calls.

A major part of any strategy to control a disease like this is preparing first responders, healthcare providers, and healthcare systems. This is a whole of government effort to: 1) establish plans to understand healthcare use and potential surges; 2) develop [guidance](#) on infection control, hospital preparedness assessments, personal protective equipment (PPE) supply planning, and clinical evaluation and management; 3) reinforce infection control principles to ensure that the healthcare practitioners who are treating these patients are kept safe; 4) leverage existing telehealth tools; and 5) engage supply chain partners to understand supply usage and needs. Again, a lot of this information can be found on the CDC website.

If this disease continues to spread globally, it is possible that there will be community spread in the US. As the outbreak has surged in the past week, public health has become increasingly concerned that at some point in the future, community spread may be seen. It should not be a surprise with a respiratory viral disease spreading like this that there might be community spread. What they are asking of folks in the community and family readiness space is to start preparing for that. While they are not asking anyone to implement changes, they are asking them to be prepared so that if these changes need to be implemented, people have already had the conversations. CDC is developing [business guidance](#) for public and private sectors adaptations like telework and flexible sick leave policies. These are the same kinds of things CDC worked on in the last influenza pandemic, so they have a head start in doing some of this. The agency is publishing guidance for childcare programs, K-12 schools, and colleges and universities in case, for example, schools need to be on hiatus at some level. Other countries have done this. CDC wants schools, systems, and families to have thought in advance about how this might be implemented. CDC is providing planning guides for use by families, community- and faith-based organizations, and event planners of mass gatherings. In addition, CDC believes that it is important to educate communities about non-pharmaceutical interventions (NPIs).

Work has already begun on vaccines on the fastest possible path. There are multiple vaccine candidates in the US and globally, including one on which NIH is working. Even as fast as that possibly could be, the timeline for that is 12 months—optimistically. This makes it even more important to think through NPIs. If there is indeed broader spread in the US and it is necessary to implement interventions, social distancing is one of the tools upon which it may be necessary to rely. This is why CDC has been pushing folks to think in advance about NPIs.

Discussion Points

On behalf of everyone in the room, Dr. Schaffner (NFID) expressed enormous appreciation to Dr. Messonnier for all she is doing and the leadership she is providing. This resulted in a standing ovation for Dr. Messonnier. In terms of testing, Dr. Schaffner conveyed that there is a desire in the infectious disease community to assist in the diagnosis of cases as early as possible and everyone would love to start testing more frequently than they are able to now.

Dr. Messonnier responded that they should celebrate the successes and admit the places where things have not gone as smoothly as they would like. CDC's partners in China posted the sequences of the strain within two weeks of public announcement of the outbreak, which is remarkable. CDC scientists were able to rapidly turn that genetic sequencing data into diagnostics that were rapidly available in the US under an FDA Emergency Use Authorization (EUA). This meant that CDC was able to start testing. The first case in the US was identified with that RT-PCR kit. CDC's desire has been to get this test out to its state and local partners as quickly as possible. In doing that and doing the quality control that would be expected of CDC to ensure that the test was as perfect as possible, some of the state and local health departments

ran into problems in terms of assuring quality control. Only 12 state and local health departments are currently using the test. CDC is moving as quickly as possible in very close partnership with the FDA to disseminate the test to the rest of the public health laboratories in the US. To do what Dr. Schaffner is asking and what everyone wants, commercial availability of these kits is key. It is commercial availability that would provide the tool to a clinician who needs to test. Certainly, that is everyone's goal. CDC is working very closely with the FDA to get that moving forward. That is why right after CDC grew the virus, they put it at the NIH's BEI Resources Repository on purpose because the agency wants to facilitate commercial companies turning the diagnostics into a commercially available product. That is moving as quickly as the community can make it move. That is never fast enough, but it is their intention.

Dr. Weber (SHEA) suggested that there are two things he thinks CDC can help with, the testing and PPE, including N95 masks and ventilators, so that they can be prepared in case there are large numbers of patients. He noted that the University of North Carolina (UNC) has one of the world's experts in coronaviruses, Dr. Ralph Baric. UNC has already developed its own test that is sensitive and specific, and has been approved by the county health director, state epidemiologist, and the health department. They plan to begin testing using it as a research test and sending parallel tests to CDC. This would allow them to treat a person as a suspect case and protect their health care personnel and the community pending the CDC test. Based on the recent FDA communication, their laboratory directors feel that they are unable to use that test. They did develop their own test for SARS, MERS, and 2009 novel influenza. He expressed hope that CDC would get the FDA to allow UNC to begin using the test on a research basis until CDC pushes their tests out. They do not know what is in the Strategic National Stockpile (SNS). They know that for N95 respirators, they need to train people per Occupational Safety and Health Administration (OSHA), and train respiratory therapists if ventilators are needed. Realizing that it may not be prudent to release all of the numbers about where they are stored and how much, it would at least help if states knew what is stored so that they can be prepared with trained people if they need that equipment as opposed to reading manuals the day it arrives.

Dr. Messonnier responded that FDA has oversight over the diagnostic tests. She inquired as to whether the FDA liaison were equipped to speak to that. She emphasized that it was well-heard and their FDA colleagues are in lock-step with CDC in trying to resolve this problem. In terms of the second question, the SNS is not a CDC resource. It belongs to the Assistant Secretary for Preparedness and Response (ASPR), so she could not speak directly to that question. However, this issue is a major focus of CDC's preparedness activities. The importance of PPE to protect the healthcare sector is vitally important to CDC. There is guidance on the website that focuses on the use side. If they have models of a prolonged outbreak, which they do, there is a potential to have supply issues. It really depends upon how long an outbreak lasts and the severity. CDC is asking the healthcare sector now to use the CDC guidance to think through how they might be sparing of those resources in the eventuality that they might be needed later.

Dr. Fink (FDA) said he wished he was equipped, but the testing is under a different center entirely.

Dr. Maldonado (AAP) echoed the sentiments regarding the laboratory tests. Stanford also has a PCR that looks pretty sensitive and specific and they are just waiting to be able to use it. The reason that is important is that right now, they are doing well even in California where a number of people are coming in from the Pacific Rim area. If they think that there may be other places where screening needs to be done, there may wind up a surge in the hospital. While they can handle this, as with 2009 H1N1 it will be difficult to cohort patients together if it is not clear how

to separate them, and this could result in more transmission. Given there is a Level 2 travel advisory now for Iran, Italy, and Japan, university students are coming back and people wonder whether they should be treated with self-isolation. They are doing that for healthcare workers who have returned from South Korea. The question remains whether isolation should be recommended for Level 2 and wondered whether updates would be coming soon about what is going to occur in Europe.

Dr. Messonnier emphasized that this is proceeding in real-time. It has been only 2 months and there is not enough of a track record of this pathogen. Everything they are learning is in some ways new. While they can base information on what they have learned from other viruses, everything that is being learned must be considered, synthesized, and tracked to determine how it impacts the response. Right now, CDC is not recommending that travelers from Italy be treated that way because widespread transmission has not been shown. CDC and CSTE are struggling together regarding the question of what the definition is for “persons under investigation (PUI).”

Dr. Hahn (CSTE) emphasized that things are changing very fast. One discussion regards the increasing number of countries being added into the higher levels, which is changing daily, and the fact that there is no way public health can track everyone coming back from Europe. It will become untenable at a certain point to track travelers. As they all work together, they probably will make a plan to have a lower level for other countries as they come on board. Public health simply cannot maintain and track those. Very robust conversations are underway with regard to moving into Phase 2 of the response and the realization that the virus cannot be kept out. She expressed hope that in the next couple of days, there would be some reflections on the CDC website about some of the decisions being made.

Dr. Messonnier expressed appreciation for everyone’s support, as many have been planning for a pandemic for their entire careers. That planning is exactly what CDC is depending on, and is equally depending on all of the sectors of the healthcare community that they have all built relationships with and worked with for many years. This is a setting in which it is going to take the entire village to be able to respond. They need to prepare for something serious. Of course, they are all going to hope that this is not what comes to pass. But, it really is the community of everyone that will get the US ready.

Dr. Bernstein stressed that Dr. Messonnier is spearheading a truly impressive effort by CDC in such an amazingly short timeframe. The knowledge and experiences from past pandemics seem to be helping guide emergency readiness preparation that is making a huge difference in informing and educating the public in the US and around the world. He expressed gratitude to Dr. Messonnier and the hundreds of CDC personnel for their ongoing job well done. He thinks this has only just begun and a lot more will unfold as time goes on.

Dr. Messonnier closed by saying that she happens to be the most visible face at the moment, but the entire leadership of the agency is at the table working on this. CDC’s Incident Manager is Dr. Dan Jernigan who many know as the Flu Czar. They are drawing upon the entire expertise of the agency, so this is pulling everyone in together to make this work.

Influenza

Introduction

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

Dr. Atmar reminded everyone that during the October 2019 ACIP meeting there was an overview of early 2019-2020 season influenza activity; a presentation from Sanofi Pasteur of a pre-licensure study of quadrivalent high-dose inactivated influenza vaccine (IIV), Fluzone® High-Dose Quadrivalent, which was subsequently licensed by FDA on November 4, 2019; and a discussion of a planned systematic review of influenza vaccines for older adults.

Since October 2019, the WG heard a presentation and discussion of preliminary safety results from a comparative study of adjuvanted and high-dose inactivated vaccines among persons 65 years of age and older; heard a presentation from Seqirus™ of a pre-licensure study of quadrivalent adjuvanted inactivated influenza vaccine, FLUAD® Quadrivalent that was licensed by FDA on February 21, 2020; and discussed selection of efficacy/effectiveness and safety outcomes for review of influenza vaccines for older adults.

The agenda for this session included the following presentations:

- Older Adult (65+) Adjuvanted Quadrivalent Influenza Vaccine (aIIV4) Phase III Trial
- 2019-20 US Influenza Surveillance Update
- Interim Estimates of 2019–20 Seasonal Influenza Vaccine Effectiveness against Medically Attended Influenza from the US Flu VE Network
- Safety of Adjuvanted vs. High-Dose Inactivated Influenza Vaccines in Older Adults: Preliminary Safety Results
- Summary and WG Considerations

Older Adult (65+) Adjuvanted Quadrivalent Influenza Vaccine (aIIV4) Phase III Trial

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

Dr. Sylvester expressed gratitude for the opportunity to present the results of the pivotal Phase III trial evaluating the efficacy of the Seqirus™ adjuvanted quadrivalent influenza vaccine (aIIV4), also known as FLUAD® Quad. This vaccine is now licensed in the US for persons 65 years of age and older.

In terms of background, MF59® adjuvanted trivalent influenza vaccine (aIIV3) or FLUAD® Trivalent was licensed based on immunogenicity criteria and has been in use for over 20 years. It was first licensed in Europe in 1997 and FLUAD® Trivalent was approved by the FDA in November 2015 for US in individuals 65 years of age and older. Several effectiveness studies have been conducted with FLUAD® Trivalent and have provided evidence of clinical benefit compared to standard influenza vaccines¹⁻⁴. Because FLUAD® Trivalent was licensed under an

accelerated pathway with the FDA using immunogenicity results, there was a post-marketing commitment to conduct an efficacy trial. Seqirus™ negotiated with the FDA to fulfill this post-marketing commitment with a trial using the quadrivalent instead of the trivalent, which Dr. Sylvester presented during this session [¹Mannino S, et al. *Am J Epidemiol.* 2012;176:527-533; ²Van Buynder PG, et al. *Vaccine.* 2013;31:6122-6128; ³Lapi F, et al. *Expert Rev Vaccines.* 2019 Jun;18(6):663-670; and ⁴Peabody R, et al. *Vaccine.* 2019].

The trial was an absolute efficacy study in subjects 65 years of age and older conducted over 2 consecutive influenza seasons, one in the Northern Hemisphere for the 2016-2017 season and the other in 2017 in the Southern Hemisphere. It is important to note that the predominant circulating strain during the study period was A/H3N2. Over 6600 subjects were randomized 1:1 to receive 0.5-mL of FLUAD® Quad or a non-influenza comparator, the combination vaccine of tetanus, diphtheria, and acellular pertussis (Tdap/Boostrix®). This was a multi-center study conducted in 12 countries (Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand and Turkey).

The study was case-driven. To analyze the results, at least 238 PCR-confirmed cases were needed to demonstrate the primary endpoint of the study, which was the efficacy of PCR-confirmed influenza regardless of the match of the virus with the vaccine strain and with a lower bound of the 95% confidence limit of >40% as negotiated with Center for Biologics Evaluation and Research (CBER). Secondary endpoints included efficacy against strains antigenically matched to the vaccine strains for those isolates that were culture-positive with the same lower bound of >40%. A subset of participants also were evaluated for immunogenicity in both vaccine groups by hemagglutinin inhibition (HI) assay 3 weeks after vaccination. The primary safety objective was to evaluate the safety of FLUAD® Quad through the assessment of local and systemic solicited and unsolicited adverse events for the entire study period up to one year.

This was a randomized observer-blinded study in which the two treatment groups were well-matched demographically. The majority were between the ages of 65 and 75 years of age. Given the countries where the study was performed, 80% of the subjects self-reported either being white or Asian. The comorbidity score is based upon a published paper by Hak et al in which a comorbidity score of <50 is predictive of a lower risk of influenza-related complications [Hak E, et al. *J Infect Dis.* 2004 Feb 1;189(3):450-8].

In terms of the subject flow for the study, over 6600 subjects were randomized 1:1 as noted earlier to receive 0.5-mL of FLUAD® Quad (n=3394) or Boostrix® (n=3396). Blood samples from approximately 2800 subjects were collected at Day 1 to baseline and Day 22 for immunogenicity assessment. As mentioned earlier, the primary endpoint was absolute VE against PCR-confirmed influenza due to any strain and the secondary endpoint was Absolute vaccine efficacy against culture-confirmed influenza due to strains antigenically matched to the vaccine strains.

Regarding the immunogenicity results, FLUAD® Quad elicited good HI titers for all strains. Between 60% to 85% of the subjects achieved at least a 4-fold rise in titers, and 80% of the subjects demonstrated titers of ≥1:40 for HI, which satisfied the CBER criteria for immunogenicity for all 4 strains.

In terms of case accrual, there was active surveillance for influenza. All subjects were contacted weekly for 6 months or until the end of the influenza season, whichever was longer, to assess influenza-like illness (ILI) symptoms. The purpose of the active surveillance was to trigger a visit to collect a nasopharyngeal swab at or near the onset of these defined symptoms. Cases also were evaluated based on different definitions of ILI, for which the primary study endpoint was “at

least one respiratory and at least one systemic symptom” and the secondary endpoint was “>37.2 °C + cough/sore throat.” These two definitions were included as part of the protocol. Two additional definitions were added post-hoc: “≥37.8 °C + cough/sore throat” and “>38°C + cough.” The main differences between these definitions were the subject’s temperature and the presence of symptoms more specific for influenza moving from the primary and secondary endpoints through the two post-hoc definitions.

In terms of the ILI case accumulation for each of the 4 definitions, moving from the primary, secondary, and post-hoc analysis definitions, the number of ILI cases decrease. However, the proportion of those cases that were PCR-confirmed increases—less sensitive, but more specific for influenza. It is interesting to note that the number of cases that were similar to the vaccine strain were less than 10%, meaning that 90% of the cases were dissimilar to the vaccine strain.

Regarding the primary endpoint of the study, PCR-confirmed influenza regardless of strain. The protocol-defined ILI definition showed an efficacy of about 20% with the lower bound of the 95% confidence interval at >40%, which is a non-significant result per CBER criteria. As the ILI definitions increases in specificity for influenza, the efficacy increases up to 50%. For strains similar to the vaccine, the range of the VE was much higher at 50% to 75%. With so few cases that matched the vaccine strains, the confidence limits are extremely wide and it is necessary to be cautious about drawing inferences from these data.

In terms of safety, local AEs were recorded within the first week. The FLUAD[®] Quad arm had higher rates compared to the Boostrix[®] Tdap arm. These events were mostly mild to moderate and self-limited. The most commonly reported local solicited AE was injection site pain. Administration of FLUAD[®] Quad also was associated with higher rate of frequency of the systemic solicited AEs within the first week of the study compared to the control vaccine. The most frequent reported systemic AEs in both groups were headache, fatigue, myalgia, and arthralgia. Severe systemic solicited AEs were uncommon and varied between 0% to 1.1% of subjects in the FLUAD[®] Quad group and 0.2% to 0.6% of subjects in the Boostrix[®] group.

During a 1-year follow-up, there were no differences between the vaccine groups and the percentage of any of the unsolicited SAEs, unsolicited AEs leading to death, unsolicited AEs leading to premature withdrawal from the study, any new onset of chronic diseases (NOCD) and adverse events of special interest (AESI). Two subjects reported SAEs that were assessed to be related to the study vaccine, one with rheumatoid arthritis (RA) in the FLUAD[®] Quad group and the other with a mild cardio infarction in the Boostrix[®] Tdap. The RA case was assessed by the investigator to be related to the study vaccine. There were no deaths related to the vaccine.

As mentioned earlier, the primary endpoint of the study (PCR-confirmed influenza) showed a VE of 20%, a non-significant result. As the ILI definition became more specific, including higher levels of temperature, the efficacy increased up to 50%. To provide some context to these results, Dr. Sylvester shared VE data during the time period this study was conducted. There have been multiple published test-negative design studies from the Northern and Southern Hemispheres showing fairly low VE in subjects 65 years of age and older at about 20% against all strains. In Europe, overall VE was 38% and VE in those 65 years of age and older was 23%. In the US, overall was 40% and in those 65 years of age and older was 20%. In Australia, overall was 33% and in those 65 years of age and older was -12%.

With regard to the study limitation, the study was relatively short at a little over a year over the two seasons and was dominated by H3N2 circulating strains. There was a wide range of circulating antigenically and genetically different strains of influenza A/H3N2. As noted earlier,

over 90% of the culture-confirmed influenza isolates were antigenically different from the strains in the vaccine. In the demographics, the study population was relatively healthy.

In conclusion, FLUAD[®] Quad elicited a robust immune response for all 4 strains, satisfying the CBER criteria for immunogenicity. The FLUAD[®] Quad VE results were 19.8% to 51% depending upon the ILI definition and symptomatology. FLUAD[®] Quad had an expected and acceptable tolerability profile similar to FLUAD[®] Trivalent vaccine. FLUAD[®] Quad received FDA licensure on February 21, 2020.

Discussion Points

Referring to Slide 15 and the increasing efficacy, Dr. Talbot said her suspicion was that the increasing temperature requirement was dropping off the old of the old. In addition, she noted that Slide 26 appeared to refer to the world's circulation, and wondered what the Seqirus[™] sequencing data looked like.

Dr. Sylvester said that others have made this observation. They looked at the difference in the two age groups to see if there was a difference, but there was not. He indicated that Slide 26 was his back-up slide and is larger data, not US data. Regarding the Seqirus[™] sequencing data, they showed only 10% matching so they do have a wide variety. However, he did not have a graph similar to the back-up slide for the world circulation. While he did not have any clinical quantification with him, he indicated that he would find out whether his clinical colleagues could provide that.

Dr. Atmar asked whether the patient with RA in the FLUAD[®] Quad group was in the immunogenicity subgroup and, if so, whether the pre-vaccination sera were evaluated for markers of RA.

Dr. Sylvester responded that the diagnosis was made 7 months and 1 week after the individual, a white male 65 years of age, received the vaccine. He will check to find out whether this patient was part of the blood drawing group.

Dr. Whitley-Williams (NMA) observed that it was disappointing that there were almost no African American or Black populations involved in the study. Given the diversity of this country, the persons who would be eligible for this vaccine, and the health disparities that exist, particularly with influenza vaccine and complications, it is disappointing that there were not efforts to include more of the Black population.

Dr. Sylvester agreed and indicated that moving forward, they are trying to elicit either countries or populations in the US to be able to have a representative sample.

2019-20 U.S. Influenza Surveillance Update

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

Ms. Brammer presented surveillance data from the 2019-2020 influenza season, which was another busy and unusual influenza season. The update she provided represented data through *Morbidity and Mortality Weekly Report (MMWR)* Week 7, which was the week ending February 14, 2020. Based on information from US clinical laboratories, influenza B viruses were

predominant early in the season and influenza A viruses increased as the season progressed. As of Week 7, 29.6% of specimens during that week were positive for influenza and 63.5% were influenza A viruses. Based on the more detailed data from US public health laboratories, 64.9% reported were influenza A during Week 7. That proportion has been increasing. For the season overall, influenza A was a little over 50%. Among the influenza A viruses during Week 7, 96% were influenza A(H1N1)pdm09 viruses. For the season overall, that proportion is 91%. Among the influenza B viruses, the vast majority have belonged to the B(Victoria) lineage at 98%.

Outpatients visits for ILI went above baseline for the first time during the week ending November 9, 2019 and have been above baseline for 15 weeks. There have been 2 peaks. The first occurred during the last week of 2019, with 7.1% of patient visits being for ILI. The second slightly smaller peak occurred during Weeks 5 and 6, which were the last week of January and first week of February when 6.7% of patient visits were for ILI. Based on the state-level ILI data for Week 7, 44 states, New York City (NYC), and Puerto Rico (PR) were still experiencing high levels of ILI similar to the previous week and only 1 state lower than the peak during Week 5. There was a lot of ILI.

Looking at the overall hospitalization rate, during Week 7 that cumulative rate had risen to 47.4 influenza laboratory-confirmed hospitalizations per 100,000 population. Compared to other years, it is higher than some but not particularly high at this point. The rate of hospitalizations for persons 65 years of age and older was 116.7, which is relatively low compared to other seasons. However, the picture is very different for children. Among children 0 to 4 years of age, the cumulative rate thus far is 72.5 per 100,000. This is above what was observed at the end-of-season for both 2017-2018 and 2018-2019 and just below the same week during the second wave of the 2009 pandemic. Children 5 to 17 years of age were higher than any other seasonal influenza season at this point in time and approaching the 2017-2018 and 2018-2019 end-of-season rates, but still well below the pandemic rate.

Adults 18 to 49 years of age also have relatively high hospitalization rates. Their rate for Week 7 is higher than for any other seasonal influenza season, but is still somewhat below the 2017-2018 season, which was their high season. Adults 50 to 64 years of age are starting to look more like adults 65 years of age and older, with hospitalization rates well below the 2017-2018 and 2018-2019 seasons.

In terms of pneumonia- and influenza-associated mortality from the National Center for Health Statistics (NCHS), pneumonia and influenza mortality has been relatively low this year. Mortality has been above the threshold for only 3 weeks, and the amount above the threshold has been fairly small. The peak thus far was 7.5% during the first week of 2020 compared to the threshold of 7.0%. However, looking at influenza-associated pediatric deaths, the picture is different. Thus far this year, there have been 105 influenza-associated pediatric deaths. Unfortunately, it does not look like the rate of reporting of those deaths is slowing at this point. Among children for whom CDC has information, 72 of those deaths were due to influenza B viruses. All 12 that were lineage tested belonged to the B(Victoria Lineage). There were 33 influenza A deaths. Of those, 19 that were subtyped were H1 and 1 was subtyped as H3. Typically, about 20% of these children are vaccinated against influenza. This year is running about the same or somewhat lower.

With regard to impact overall, this is CDC's second year of providing weekly burden estimates as the season progresses. Between October 1, 2019 and February 15, 2020, CDC estimates that there have been at least 29 million influenza illnesses, 13 million medical visits for influenza, 280,000 hospitalizations, and at least 16,000 deaths due to influenza.

Regarding the viruses that have circulated this season, all 563 influenza A(H1N1)pdm09 viruses tested belong to genetic group 6B.1A. There is some genetic diversity within this subclade. All 74 A(H1N1)pdm09 viruses antigenically characterized using a HI assay with ferret antisera were similar to the cell culture-propagated A/Brisbane/02/2018-like reference virus representing the 2019-20 Northern Hemisphere vaccine component. Of the influenza A (H3N2) viruses, 365 of 381 (95.8%) belong to the 3C.2a1 subclade and 16 (4.2%) belong to the 3C.3a clade. This was the clade that emerged last season and became predominant by the end of the season. Although the majority of the viruses belonged to the 3C.2a1 subclade, 31 of 72 (43.1%) of the A(H3N2) viruses antigenically characterized by FRA were well-inhibited by ferret antisera raised against A/Kansas/14/2017 (3C.3a), a cell-propagated reference virus representing the A(H3N2) component of 2019-20 Northern Hemisphere influenza vaccines.

Two genetic groups of B/Victoria lineage viruses are co-circulating, V1A.1 and V1A.3. Of the B/Victoria lineage, 50 of 655 (7.6%) viruses belonged to the V1A.1 subclade, which is the virus with a 2-amino acid deletion. The remaining 605 belonged to the V1A.3 subclade, which had a 3-amino acid deletion. The B/Colorado/06/2017 reference virus representing the B/Victoria lineage virus in the 2019-2020 Northern Hemisphere vaccines belongs to the V1A.1 subclade. Again, even though the majority of the viruses are in a different genetic group from the vaccine, 53 of 88 (60.2%) of the B/Victoria lineage viruses antigenically characterized by HI using ferret antisera were similar to the cell-propagated B/Colorado/06/2017-like V1A.1 reference virus. This again indicates that there is cross-reactivity between these genetic groups among the B/Victoria similar to the H3N2 viruses.

All B/Yamagata lineage viruses tested belong to a single genetic group, Y3, of which very few were seen this season. All influenza B/Yamagata-lineage viruses antigenically characterized are similar to cell-propagated B/Phuket/3073/2013 (Y3), the reference vaccine virus representing the influenza B/Yamagata-lineage component of the 2019-2020 Northern Hemisphere quadrivalent vaccines.

The WHO Consultation on the Composition of Influenza Virus Vaccines for Use in the 2020-2021 Northern Hemisphere Influenza Season is taking place February 24-28, 2020. That will be announced on February 28th and will be followed on March 4, 2020 by a meeting of FDA's Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC), who will make the US-specific recommendations for next season's vaccine.

In summary, influenza activity remains elevated. Influenza B/Victoria lineage viruses predominated early in the season, but A(H1N1)pdm09 viruses have increased in recent weeks. For the season overall, approximately equal numbers of B/Victoria and A(H1N1) have been reported. Overall severity has been low, but hospitalization rates among children and young adults have been high. So far, 105 influenza-associated deaths in children have been reported.

Interim Estimates of 2019–2020 Seasonal Influenza Vaccine Effectiveness Against Medically Attended Influenza from the US Flu VE Network

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

Dr. Flannery shared the following table to connect the genetic strains together with the names of the 2019-2020 Northern Hemisphere influenza vaccine components:

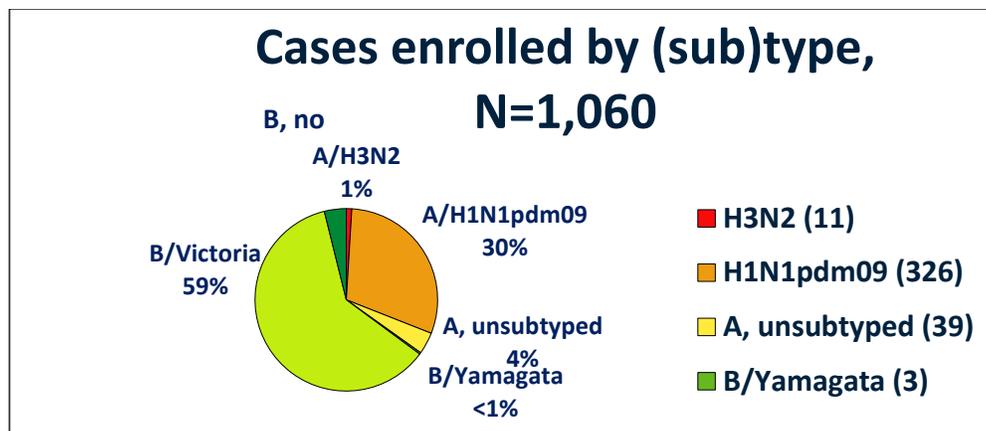
A(H1N1)pdm09	A/Brisbane/02/2018 (6B.1A)
A(H3N2)	A/Kansas/14/2017 (3C.3a)
B Victoria	B/Colorado/06/2017 (V1A.1)
B Yamagata	B/Phuket/3073/2013 (Y3)

He presented data from the 5 US Flu VE Network sites with which CDC has cooperative agreements. The sites and Principal Investigators (PIs) are as follows:

- Baylor Scott and White Health (Manju Gaglani)
- Kaiser Permanente Washington (Mike Jackson & Lisa Jackson)
- Marshfield Clinic Research Institute (Ed Belongia & Huong McLean)
- University of Michigan (Arnold Monto & Emily Martin)
- University of Pittsburgh (Rick Zimmerman & Tricia Nowalk)

The methods are the same as have been used previously for the interim estimates. As a reminder, the case definition includes acute respiratory illness with a cough, so it is a more sensitive case definition for surveillance than the CDC ILI definition that includes fever. The clinics in these sites enroll outpatients >6 months of age with acute respiratory illness with cough ≤7 days duration. The data for this presentation included enrollment between October 23, 2019 through January 25, 2020. The test-negative design used compares vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls. The vaccination status for these interim reports is based on receipt of at least one dose of the current season's vaccine. Vaccination status is determined based on a combination of medical records, immunization registries, and/or self-report. They do not have data on vaccine type-specific VE, but will have this at the end of the season when these documented records are all available. They can say that the vast majority of the vaccinated people in this dataset have received some type of injectable inactivated vaccine and not live attenuated influenza vaccine (LAIV). Fewer than 10 children in this dataset received LAIV, so there are no estimates for LAIV at this time. The adjusted estimates include study site, age, sex, self-rated general health status, race/Hispanic ethnicity, interval from onset to enrollment, and a 2-week interval for calendar time.

There were 4112 participants enrolled from October 23, 2019 through January 25, 2020 at 52 clinics at 5 sites. About 1060 (26%) tested influenza RT-PCR positive and about 3052 (74%) in the control group test influenza RT-PCR negative. The distribution, type, and subtype are shown in the following pie graph:



As Ms. Brammer showed earlier, at the beginning of the seasons more B/Victoria was circulating than H1N1. Since that time, there has been more H1N1 than B/Victoria. Those continue to be the predominant influenza viruses circulating in the VE Network sites.

As a reminder, the enrolled participants are people presenting with acute respiratory illness (ARI) of all ages. Laboratory-confirmed influenza accounts for more than 40% of all ARI in these clinics during the peak of the season. They are maintaining about 40% positivity for enrollment currently.

In terms of the overall VE against any influenza, about 37% of the influenza positives were vaccinated and about 55% of the influenza negatives were vaccinated. The unadjusted estimate was 53%. After adjustment, the overall VE of this interim estimate is 45% with a confidence interval from 36% to 53%. Some age group difference is observed in VE. The estimate for those 18 to 49 years of age is 25%. All 3 age-specific estimates are statistically significant.

The overall estimate for B/Victoria was 50%, the 6 months to 17 years of age estimate was 56%, and the 18 years of age and older estimate has been combined because there were too few cases in the 50 year of age and older group to separate that out. There really is a shift in the age distribution of influenza B at the study sites toward the younger population. The estimate in those 18 years of age and older was somewhat lower at 32%, but was still statistically significant. In terms of some of the sequencing that has been done for viruses that are collected from the Flu VE Network. Out of the 670 influenza positives, 262 B/Victoria viruses have been sequenced. Among those, 256 (98%) V1A.3 (2020 S. Hemisphere vaccine component, which is not the genetic group V1A.1 in the current vaccine.

Regarding H1N1-specific VE, overall VE was 37% with confidence intervals from 19% to 52%. The age-specific estimates show a great deal of difference from two significant estimates of 51% in the 6 month to 17 years group and 50% in the 50 and older group. However, VE was 5% and not significant for those 18 to 49 years of age. The data from sequencing is not very informative in that at this level, the sequencing identified 94 (100%) of the H1N1 viruses from the Flu VE Network as belonging to the vaccine genetic group 6B.1A. There has been some variety in the H1N1 viruses that are circulating. It is unknown whether that is related to the lower VE among those 18 to 49 years of age at this point.

These data from the US were published the week before this meeting in the *MMWR*. In *Eurosurveillance* during the same week, CDC's colleagues from Canada presented the VE estimates for the 2019-2020 seasons for Canada. The vast majority of their estimate for influenza B, which includes all influenza B, are B/Victoria. Canada's estimates are slightly higher than the US estimate for influenza B, but are comparably reassuring in that the vaccine in Canada does seem to provide protection against the majority B/Victoria virus that is the triple deletion and not the virus that is in the Northern Hemisphere vaccine formulation. The second piece of data from Canada is that they did have enough H3N2 in their surveillance network to provide an All Ages and a 20-64 year old estimate. The main H3N2 virus, like in the US, is not the subclade or clade that is in the vaccine, the 3C.3a. As in the US, Canada is seeing a majority of 3C.2a1 virus. Again, this is evidence that vaccine is providing some protection despite circulation of virus that is actually different from the genetic group that is in the vaccine. The H1N1 estimates that differ in Canada from what is observed in the US Flu VE Network at this point is that their All Ages estimate is 44%, which is very similar to the US All Ages estimate. The estimate for 1 to 19 year olds 63% and for 20 to 64 year olds is 39%, which although slightly lower than in previous seasons in Canada in the 1 to 19 year olds is higher and statistically significant than what is seen in the US Flu VE Network [Skowronski et al, *Eurosurveillance* 21 Feb 2020. www.eurosurveillance.org].

The other thing to put this into context is the pyramid from the website that shows over the past 10 years or since the pandemic, the number of deaths hospitalizations, and illnesses that occur in each influenza season. The higher limits are from the 2017-2018 season shown in the table on the right. The last season had 35 million estimated illnesses, almost half a million hospitalizations, and 34,000 deaths. The deaths, hospitalizations, and cases averted by vaccination last season were published in January 2020 by Chung et al in *Clinical Infectious Diseases*. End-of-season VE for the 2018-2019 season was around 26%. There was very low effectiveness against H3 that predominated for half of the season. Despite that disappointingly low effectiveness, the deaths, hospitalizations, and cases averted are still substantial. Estimates from the 2019-2020 season are expected sometime in Fall 2020.

In summary, the interim estimates from the 2019-2020 season indicate that vaccination reduced medically-attended illness due to any influenza virus type by 45% (CI: 36 to 53) based on enrollment through January 25, 2020. Encouraging signs are seen of VE of 55% against any influenza in children who have been hit particularly hard by influenza this season. Vaccination provided 50% (CI: 39 to 59) protection against the predominant influenza B/Victoria virus (clade V1A.3). Overall effectiveness against H1N1pdm09 was 37% (CI: 19 to 52). As H1N1pdm09 circulation has increased since January 2020, increased enrollment is expected to improve the precision of age-specific estimates later in the seasons.

Discussion Points

Regarding the test negative design, Dr. Lee asked whether the reason for the lower effectiveness rate in the 18 to 49 year olds had anything to do with household vaccination rates in terms of whether they know if these are parents of children who were vaccinated, which somehow may influence the estimates for that age group. In addition, she wondered whether infant deaths looked similar to prior years in which approximately 50% of the infants were completely healthy and whether there was any information about comorbidities.

Dr. Flannery responded that the test negative design does not really account for indirect effects, and indirect effects are relatively hard to measure. It is a pretty good design for individual effects of the vaccine. The main reason for the test negative design is to control for differences in the population in health-seeking behavior among those who are vaccinated and those who are not vaccinated. If there is individual protection of influenza vaccine, it should be seen with this design even if there is a large indirect effect if that age group is having more exposure to young children or where the vaccine is less likely to work because they have some intense exposure. Just to put this in perspective for last year's H1N1 estimates, good effectiveness was observed in that same age group. There was a change in the vaccine virus and in what was circulating, but there was effectiveness of H1N1 for last year's vaccine at this time, which is not seen this year.

Ms. Brammer indicated that this year is similar in terms of infant deaths in that 53.5% of the infants had no previous medical conditions.

Dr. Bernstein asked whether there was an explanation for the fact that the B/Victoria strain in circulation is not matching the vaccine strain well, yet VE in children was 55% in the younger age group.

Dr. Flannery clarified that the point he did not make in the presentation was that the B/Victoria VE this season with the difference in the genetic group of what is circulating from what is in the vaccine is similar and in the same range of VE that has been seen against B/Victoria in seasons where it has been well-matched. It is difficult when it is said not to be matched, because that is usually based on antigenic differences. As Ms. Brammer showed, the antigenic differences are not so clear in the comparison. The majority of viruses that have been antigenically characterized, or 60%, still show as similar to the vaccine virus. There is obviously some cross-reactivity, which is good news for children. It is somewhat surprising that the VE against B/Victoria is as high as it is in children with both the severity of the season and the vaccine being different from what is circulating. At this point, it is reassuring that the vaccine is providing protection. Low VE cannot be said to be contributing to the particularly bad season that is occurring, given that some protection is being seen.

Dr. Frey asked how many of the children who died were vaccinated.

Dr. Brammer indicated that among the children who died, the vaccination rate is very similar to what has been seen in previous seasons in which only about 20% of the children are vaccinated. Through Week 7, with the limited information CDC has, it is 16.6% so far this year.

Safety of Adjuvanted vs. High-Dose Inactivated Influenza Vaccines in Older Adults: Preliminary Safety Results

Kenneth Schmader, MD
Duke University Medical Center

Dr. Schmader presented the preliminary results of the study of the safety of adjuvanted versus high-dose IIV in older adults. He noted that this work was supported by CDC through the Clinical Immunization Safety Assessment (CISA) Project in collaboration with Duke University Medical Center (Lead Site), Boston University Medical Center (Contributing Site), and Cincinnati Children's Hospital Medical Center (Contributing Site, Boston University Sub-Contract). He also noted that the findings and conclusions in this presentation were those of the presenter and do not necessarily represent the official position of CDC.

In terms of the rationale behind the study to prevent influenza in older persons, ACIP recommends vaccination with any US-licensed, age-appropriate influenza vaccine. The trivalent high-dose (HD-IIV3; Fluzone[®] High-Dose) and adjuvanted (aIIV3; FLUAD[®]) influenza vaccines are licensed for use only in persons aged 65 years and older in the US and may have improved effectiveness compared to standard dose (SD)-IIV3. Therefore, clinicians and patients have an important choice to make. Important factors in making that choice are safety and reactogenicity. However, the safety of HD-IIV3 and aIIV3 has not been compared directly head-to-head in the same clinical trial in the US. Furthermore, the relative impact of HD-IIV3 and aIIV3 reactions on health-related quality of life (HRQOL) has not been studied. That is a novel component of this study.

The first primary study objective was to compare the proportions of moderate-severe injection-site pain after aIIV3 and HD-IIV3. This was selected as a primary objective because injection-site pain likely would be causally related to the vaccine, and pain that is moderate (defined as some limitation in normal daily activities) or severe (defined as completely unable to perform normal daily activities) are obviously clinically meaningful. The hypothesis was that the proportion of subjects who have moderate-severe injection-site pain within the first week post-vaccination will be non-inferior (not higher) for aIIV3 compared to HD-IIV3. The rationale for the non-inferior analysis lay in the fact that the adjuvanted vaccine was licensed in 2015 as the first adjuvanted influenza vaccine used in the US; whereas, HD-IIV3 was selected as a comparator because it had been licensed in the US since 2010 and at the time of the study was in wide use. There was substantive evidence supporting its safety. The co-primary study objective was to compare SAEs and adverse events of clinical interest (AECI) after aIIV3 and HD-IIV3 in the study population and by age-groups of 65-79 years and ≥ 80 years. Due to time limitations, Dr. Schmader presented on the results for the full study population, not the age group analysis. The secondary endpoints were to: 1) compare the proportions of local and systemic reactions (other than moderate-severe injection-site pain) after aIIV3 and HD-IIV3 in the full study population and by age group (65-79 years and ≥ 80 years); and 2) describe and compare change in HRQOL after aIIV3 and HD-IIV3 in the full study population and by age group.

In terms of the study design and participants, this was a randomized, blinded clinical trial of aIIV3 versus HD-IIV3 during the 2017-2018 and 2018-2019 influenza seasons. The sites were Duke University (2017-2019), Boston University (2017-2019), and Cincinnati Children's Hospital Medical Center (2018-2019). The participants were community-dwelling volunteers aged ≥ 65 years of age with the main eligibility criteria being not being immunosuppressed, being cognitively intact, having no co-vaccination, and having no influenza vaccine contraindications. The goal was to enroll $\geq 20\%$ individuals aged ≥ 80 years. The participants were randomized 1:1 to receive a 0.5 ml intramuscular (IM) dose of aIIV3 or HD-IIV3 and stratified by age group (65-79) and (≥ 80) years. For the safety and reactogenicity assessments, participants were monitored in clinic ≥ 15 minutes post-vaccination for AEs, including syncope. Solicited reactogenicity events and unsolicited AEs were assessed using a standard symptom diary starting at Day 1 (vaccination day) through Day 8. SAEs were assessed during Day 1 through Day 43 post-vaccination. AECIs included syncope during clinic post-vaccination monitoring, anaphylaxis in first 24 hours after vaccination, and Guillain-Barré syndrome (GBS) within 43 days post-vaccination, and new onset immune-mediated conditions within 43 days post-vaccination.

For the HRQOL assessments for both seasons, the main measure was the EuroQOL-5 dimensions-5 levels (EQ-5D-5L). This measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses were converted to a utility index summary measure that ranges from -0.109 (worst health) to 1.000 (best health). The EuroQol-Visual Analogue Scale (EQ-VAS) also was used, which is a self-rated health measure in a thermometer format on a 0 to 100 scale with 100 being the best imaginable health stage and 0 being the worst in the participant's estimate on that day.

The sample size estimate was 668 participants, with 334 per group. This assumed that 5% of older adults have moderate to severe injection-site pain after allV3 or HD-IIV3 based on prelicensure studies, a clinically meaningful non-inferiority margin of 5%, a one-sided alpha of 0.025, and at least 80% power to demonstrate proportion of moderate-severe pain non-inferior after allV3 versus HD-IIV3. For the primary outcome of moderate to severe injection site pain, the investigators used a one-sided alpha of 0.025 level, an upper bound of a stratified by site Newcombe binomial confidence interval, and a non-inferiority margin of 5%.

Regarding the results, a total of 778 participants were assessed for eligibility. Of those, 21 were excluded as 13 did not meet the eligibility requirements and 8 declined to participate. A total of 757 were randomized. The Full Analysis Population 1 was comprised of individuals who were randomized, vaccinated, and had at least one day of symptom diary data. This population was used for SAEs, AECIs, and HRQOL analyses. The Full Analysis Population 2 were individuals who were randomized and vaccinated, and this was for injection site and all other reactions. There were 2 people missing symptom diary data in the HD-IIV3 group, so there were 377 in that group.

In terms of the summary of participants enrolled and randomized by site, it is important to note that 21.5% of the participants were ≥ 80 years of age. This met the goal of 20% or more. Regarding demographic characteristics, the median age was 72 years. The percentage of females was similar in both groups at 56% for allV3 and 54% for HD-IIV3. For reference, females represent 56% of the general US population over age 65 based on 2018 data. With respect to race, 76% to 80% of participants were white and 15% to 18% were Black. Again, for reference, in the general US population over 65 years of age, 77% are white and 13% are Black. The investigators measured 15 other chronic medical conditions (cardiovascular, respiratory, and others) in older adults and found them to be equally balanced between the two groups.

Regarding the primary outcome results for injection site pain, the majority of individuals in both groups reported no injection site pain. For moderate to severe pain, the allV3 group was 3.2% and the HD-IIV3 group was 5.8%. For the non-inferiority analysis, the percent difference was calculated for allV3 minus HD-IIV3, which was -2.7%. The upper limit of the 95% CI of the difference for allV3 minus HD-IIV3 was 0.36% and the noninferiority margin was 5%. The proportion of participants with moderate to severe injection-site pain after allV3 was non-inferior (not higher) than the proportion after HD-IIV3. For the co-primary objective, no SAEs were determined to be related to the vaccination. Also, there were no significant differences in the proportion of SAEs between the vaccine groups. There were 9 participants in the allV3 group who had ≥ 1 SAE after allV3 (2.4%; 95% CI: 1.1, 4.5), and 3 participants had ≥ 1 SAE after HD-IIV3 (0.8%; 95% CI 0.2, 2.2). No AECl occurred.

In terms of moderate to severe local reactions after aIIV3 and HD-IIV3, no local reactions led to a medical visit. Local reactions included injection site pain, redness, shoulder pain, swelling, and tenderness. The absolute differences were small between these groups. In fact, the largest difference was only 3.7% in swelling, which was higher in the HD-IIV3 group. Tenderness did not meet the non-inferiority criteria for aIIV3, while all of the other reactions did. None of these local reactions led to a medical visit. Regarding moderate to severe systemic reactions after the two vaccines, the reactions included chills, diarrhea, fever, headache, myalgia, nausea, vomiting, arthralgia, fatigue, and malaise. Again, the absolute differences were small between the groups. The largest difference was fatigue at 3.1%, which was higher in the adjuvanted group. Arthralgia, fatigue, and malaise did not meet non-inferiority criteria but the other reactions did. There were no systemic reactions that led to a medical visit.

Turning to the secondary objectives from Day 1 pre-vaccination to Day 1 post-vaccination, for the EQ-5D-5L. The difference of -0.05 (-0.06, -0.04) was the exact same between the two groups, with no significant difference. The scores increase slightly for the groups. Higher scores are better, but the differences are not clinically meaningful. For the EQ-VAS, the difference was -2.22 (-3.38, -1.06) in the aIIV3 group and 2.45 (-3.45, -1.54) in the HD-IIV3 group. Again, there was no significance between group differences. The scores increased again, which was not clinically meaningful. The pre-vaccination mean day scores for the EQ-5D-5L was 0.89 for the aIIV3 group and 0.90 for the HD-IIV3 group, meaning that this is a relatively healthy and independent group of elders.

In summary, the proportion of participants with moderate-severe injection-site pain was not higher after aIIV3 than HD-IIV3. There were no vaccine-related SAEs. The short-term post-vaccination HRQOL was not affected by either vaccine. The safety findings in this study were consistent with pre-licensure data for aIIV3 and HD-IIV3. From the standpoint of safety, either vaccine is an acceptable option for the prevention of influenza in older adults.

Discussion Points

Dr. Szliagyi inquired as to whether there was a reason for the fact that the population was quite healthy.

Dr. Schmader indicated that this is very typical in vaccine trials in older adults comprised of community-dwelling volunteers. People from nursing homes do not volunteer for these studies. It is possible to recruit them, but it is much more difficult. This is a recurring issue and represents a major gap in the literature not only for vaccines, but also for medications.

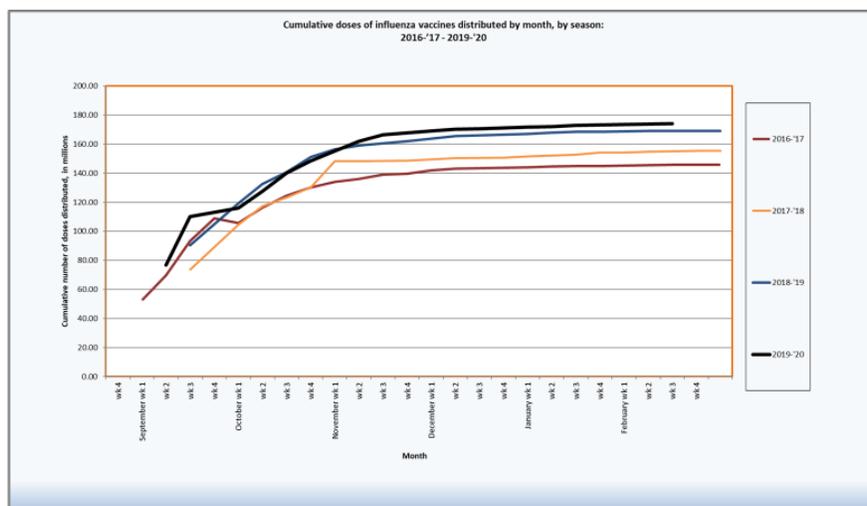
Dr. Talbot asked whether it was possible to assess immunogenicity and reactogenicity to determine whether there was a correlation.

Dr. Schmader responded that the immunogenicity studies are currently underway. All of the results are anticipated in a month or two, at which time they can perform that analysis.

Summary and WG Considerations

Lisa Grohskopf, MD, MPH
Influenza Division, CDC
National Center for Immunization and Respiratory Diseases
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Dr. Grohskopf thanked the WG members and CDC staff who contribute regularly to the calls every month, twice a month and often deliver extensive data and 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 the Immunization Services Division (ISD). This is an update of a graphic presented during the October 2019 ACIP meeting summarizing vaccine dose distribution for the current season and the previous 3 seasons. This graphic depicts that approximately 174 million doses of influenza vaccine have been distributed in the US as of February 14, 2020:



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
Numbers indicate the number of influenza virus antigens: <ul style="list-style-type: none"> <input type="checkbox"/> 3 for trivalent: an A(H1N1), an A(H3N2), and one B (from one lineage) <input type="checkbox"/> 4 for quadrivalent: an A(H1N1), an A(H3N2), and two Bs (one from each lineage) 	

A discussion was presented during the October 2019 meeting of the rationale and design for a systematic review of influenza vaccines in older adults that have been discussed in the WG for a number of calls. Older adults ≥ 65 years of age are recognized as a group that is at increased risk for severe illness and complications due to influenza infection. They also are a group who tend not to have as good results in terms of efficacy or effectiveness with vaccines as compared to younger, healthier age groups. They also are the group age-wise who have the most in terms of number of influenza vaccines that suitable for them purely based on age indications. Since 2013-2014, there has been a decent expansion of the number of different types of vaccines available, which are shown in the following table:

US Licensed Influenza Vaccines Available for 2019-2020

Available vaccines by FDA-licensed age indication:

Vaccine type	6 through 23 mos	2 through 3 yrs	4 through 17 yrs	18 through 49 yrs	50 through 64 yrs	≥ 65 yrs
IIV4s (egg-based)	Afluria Quadrivalent Fluarix Quadrivalent FluLaval Quadrivalent Fluzone Quadrivalent					
IIV4 (cell-based)			Flucelvax Quadrivalent			
RIV4 (recombinant)				Flublok Quadrivalent		
Adjuvant IIV3 (egg-based)						Fluad
High-dose IIV3 (egg-based)						Fluzone High-dose
LAIV4 (egg-based)		FluMist Quadrivalent				

- ACIP recommends that a licensed, age-appropriate influenza vaccine should be used.
- No preferential recommendations are made for any specific influenza vaccine for any age group, where there is more than one that is appropriate.

This includes 2 vaccines that are licensed specifically for adults 65 years of age and older, which is the adjuvanted aIIV3 and HD-IIV3. The aIIV3 has MF59[®] adjuvant the HD-IIV3 has a higher antigen dose of the hemagglutinin and antigen. Both are licensed for this age group in order to encourage a stronger immune response and better effectiveness or efficacy. Both adjuvanted and high-dose inactivated vaccines have been studied as compared to unadjuvanted standard-dose inactivated vaccines in this population. For each vaccine, there is some evidence of better efficacy in this age group depending upon the study. There also has been at least one study of RIV, which was first licensed in 2013-2014 as a trivalent and then became available as a quadrivalent in the 2017-2018 season. This is licensed for individuals 18 years of age and older, but has been specifically studied in adults 50 years of age and older in an RCT compared to a quadrivalent inactivated vaccine. Out of a total of the 9 US licensed influenza vaccines available for 2019-2020, 8 of which are appropriate by age indication. ACIP recommends that a licensed, age-appropriate influenza vaccine should be used. No preferential recommendations are made for any specific influenza vaccine for any age group, where there is more than one that is appropriate. This is the case for many age groups, but particularly for individuals 65 years of age and older.

As alluded to in Dr. Schmader's presentation, providers and the public do ask questions about whether one vaccine is more appropriate for any given person. During the October 2019 ACIP meeting, the WG discussed the status of the development of a protocol for a systematic review of influenza vaccines. The systematic review/meta-analysis question regards "whether 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 any one or more of these vaccines over other age-

appropriate influenza vaccines for persons ≥ 65 years of age.” This is a relatively complicated question given the number of vaccine comparisons embedded in there.

The PICO essentially has not changed since the WG first presented this. The population is adults ≥ 65 years of age. The interventions include US-licensed, or similar in formulation/manufacture to US-licensed, trivalent/quadrivalent high-dose IIV, adjuvanted IIV, or RIV. The comparators include other trivalent or quadrivalent influenza vaccine (US-licensed, or similar in formulation/manufacture to US-licensed), non-influenza control vaccine, placebo, and no vaccine.

Outcomes have had an update since the last pre-station, at which time the efficacy/effectiveness outcomes had been settled. Safety outcomes are somewhat more complicated and required further discussion. Much of the discussion centered around lumping versus splitting. There are many ways to enumerate safety events. A total of 8 primary outcomes were settled upon for efficacy/effectiveness and safety, which are as follows:

- Efficacy/Effectiveness
 - All influenza A and B
 - Influenza-associated outpatient/emergency visits
 - Influenza-associated hospitalizations
 - Influenza-associated deaths

- Safety
 - Any systemic adverse event (Grade ≥ 3)
 - Any injection site adverse event (Grade ≥ 3)
 - Any serious adverse event (SAE)
 - Guillain-Barre syndrome

There also are some secondary outcomes. To the extent data are available, the following will be summarized:

- Influenza-associated outpatient/emergency visits, hospitalizations, and deaths stratified by influenza virus type/subtype
- SAEs judged to be related to study intervention

Inclusion/Exclusion criteria are similar to what was presented in October 2019 and 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

- Main inclusion criteria:
 - Randomized studies (individually- and cluster-randomized designs)
 - Retrospective case-control and cohort studies (traditional and test-negative designs)
 - Retrospective and prospective cohort studies

- ❑ Main exclusion criteria:
 - Data involving influenza vaccines not licensed in the US for persons ≥ 65 years of age
 - Studies/data for which the entire population falls outside the age range of interest
 - Studies/data assessing monovalent or bivalent vaccines
 - Case series, case reports, registry reports without comparator or denominator information
 - Animal studies
 - Interim reports superseded by final reports

The outcomes were finalized in November 2019, the protocol was finalized in December 2019, and literature screening began in January 2020. There are a substantial number of reports to screen at upwards of 8000. The WG will present the findings as soon as they are able.

Discussion Points

Dr. Lee thought it seemed like they might be headed toward a question about a preferential recommendation, which raised a couple of issues. One issue pertains to what would constitute a meaningful difference, and she wondered whether the WG would opine that to say what that difference may or may not be. It may not be statistically significant, but it may be clinically meaningful. The second issue pertains to determining comparative effectiveness conditioned on the same season, because her assumption is that there will be considerable data of several seasons that the comparison will be very challenging for different vaccines.

Dr. Grohskopf replied that they did not define a meaningful difference in the protocol, partly because everyone is aware of the variability of the way influenza behaves and the way VE differ from season-to-season. In terms of what they have seen, even relative VE is not the same from study-to-study. It is daunting to try to define a clinically meaningful difference when there are so many things going into the equation that cause variability. They anticipate seeing a lot of variability. Based on the WG discussions, the general feeling among the WG members about the reason for doing this is that people do ask why there is not a preferential recommendation. Given all of the evolving literature, it is a good time to examine whether there are enough data and if not, why not or if so, why so. There is going to be a lot of variability, but they will have to determine how much.

Dr. Foster (APHA) inquired as to why FLUCELVAX[®], the cellular cultured vaccine, was not included in this evaluation.

Dr. Grohskopf indicated that the cell-based inclusion was discussed. One reason was that to the WG's acquaintance, more data were available for the other 3 vaccines for this particular age group specifically. The review is quite complicated already with the 3 vaccines. To add the 4th would broaden the review quite a bit more in terms of relative comparisons. Because the cell-based vaccine is licensed for individuals 4 years of age and older, the WG's feeling was that this is likely to be addressed in a broader review in terms of egg-based versus non-egg-based for a broader scope of the population. The cell-based vaccine has been available for a number of seasons. In terms of manufacturing, the propagation of those reference strains has been since that vaccine was licensed in canine kidney cell lines rather than eggs. This is the first season in which all 4 of the reference strains are cell-derived. Therefore, it seemed best to hold off on FLUCELVAX[®] for a later review.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Wharton presented the CDC agency update. During the December 2019 meeting of the Board of Scientific Counselors, Deputy Director for Infectious Diseases (BSC, DDID) established the Vaccine Confidence Work Group to identify gaps in CDC activities to increase vaccine coverage; inform the centers' efforts to provide recommendations to CDC on the agency's strategy to strengthen vaccine confidence; and maintain high vaccine coverage at the national, state, tribal, and local levels. Over the next two years, the Vaccine Confidence Work Group will collect and analyze relevant information and provide findings and observations to the BSC DDID for deliberation and potential votes. The Vaccine Confidence Work Group will be chaired by external experts; and will be supported by staff from across CDC, including the Immunization Services Division (ISD), the Immunization Safety Office (ISO), and the Division of Viral Diseases (DVD).

For measles during 2019, a total of 1282 individual cases were confirmed in 31 states. In October 2019, New York State (NYS) announced the end of the state's nearly year-long outbreak of measles. With that declaration, the US was able to maintain its measles elimination status. The Pan American Health Organization has established a regional verification Commission and CDC will provide evidence regarding the sustainability of measles elimination. In December 2019, American Samoa declared a measles outbreak. CDC has provided technical guidance on case and contact investigations, infection control, vaccine acquisition and usage, and mass vaccination efforts. The agency also provided American Samoa with additional funding to support their response to the outbreak and purchase additional doses of measles, mumps, and rubella (MMR) vaccine.

The previous day, a comprehensive update was provided on the influenza vaccine season. Dr. Wharton added a couple of brief updates that she did not believe were included. CDC tracks influenza coverage weekly through the National Immunization Survey and is able to provide estimates that are updated weekly. She was pleased to see this year that coverage appears to be tracking a little above last year. It is currently around 60%. If it continues to increase, coverage will likely be higher than it was at the end-of-season last year. CDC is also pleased to see an increase in doses of pediatric influenza vaccine ordered by states for use in the Vaccines for Children (VFC) Program. Obviously, vaccine availability does not necessarily mean there will be higher coverage, but there cannot be higher coverage if there are not more dosage available. Therefore, CDC is pleased to see that increase in doses ordered for next season for the VFC Program.

Finally, the 2020 National Adult and Influenza Immunization Summit (NAIIS) annual in-person meeting will be convened on May 18-20, 2020 at the Westin Peachtree Plaza Hotel in Atlanta, Georgia to be followed by CDC's National Immunization Conference (NIC), which will be convened May 19-21, 2020 also at the Westin Peachtree Plaza Hotel in Atlanta, Georgia. Information about both of those meetings is available online.

Department of Defense (DoD)

Dr. Deussing conveyed the DoD's appreciation to ACIP and CDC for continued inclusion of the DoD in this meeting and the ACIP working groups. The DoD is closing out its 2019-2020 influenza vaccination campaign after reaching its annual goal of vaccinating over 90% of personnel by January 15, 2020. This included Active Duty, Select Reserve Forces, and healthcare providers. New for the 2020-2021 season, the DoD will introduce Southern Hemisphere influenza vaccine to support operational activities in applicable regions. The DoD, in coordination with other agencies, is moving forward with limited implementation of the newly licensed Bavarian Nordic smallpox and monkeypox vaccine. The Immunization Healthcare Division (IHD) is developing a protocol to evaluate this vaccine for cardiac safety, interaction with other vaccines, and optimum booster interval. The Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) is now in its second research year. Over 5800 patients were enrolled this year at 9 different research sites. This study group is co-chaired by the IHD and the Uniformed Services University (USU) Infectious Disease Clinical Research Program (IDCRP). The South Atlantic and Pacific Regional Vaccine Safety Hubs continue to actively present research on a number of subjects, including atypical shoulder pain and dysfunction following immunization, vaccine hesitancy in the military system, and effects of anti-inflammatories and analgesics post-immunization. In FY2019, the IHD responded to over 1400 calls to its call center, reviewed 1022 VAERS cases, reviewed 480 clinical cases, and conducted 322 onsite quality assurance surveys to ensure the highest standards of care throughout the DoD.

Department of Veterans Affairs (DVA)

Dr. Kim provided 4 announcements for the DVA. The first is that the VA updated its clinical preventive services guidance and national electronic decision support tools, which are also known as clinical reminders, for HPV and pneumococcal immunizations based on the most recent ACIP recommendations. Located on the VA internal website for clinicians, the VA guidance also includes public facing links and resources for staff to use with their patients. Second, from August 1, 2019 through February 1, 2020, over 1.9 million influenza vaccinations were administered within VA facilities. This does not include vaccines received outside of the VA. In addition, more than 109,000 enrolled veterans received a no-cost influenza vaccine through a partnership with Walgreen's. Third, VA Notice 2020-02 was released to the field on the storage of vaccines and medications in pharmaceutical grade purpose-built refrigerators and freezers at VA medical facilities. Fourth, the VA public facing "Staying Healthy: Recommendations for WOMEN" and "Staying Healthy: Recommendations for MEN" have been updated based on the CDC 2020 Adult Immunization Schedule and are available on the VA National Center for Health Promotion and Disease Prevention [website](#).

Food and Drug Administration (FDA)

Dr. Fink indicated that first and foremost, FDA is engaging with vaccine manufacturers, other federal agencies, and regulatory and public health authorities across the world to facilitate development of vaccine candidates to address the current COVID-19 outbreak. Since the last ACIP meeting, there have been 4 major vaccine approvals. ERVEBO, the VSV-vectored Ebola vaccine, was approved in December 2019. There have been 3 influenza vaccine approvals, two of which were to add quadrivalent formulations to previously approve trivalent seasonal influenza vaccines. This includes a quadrivalent formulation of Fluzone® High-Dose indicated for use in individuals 65 years of age and older that was approved in November 2019; and a quadrivalent formulation of Flud®-MF59®-adjuvanted influenza vaccine that was approved at

the end of January 2020, also for use in individuals 65 years of age and older. The fourth approval was for an adjuvanted H5N1 vaccine for positioning in the Strategic National Stockpile (SNS). This is an MF59[®]-adjuvanted vaccine that is manufactured using the same platform as FLUCELVAX[®], the licensed seasonal influenza vaccine. The trade name is AUDENZ. This vaccine was studied for safety in nearly 4000 individuals, which included over 300 pediatric subjects and nearly 1800 individuals 65 years of age and older. The effectiveness was inferred by hemagglutinin inhibiting antibody responses post-vaccination and from efficacy data with FLUCELVAX[®], the vaccine manufactured using the same platform. This H5N1 vaccine was approved under FDA's traditional approval pathway for adults 18 years of age and older because FLUCELVAX[®] is approved under that pathway as well. For pediatric individuals under the age of 18 years, FLUCELVAX[®] is approved under either an accelerated approval provision or not yet approved, as is the case for individuals less than 4 years of age. Once the ongoing studies to support traditional approval of FLUCELVAX[®] are completed, that will serve as the basis for full approval of AUDENZ in those pediatric age groups.

Health Resources and Services Administration (HRSA)

In terms of Ebola vaccine coverage by the Countermeasures Injury Compensation Program (CICP), Dr. Rubin reported that Ebola vaccine is a covered countermeasure based on the current declaration. Injury claims from the Ebola vaccine are eligible for benefits as long as they meet program requirements. As of January 1, 2020, the CICP has compensated 39 claims totaling \$5.5 million. The national Vaccine Injury Compensation Program (VICP) has continued to process an increased number of claims. In Fiscal Year 2019 (FY2019), 1282 claims were filed with the VICP. In that same FY, \$196.2 million was awarded to petitioners and \$29.2 million was awarded in attorney fees and costs. These include fees for compensated, dismissed, and interim cases. As of January 1, 2020, a total of 289 claims were filed with the program and \$57.2 million was awarded to petitioners and attorneys for attorney fees and costs. As of January 1, 2020, HRSA has a backlog of 913 claims alleging vaccine injury awaiting review. More data about the program can be obtained on the website.

Indian Health Service (IHS)

Dr. Weiser reported as of February 10, 2020, IHS has administered 267,565 doses of influenza vaccine with population coverage among children 6 months to 17 years of age of about 36.1% and among adults 18 years of age and older, 33.6%. In addition, IHS facilities have a mandatory HCP influenza policies. Internal influenza vaccine coverage among federal IHS HCP was 94.8% as of December 31, 2019. One of the software updates that IHS is grateful to be anticipating will be established soon is the final phase of new immunization forecasting software, which finally will allow IHS to catch up with some of its newer vaccine recommendations. This is expected to go live in the next 30 to 60 days. Addressing vaccine hesitancy, the Northwest Portland Area Indian Health Board (NPAIHB) Tribal Epidemiology Center (TEC) with funding from CDC is working with various stakeholders, parents, community members, HCP, and a community organization called Boost Oregon to develop approaches and communication strategies to strengthen conversations among HCP and community members around the importance and benefits of childhood vaccines and to reduce vaccine hesitancy within tribal communities. The projects aims are to: 1) educate patients and parents about childhood vaccines; 2) increase HCP's confidence and ability to discuss patient and parent concerns about vaccines; and 3) encourage providers to strongly recommend immunizing all children according to the ACIP published vaccination schedules for children and adolescents.

National Institutes of Health (NIH)

Dr. Mulach reported National Institute of Allergy and Infectious Diseases (NIAID) is supporting the development of a number of COVID-19 vaccine candidates by intramural and extramural investigators. Multiple approaches are being assessed, including vaccines based on technologies that have shown promise against coronaviruses that cause SARS and MERS. The Vaccine Research Center (VRC) at NIAID is collaborating with the company Moderna on the development of a vaccine candidate using a messenger ribonucleic acid (mRNA) vaccine platform expressing a recombinant spike protein of SARS-CoV-2. It is anticipated that this experimental vaccine will be ready for clinical testing in the next few months. NIH will continue to conduct pre-clinical studies as well as the first in-human study of this candidate and other candidates. NIH is coordinating closely with its colleagues at CDC, the Department of Health and Human Services (HHS), FDA, DoD, and other federal partners.

On February 26, 2020, NIH announced the start of a randomized controlled clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnosed with coronavirus disease 2019 at the University of Nebraska Medical Center (UNMC) in Omaha. This is the first clinical trial in the US to evaluate an experimental treatment for COVID-19. The first trial participant is an American who was repatriated after being quarantined on the Diamond Princess Cruise Ship that docked in Yokohama, Japan and volunteered to participate in the study. The study can be adapted to evaluate additional investigative treatments and to enroll participants in other sites in the US and worldwide.

As Dr. Messonnier mentioned the previous day, CDC received a clinical specimen of the first US patient infected with SARS-CoV-2, prepared the sample, and sent it to the NIH BEI Repository. That sample has been grown up and is available to investigators to use in their research endeavors for those who are registered. NIH is providing additional materials for coronavirus research, which are being updated on a daily basis as more information is acquired. The BEI Repository website contains further information about those resources.

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

Dr. Elam, Research & Policy Strategist for OIDP, provided a brief update on OIPD immunization-related activities and the National Vaccine Advisory Committee (NVAC). The last NVAC meeting occurred February 13-14, 2020 and focused on vaccine confidence and innovation. The agenda included presentations on recent research in vaccine innovation, updates related to the coronavirus outbreak, and efforts to advance the 2019 *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health*. The agenda also included sessions on challenges and opportunities for combatting misinformation online, speakers from large social media companies such as Twitter, and the use of storytelling to increase vaccination awareness and rates. The Assistant Secretary for Health (ASH) in a prior meeting charged NVAC to develop and formally submit reports with implementable recommendations for vaccine confidence and immunization equity. During the meeting, each of the subcommittees provided an update on their progress in preparations for drafting and submitting these reports on time. The next public NVAC meeting will take place June 9-10, 2020 in Washington, District of Columbia (DC). For those who cannot attend in person, there will be a live webcast. Information for this upcoming meeting and past meetings can be found on OIDP's website.

OIDP will be releasing the 2020 National Vaccine Plan (NVP) late this year. During the last ACIP meeting, Dr. Tammy Beckham, OIDP's Director, updated this committee on the progress related to the development of the 2020 NVP. The work on this plan is ongoing and includes review and incorporation of feedback solicited through public comment and stakeholder discussions that took place in October 2019. This consisted of 26 one-hour discussions with individuals and a variety of stakeholder groups including healthcare providers, industry, academia, and patient advisory organizations. Much of the feedback received aligned closely with previous NVAC recommendations including aspects such as a goal for innovation, and a global goal relevant to the ongoing coronavirus outbreak. At present, OIDP is integrating the feedback received into a concise actionable 5-year plan that will provide vaccine strategies across the life course, guide priority actions for 2020-2025, and identify indicators to measure progress toward planned goals.

As will be emphasized in the next NVP, vaccine innovation continues to be a priority at HHS as they recognize the critical role of innovation within the US vaccine and immunization enterprise. OIDP is putting innovation into practice in multiple ways. For example, in order to improve pertussis vaccine performance, OIDP convenes scientific, policy, and regulatory experts to discuss ethics, feasibility, and regulatory considerations of a controlled human challenge model. This human challenge model will provide a better understanding of the immune system's response to infection, including colonization, and guide pertussis vaccine development in the US. As opposed to current practice, the challenge model will entail colonization as the desired endpoint. The output of this meeting was instructive and will serve to guide future policy. A White Paper will be published in Spring 2020.

Human papillomavirus (HPV) remains a significant public health challenge, with vaccination completion rates for adolescents barely above 50%. The ASH has prioritized increasing HPV vaccination rates nationally in order to reduce vaccine-preventable cancers. As a result, OIDP is implementing innovative approaches to significantly improve HPV vaccination rates within the next 5 years. This is being achieved through a number of activities, including working with the CDC, the American Medical Group Association (AMGA), and the American Cancer Society's (ACS's) National HPV Vaccination Roundtable to establish a Learning Collaborative among integrated delivery networks and other large health systems. Additionally, OIDP has launched the innovative Million Cancer Preventing Congregations program, a faith-based initiative that empowers leaders to participate in prioritizing HPV vaccination and cancer prevention within their congregations.

In addition, Dr. Elam provided an update on two national plans that will be released later in 2020. First, OIDP is updating the National Viral Hepatitis Action Plan, which was first released in 2011. This plan provides goals, strategies, and indicators to achieve a coordinated national response to Hepatitis A, B, and C infections. The updated plan is scheduled to be released in Summer 2020 and will prioritize available hepatitis vaccinations. OIDP is also advancing the first ever STI Federal Action Plan. Recent data show that rates of STIs have grown considerably over the past 5 years and had reached an all-time high in 2018. Acknowledging this serious public health concern, HHS is developing the STI Federal Action Plan to guide a strategic federal response. This plan will focus on the 4 most common STIs that have the greatest public health impact in the US: chlamydia, gonorrhea, syphilis, and HPV. HPV vaccination will be emphasized as a cancer-preventing measure. The plan will focus on cross-cutting issues, including stigma, disparities, and social inequities.

Rabies Vaccine

Introduction

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

Dr. Frey introduced the Human Rabies Prevention 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
- 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, such as the World Health Organization (WHO)
- Review rabies exposure risk and risk assessment guidelines for the general population and by occupational and recreational groups
- 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, children, 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

To recap the October 2020 meeting, the following information was presented and discussed:

- Background: epidemiology, clinical course, and rabies biologics in the US
- Factors that contribute to decisions for PrEP and PEP
- The role of neutralizing antibodies as a marker for adequate vaccine response
- Introduction to PrEP schedule considerations, including:
 - Immunogenicity and duration of immunity
 - Route of vaccine administration
 - Role of booster doses for select populations
 - Reasons for PrEP failures

Since the last ACIP meeting, the WG concluded data review and discussions about PrEP topics and began discussing PEP to include PEP schedules, data about rabies immune globulin (RIG) administration, and presentations about newly licensed RIG products. Presentations during this session included the following:

- Background to PrEP, vaccine safety, and WG considerations
- Rabies vaccine schedule and duration of immunity (systematic review data)
- Other guidance and next steps for the WG

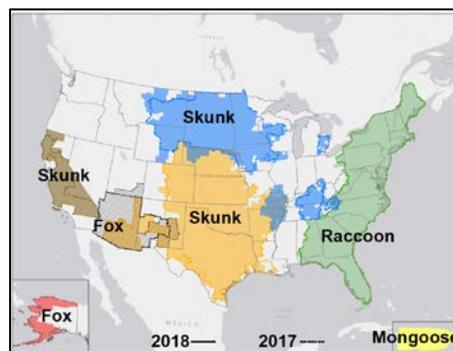
Regarding the new tentative timeline, the WG hopes to provide PrEP GRADE and EtR and some PEP data in June 2020. In October, the WG anticipates having a PrEP vote and to continue presentations about PEP data, including GRADE and EtR. A vote is anticipated on PEP in February 2021.

Background to Rabies Pre-exposure Prophylaxis, Vaccine Safety, and Work Group Considerations

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 an acute, progressive encephalomyelitis that is nearly always fatal. It 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. There have been no known laboratory-confirmed cases of human-to-human transmission through exposure to infected persons. In the US, there are approximately 0 to 4 cases per year. Human cases mostly come from infected animals.

There are few animal species that are reservoirs for rabies. Rabies virus variants (RVV) are named for animal reservoir species in which they circulate. They are confined to geographically definable regions. Infection can be transmitted from the reservoir species to other species, for example, a raccoon RVV can spread from a raccoon to a cat to a human. It is important to understand that the RVV does not denote the animal to which the human was exposed. Within the US, canine RVV has been successfully eliminated. This leaves terrestrial or wildlife rabies and non-terrestrial rabies. Non-terrestrial rabies is rabies where the reservoir is bats. Bat RVV is widespread and is present in 49 of 50 US states—all but Hawaii. Terrestrial or wildlife rabies is rabies for which the reservoir is wildlife (e.g., skunk, fox, mongoose, and raccoon). Depicted in this map is the distribution of terrestrial RVV in the US:



Activities that have led to confirmed cases in the US are ones that bring humans closer to rabid animals or rabies virus. They occur in domestic and international settings. In both of those settings, recreational and occupational work like laboratory and field work have been involved. Domestically, there are other potential exposures including contacts in everyday life, which occurs if there are bats in the home or a residence is in a wooded area with opportunities for exposure to rabid animals. There have been rare transmissions from organ and tissue transplants as well.

For these reasons, preventing rabies is a priority. Vaccinating domestic and wild animals is one way of doing that. For example, USDA, health departments, and others work on oral rabies vaccine campaigns for this purpose. Vaccinations in humans, PrEP and PEP, have been found to be highly effective in preventing rabies and likely contribute to the low number of cases in the US. PrEP was the focus of this session. It is comprised of a rabies vaccine schedule. Over 15,000 persons receive PrEP annually in the US.

In terms of US rabies vaccine, PrEP and PEP are important. A lot of factors contribute to the ACIP recommendations for these. There are 2 rabies vaccines currently licensed in the US. There is a human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV). The brand name and manufacturer are listed in the second and third columns in the following table:

Vaccine	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

Both vaccines are licensed in the US for intramuscular (IM) administration only. Both vaccines have been around for decades and no concerns were raised during the 2008 ACIP recommendations. However, because these vaccines are an important part of PrEP and PEP regimens, the WG did review the available data. The WG looked at passively collected data from the Vaccine Adverse Event Reporting System (VAERS). In terms of data for HDCV, VAERS received 1666 reports during 1990-2019. The take-home point is that the majority (94%) of reports were for non-serious events. Systemic reactions observed included headache (18.8%), pyrexia (18.1%), and nausea (17.1%). Serious adverse events (SAEs) like angioedema were rarely reported. These findings are consistent with pre-licensure and post-marketing studies [Moro PL, et al PLoS Negl Trop Dis. 2016 Jul 13;10(7):e0004846 ; VAERS: Vaccine Adverse Event Reporting System].

For PCECV, VAERS received 739 reports. Here as well, most (93%) were non-serious. The most common systemic reactions observed were headache (19.5%), pyrexia (18.5%), and nausea (18.1%). These findings are also consistent with findings of pre-licensure studies and do not represent new information [Moro PL et al. Travel Med Infect Dis. 2019 May - Jun;29:80-81; Dobardzic A et al. Vaccine. 2007;25:4244–51; VAERS: Vaccine Adverse Event Reporting System].

To ensure that any published data about safety since the 2008 ACIP recommendations were evaluated, the literature for trials was reviewed. Safety data from 25 trials were found to have been published since the 2008 ACIP recommendations. These publications involved comparison of a new vaccine and one of the 2 US vaccines, intradermal administration, and intramuscular co-administration with other vaccines (e.g., Japanese Encephalitis vaccine), varying schedules, and use in pregnant persons and children. In the end, the findings were consistent with what has been previously reported and no change was found in the safety profile.

In terms of who should receive rabies PrEP, the purpose of PrEP is to provide partial immunity to persons who are at risk for rabies. It is not a substitute for PEP. Persons who receive PrEP still need PEP after an exposure. Rabies immune globulin would not be needed for these people, and the vaccine series would be shorter. However, receiving PrEP does not negate the need for PEP. It is intended for persons who may have unrecognized or frequent exposures to rabies virus. For persons who have a delay in starting PEP (for example, if they are in a rural area and have to travel to the capital city of an international country), PrEP provides a bridge until they have access to PEP. The recommendations for PrEP vary depending upon the level of risk to unrecognized exposures. Risk categories for PrEP were developed with this in mind. They were developed to outline the populations who should receive PrEP based on a shared risk level and the corresponding recommendations for schedules and frequency of titer checks that are specific for that level of risk. They are named for the level of risk for unrecognized exposures where “Continuous” is the highest risk, followed by “Frequent” and “Infrequent,” and finally “Rare” which is the least risk. The “Rare” category is the general population.

Dr. Rao walked through the important features of this table from the 2008 ACIP rabies recommendations, as all of the presentations during this session were based on understanding this table:

Risk Categories for PrEP

TABLE 6. Rabies pre-exposure prophylaxis guide — United States, 2008

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titers acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, carriers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. All persons who frequently handle bats.	Primary course. Serologic test yearly; booster antibody titer acceptable level.*
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal-control staff working with terrestrial animals in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in areas where rabies is epizootic.	No vaccination necessary.

*Note: *Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test. A booster dose should be administered if the titer falls below this level.*

Focusing on the left side of the table, the first column is the risk category. Starting at the bottom is the “Rare” risk. There is increasing risk for inapparent or unrecognized exposures moving upward on the table to the “Continuous” category. The second column, “Nature of Risk” describes features of each risk category. For example, the nature of risk to unrecognized exposures is the highest for the “Continuous” risk category. Persons who fall into this risk are exposed to rabies virus in high concentrations and frequently. They can be exposed from bites, non-bites, or aerosol/droplet exposure. The nature of this risk decreases in intensity moving down the second column. For the general population, in the “Rare” category, exposure is always episodic if it occurs and the source is recognized. The recommended schedule and the frequency of titer checks differs depending on the risk category. The information in the third column, the “Typical Populations” column, is for that reason critical to front line providers. It enables them to identify the category in which their patient falls so that they can follow across and determine the PrEP recommendations. The populations described in the third column depend on several factors, including activity performed by the population, geographic region of mammal that someone might be exposed to, and access to safe and effective PEP. Dr. Rao spoke about each of these in more detail.

“Activity Performed” can mean occupational and recreational activities. Occupational exposures include jobs that require handling live rabies virus in diagnostic, research, or vaccine production capacities. For example, a rabies diagnostician. Some occupations have a lot of contact with bats, and some with terrestrial mammals. As part of recreation, too, some people have exposures that are risky for rabies. People can have contact with bats if they are a spelunker. People also travel internationally and can have exposures to rabid animals. Geographic region is important because different regions have different risks, regardless of the occupational or recreational activity that a person is doing. For example, domestically, a wildlife worker in Washington State where no terrestrial RVV are noted may have a lower risk than the same work in Pennsylvania, which is deep in the green zone where raccoon RVV is. Similarly, a spelunker entering only caves in Hawaii, where there is no rabies at all, may have a lower risk than a spelunker who enters caves in Alabama where there is bat RVV. Internationally, the important surveillance information is knowing whether canine RVV is an issue.

Geographic location is not the only important consideration for travelers. Access to PEP is a very important issue as well. Nearly all major cities have rabies vaccine and rabies immune globulin available. But if a person is, for example, doing recreational activities in a rural area, they may not have quick and easy access to the PEP that is in the major city. There may be a delay in their receiving PEP in that case. These 3 things fill in the “Typical Populations” column of the table titled “Rabies pre-exposure prophylaxis guide” from the 2008 ACIP recommendations. However, over the years, CDC has heard that this column can be hard to follow.

To the left of the “Typical Populations” column is the corresponding risk category. Some of the reasons this column was confusing is that veterinarians are listed in 2 risk categories. The text does attempt to clarify the difference between these 2 categories: Those in the “Frequent” risk category are working in areas where rabies is common and those in the “Infrequent” risk category are working with terrestrial animals in areas where rabies is uncommon or rare. But the language was cumbersome and users found it difficult to understand. The important role that geographic location or surveillance data plays in determining risk was not clear. The “Frequent” category includes all persons who frequently handle bats and the “Infrequent” category mentions travelers visiting areas where rabies is common and immediate access to appropriate medical care is limited. Given that the application of the ACIP recommendations in the last column of the table is dependent upon the clarity here, the WG decided to make some changes.

The WG decided to split of the “Typical Populations” information into 2 columns, which are in the red box on the slide as shown here:

Proposed PrEP clinical guidance

Risk category	Nature of Risk	Disease Biogeography	Typical Population	Pre-exposure recommendations
Continuous	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized. Direct and indirect exposures.*	Laboratory	Laboratory personnel working with live rabies virus in research, diagnostic, or vaccine production capacities (e.g., necropsy of suspect rabid animal or working with rabies virus cultures)	<ul style="list-style-type: none"> 1 schedule 1 frequency of serologic monitoring†
Frequent	Risk of virus exposure is common. Exposure typically recognized but could be unrecognized. Direct exposures and rarely indirect exposures	Geographic regions where bats are the only reservoirs for rabies** Geographic regions where terrestrial mammals are reservoirs for rabies	Persons who frequently handle or come into contact with bats (e.g., bat biologist) • Animal care professionals (e.g., veterinarians, technicians, animal control officers) • Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers)	<ul style="list-style-type: none"> 1 schedule 1 frequency of serologic monitoring†
Infrequent	Risk of virus exposure greater than population at large. Exposure is recognized one. Direct exposures.	Geographic regions where bats are the only reservoir for rabies Geographic regions where terrestrial mammals are reservoirs for rabies Geographic regions internationally with canine rabies	<ul style="list-style-type: none"> • Animal care professionals • Others who repeatedly handle terrestrial reservoir species • Spelunkers • Veterinarian students • Short-term volunteer hands-on animal care workers where increased risk is expected for short time periods • Travelers who will be performing activities (e.g., occupational or recreational) that put them at increased risk for exposure to rabid dogs and may have difficulty getting access to safe PrEP (e.g., in rural areas). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler's Health destination pages) 	<ul style="list-style-type: none"> 1 schedule No serologic monitoring
Rare (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	Nationwide	U.S. population at large	<ul style="list-style-type: none"> No pre-exposure prophylaxis No serologic monitoring

*Direct exposures are bite and non-bite (e.g., contamination of fresh open wound or mucous membranes with saliva), indirect exposures (e.g., dog bite).

†For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department.

‡(Viruses) acceptable antibody level is 0.5 IU/ml.

§Terrestrial mammals are non-bat species (e.g., raccoons, skunks, livestock). If you are uncertain which mammals in your region may circulate rabies, please contact your local or state health department.

**Bats are reservoirs for rabies in all US states except Hawaii

In the row for the “Continuous” risk category, the “Disease Biogeography” is the laboratory and the “Typical Population” is “Laboratory personnel who work with live rabies virus in research, diagnostic, or vaccine production capacities.” There are examples provided upon which the WG elaborated, “necropsy of suspect rabid animal or working with rabies virus cultures.” Obviously, this population is at the greatest risk of rabies exposure, and the PrEP reflect that. For the “Frequent” risk category, there are 2 different populations who have a high enough risk for rabies to be included in the “Frequent” risk category. Both are based on the principle that if someone has frequent exposure to rabies, they fall into this category. In geographic regions where bats are the only reservoirs for rabies, the typical population is “Persons who frequently handle or comes into contact with bats (e.g., bat biologist).” In geographic regions where terrestrial mammals are reservoirs for rabies, people who work with these terrestrial animals are at “Frequent” risk. Those populations include “Animal care professions (e.g., veterinarians, technicians, animal control officers)” and “Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers.” Persons with the same animal professions described here, could fall into the “Infrequent” category if the region where they work is one without terrestrial rabies.

That is seen in the first row of the “Infrequent” category. People can have professions that are similar to those in the “Frequent” category, but be listed in the “Infrequent” category as seen in the list in the “Typical Populations” column: Animal care professionals, Others who repeatedly handle terrestrial reservoir species, Spelunkers. Spelunkers was added to this row. This was previously in the “Frequent” category, but the WG felt that the recommendations for those in the “Infrequent” category might be a better fit. The second row in the “Infrequent” category includes “Geographic regions where terrestrial mammals are the reservoirs for rabies.” The population is

different from that of the “Frequent” category in that “veterinarian students” have less exposure than a veterinarian would. It also includes short-term volunteers. This also includes “short-term/volunteer hands-on animal care workers where increased risk is expected for short time periods” and people for whom frequency of titer checks would not be as important as those who would fall into the “Frequent” category.

The third row for the “Infrequent” category includes “Geographic regions internationally with canine rabies.” The “Typical Population” here includes “Travelers who will be performing activities (e.g., occupational or recreational) that put them at increased risk for exposure to rabid dogs and may have difficulty getting access to safe PEP (e.g., in rural areas). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler’s Health destination pages).” This all aligns with the soon to be updated CDC Traveler’s Health destination pages and the 2022 Yellow Book.

These are minor changes that were made to the table that are expected to clarify the contents and make it more user-friendly. The information in the last column is about PrEP schedules and the frequency of serologic titer checks is the subject predominantly of the next presentation. The WG made a few other changes to this table for clinical guidance. The minimal acceptable antibody titer level was changed to 0.5 IU/mL to ensure standardization with WHO and laboratories nationwide. The WG also recognized that the disease biogeography, because it was not its own column, may have created some confusion about the importance that should be placed on it and, therefore, highlighted the importance for local or state health departments to be contacted if there is any confusion about those issues.

In terms of vaccine series and frequency of titer checks, intradermal (ID) rabies vaccine administration has been globally recommended since the 1980s. WHO, as recently as their 2019 recommendations, recommended ID because it is dose and cost-sparing. For that population, the population the WHO guidelines are for, dose and cost-sparing recommendations could make the difference between a person getting vaccine and not getting the vaccine. So potentially life or death in the case of PEP. However, the US population is a different population. In the US, rabies vaccine is not licensed for ID use. It is packaged for one intramuscular (IM) injection. There is less of a need to vaccinate many people concurrently as there might be in developing countries, so the risk of infection that could come from multiple punctures to a vial that is intended to be a single use vial and therefore without preservatives, might not outweigh the benefits. Most of the populations for whom PrEP is recommended in the US are because of the work performed in their occupation. So presumably, occupations might pay the cost for these. For these reasons, the WG group preferred IM regimens.

The 2008 ACIP PrEP schedule is IM rabies vaccine on days 0, 7, and day 21 or 28. This is the schedule for all persons in the “Continuous,” “Frequent,” and “Infrequent” risk categories. The frequency of titer checks, however, differed depending upon the risk category. It was every 6 months for those with the greatest risk to unrecognized exposures, and it was every 2 years for those in the “Frequent” risk category. For those in the “Infrequent” risk category, the guidance was that titers are not needed. Therefore, no PrEP or titer checks were recommended in the 2008 recommendations for those in the “Rare” category. Rabies antibody titer is used as an indicator of adequate immune response to vaccine, but acceptable titer is not an indication of protection. It is a surrogate. A person with a low titer may still be immune. That person might very well still mount an anamnestic response if they had a rabies exposure. But because of the high mortality associated with rabies and the high risk for some populations, guidance has always been to try to maintain a higher than the minimum acceptable antibody titer level for

these people at their routine titer checks. A lower titer might still have protected them, but a sustained higher titer is preferred.

Given all of this, the WG's task was to: 1) evaluate whether vaccine series could be different depending upon the risk category by looking at data for a 2-dose IM series and data about a booster for those in the higher risk categories; and 2) evaluate whether frequency of titer checks could be different depending upon the risk exposure category by looking at data that helps determine whether titer checks for persons in the "Continuous" category should be more often than those in the frequent category. These data are the subject of the next presentation by Dr. Blanton.

Discussion Points

Dr. Hunter requested that Dr. Rao go back to the proposed table and walk him through what would be done for a bat biologist in an area that has geographic regions where terrestrial mammals are reservoirs for rabies.

Dr. Rao responded that anyone who is a bat biologist who is practicing in the US, for 49 out of 50 states they would fall in the "Frequent" risk category. This would be "Geographic regions where bats are the only reservoirs for rabies" where she noted that the "only" is probably not needed.

Dr. Hunter agreed that removing the word "only" would be advisable.

Dr. Bell said she was interested to see the estimate that 15,000 people a year receive PrEP, which struck her as being a lot. She was curious about whether Dr. Rao had any information about what comprises the largest proportion of this group of people. It seems like there would not be a lot of turnover for a lot of these people that would require vaccination of that many people annually.

Dr. Rao said she thought most of them were occupationally associated. It is known that among these occupations, veterinarians have to get vaccinated as part of their veterinary schooling. Based on the many manuscripts published, some of the other professions are not as good about getting vaccinated and maintaining titer checks that are required. It is assumed that the highest categories are accounting for the most number, and probably not as many travelers.

With respect to indirect exposure, Dr. Sanchez said he was not aware that rabies was spread by droplet and wondered under what situations this might occur.

Dr. Rao indicated that there have been situations in which laboratorians have, through manipulation of a virus, been exposed to aerosolization of the virus. The people in the "Infrequent" category who get a bite or scratch, that would be a direct exposure; whereas, those who are manipulating the virus might be at risk in other ways. In a clinical situation, there is concern about people who experience droplet exposure through intubation. PrEP is not indicated for clinicians and no transmissions have ever occurred in the clinical environment. The type of exposure someone may have had to a case that eventually becomes confirmed for rabies is part of the post-exposure risk assessment.

Dr. Fryhofer (AMA) noted that there are some very rural locations in parts of Georgia and she occasionally has patients who are hunters present to her office. A lot of times trappers send things to taxidermists, and taxidermists make things people put on their walls. She wondered whether there was any risk beyond the trapper for rabies.

Dr. Rao said she supposed if it were soon after the animal died and saliva was present on its nails or elsewhere, it could be a possible exposure. The risk would probably decrease once time had elapsed since the animal died. She had never heard of any kind of exposure in such a scenario.

Dr. Frey wondered how long a taxidermist waits to manipulate a dead animal or what they do with the neural tissue, brain and spinal cord, and at what point.

Dr. Petersen (SME) said that there is always the possibility that there could be transmission of rabies virus if there is saliva or other infectious material like neural tissue in contact with mucous membranes or any break in the dermal barrier. If that is documented, it would be indicated for PEP. However, at the same time, the rabies virus is not a very hardy virus. It can be killed by desiccation as well as UV light. Depending upon the state of the carcass, one could potentially determine the risk based on those factors. If it is dry, it is more than likely not a high risk. All of those types of risk assessments can be done on a case-by-case basis.

Dr. Rao added that would be primarily PEP versus PrEP.

Systematic Review: Rabies Pre-Exposure Prophylaxis Immunogenicity

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Dr. Blanton described the rabies PrEP systematic review and meta-analysis that CDC has been working on with the WG. As a way of orientation, he first spoke about the broader systematic review activity that was done and then focused specifically on the meta-analysis that was done with respect to the 2-dose vaccination series.

The systematic review was conducted looking at the immunologic response to rabies PrEP with a focus on the primary response, duration of immunogenicity, and the response to booster vaccination. The systematic review was started in 2017 and then updated through 2019. The population was very broad, including any persons with the potential for rabies exposure. The interventions included: 1) Persons receiving alternate rabies vaccination schedules using modern cell-culture vaccines; and 2) persons receiving rabies vaccination by alternate routes using modern cell-culture vaccines, primarily ID. The comparison was the gold standard ACIP recommendations, which is the rabies PrEP 3-dose, 3 to 4 week schedule by the IM route using modern cell-culture vaccines. The outcomes include rabies neutralizing antibodies reported as IU/mL 1 to 3 weeks after primary vaccination, 1 year post-vaccination, and after booster.

The literature search included examination of multiple databases (MEDLINE, Embase, Cochrane Library, WHO Index Medicus, citation sampling) for the period from January 1965 through December 2019. This represents the period during which modern rabies vaccines were either under study or available. The search terms included: (rabies OR rabies vaccine) AND

(antibodies) AND (human) AND (preexposure OR pre-exposure). The search resulted in identification of 258 unique papers. The exclusion and inclusion criteria included:

Exclusion Criteria

- Use of nervous tissue or experimental vaccines (not a licensed vaccine or ever evaluated by WHO)
- Immunocompromised populations

Inclusion Criteria

- Subjects received PrEP (schedule of 1-3 doses over any form of a schedule)
- Immune response to vaccination measured by Rapid Fluorescent Focus Inhibition Test (RFFIT), the gold standard neutralization assay
- Findings reported as geometric mean titer (GMT) (IU/mL) or as a seroconversion rate to a stated cut-off (e.g., 0.5 IU/mL)

Screening and critical review of the 258 papers resulted in 63 publications total accepted for review, ranging from 1978 through 2019. These included a total of 146 cohorts or study arms and 11,608 subjects who were involved in the selected studies. The study types, geographic locations, schedules, vaccines, and routes of administration included the following:

Study Types

- Randomized clinical trial (59%)
- Controlled clinical trial (16%)
- Cohort study (13%)
- Case/Time series (12%)

Study Locations

- Asia (41%)
- North America (29%)
- Europe (25%)
- South America (3%)
- Africa (2%)

Schedules (Cohorts)

- Single dose
- 2-dose: day 0,28; day 0,60; day 0,7
- 3-dose: day 0,3,7; day 0,7,14; day 0,7,21/28

Vaccines (Cohort)

- Purified Vero Rabies Vaccine (PVRV, broad utilization internationally)
- Purified Chick Embryo Cell Vaccine (PCEC)
- Human Diploid Cell Vaccine (HDCV)
- Others

Route (Cohorts)

- Intramuscular (IM)
- Intradermal (ID)
- Subcutaneous (SC)

Broadly for this overall systematic review what was found looking at the general schedules was that from a primary vaccination response, there really was no significant difference in the seroconversion rates between the various schedules. The WG focused on the Day 0, 7, one week schedule, which is easy to administer because it involves fewer doses and is also concurrent with the new WHO recommendations. To offer a broad perspective of the meta-analysis of the existing 3-dose schedule (0, 7, 21/28 days), this schedule is very well-established with more than 40 years of experience. There is very high (>97%) seroconversion after vaccination with a 3-dose schedule, regardless of vaccine or administration route, and a nearly 100% seroconversion rate 1 to 2 weeks after vaccination.

In terms of the comparison for the GMT for this schedule, there is a considerable amount of heterogeneity or variability between the studies for the GMT for vaccination. Looking at differences between IM and ID studies on the 3 dose/3 to 4 week schedule, IM produces significantly higher GMT, but the relative clinical difference between the significant difference is somewhat questionable. While the seroconversion at 0.5 IU/mL is not necessarily a protective level, it is recognition that this is an adequate immune response, and that a person who has an adequate immune response can receive a booster that generally is protective against rabies challenge. While the WG is not looking at the ID schedule currently, some ID studies were utilized later in the analysis because they did not want to exclude those data in an area where there are relatively few studies for some of the other schedules.

In terms of the rabies PrEP 2-dose, 1 week Schedule (day 0 and day 7), looking at primary response, of the larger systematic review, 12 total studies provided information that could be used for the pooled analysis for the 2-dose schedule, which are depicted in the following table:

Study Characteristics – primary immunogenicity

Study	Original Study Type(1)	Population	Intervention(1,2)	Comparison(1,2)	Study Subjects (In analysis)
Ajjan, 1989	CCT	Europe, veterinary students		HDCV-IM [0,7,21/28]	144 (72)
Jaijaroensup, 1999	RCT	Asia, veterinary students	PCEC-ID [0,7,21/28]	PCEC-IM [0,7,21/28]	138 (84)
Arora, 2004	RCT	North America, veterinary students		HDCV-IM [0,7,21/28]	135 (44)
Salchareon, 1999	RCT	Asia, children		HDCV-IM [0,7,21/28]	400 (190)
Briggs, 1995	Case Series	North America, veterinary students	HDCV-IM [0,7,21/28]	n/a	157
Hacilbektasoglu, 1992	RCT	Europe, at risk population		HDCV-IM [0,7,21/28]	60 (30)
Kitala, 1990	CCT	Africa, veterinary students		HDCV-IM [0,7,21/28]	80 (37)
Vodopija, 1986	RCT	Europe, general population		HDCV-IM [0,7,21/28]	92 (46)
Cramer, 2016	RCT	Europe, general population		PCEC-IM [0,7,21/28]	605 (371)
Recuenco, 2017	CCT	North America, at risk population	PCEC-ID [0,7,21/28]	PCEC-IM [0,7,21/28]	66 (30)
Soontjens, 2019	RCT	Europe, military	HDCV-2xID [0,7] PCEC-ID [0,7,21/28]	HDCV-ID [0,7,21/28]	500 (242)
Indy, 2019	RCT	North America, general population	PCEC-ID [0,7] PCEC-IM [0,7]	PCEC-IM [0,7,21/28]	60 (35)

1: Individual study arms were treated as observational cohorts for pooled analysis. 2: Serology data taken between day 14-28 (before 3rd dose administered in [0,7,21/28] cohorts) used as proxy of [0,7] schedule

One of the things that had to be done was that because these clinical trials do not have any direct ratio comparison internally, it was determined that these study arms could be broken apart and treated as more of an observational cohort for this pooled analysis. While the original studies were controlled trials, the individual study arms were treated from more of an observational perspective. That allowed for removal from these studies some of the individual

study arms that either were not the schedule of interest or included vaccines not licensed in the US. Another advantage of looking at the 0,7 schedule in the primary study is that this is the first two-thirds of the 3-dose schedule. For studies that can provide information and serological data on Days 14, 21, 28 before the third dose is received, is information that can be assessed for the primary response to the first 2 doses of vaccine. The last two studies in orange (i.e., the last two rows of the above table), Soentjens and Endy, looked exclusively at comparisons of the 2-dose vaccination schedule to the 3-dose.

In terms of the serologic response, the GMT among individuals who received only 2 doses of vaccine on Days 0 and 7, there was kinetics growth and antibody response between the groups. It is important to point out that there are a limited number of studies, but similar heterogeneity as observed in 3-dose ACIP meta-analysis. There is a robust response moving up to nearly 10 IU/mL within 1 to 2 weeks after vaccination and 12 IU/mL in the subsequent week. Looking at the seroconversion rates (SCR), very consistent results are reported across the different schedules at 1 to 2 weeks after the second dose and 3 weeks after the second dose. High SCR (98%) were achieved 7-14 days after the second dose (Day 7).

Dr. Blanton presented a slide comparing the response 30-60 days after the [0, 7, 21/28] schedule and the [0, 7] schedule. seroconversion in these groups. From a serology standpoint, we see 100% seroconversion in these groups 1 to 2 months post-vaccination. Again, the limitation is the small number of studies that were available for some of these analyses.

In terms of the data for the duration of immunogenicity and the response to booster, 13 studies had information available for this analysis, removing some of the individual cohorts that were using non-US licensed vaccines:

Study Characteristics – Duration of immunogenicity

Study	Study Type(1)	Population	Intervention(1,2)	Comparison 1,2)	Time @ Booster (m)	Total follow-up (m)	N @ booster
Pengsa, 2009	RCT	Asia, Children	PCEC-ID [0,7,21/28]	PCEC-IM [0,7,21/28]	12	36	176
Ajjan, 1989	CCT	Europe, veterinary students		HDCV-IM [0,7,21/28]	n/a	21	98
Jaljaronsup, 1999	RCT	Asia, veterinary students	PCEC-ID [0,7,21/28] PCEC-2xID [0,7,21/28]	PCEC-IM [0,7,21/28]	12	12+(14d)	110
Kamoltham, 2007	RCT	Asia, Children		PCEC-ID [0,7,21/28]	12	24	147
Sabcharoen, 1999	RCT	Asia, children		HDCV-IM [0,7,21/28]	12	12+(14d)	310
Straily, 1998	RCT	Europe, at risk population		HDCV-IM [0,7,21/28]	12 120	120+(14d)	286
Briggs, 1996	Case Series	North America, veterinary students	HDCV-IM [0,7,21/28]	n/a	12	12+(14d)	146
Dreessen, 1989	RCT	North America, general population	HDCV-ID [0,7,21/28] PCEC-IM [0,7,21/28] PCEC-ID [0,7,21/28]	HDCV-IM [0,7,21/28]	24	24+(7d)	69
Bernard, 1987	RCT	North America, veterinary students	HDCV-ID [0,7,21/28] HDCV-5C [0,7,21/28]	HDCV-IM [0,7,21/28]	12 24	24+(21d)	48
Cramer, 2016	RCT	Europe, general population		PCEC-IM [0,7,21/28]	n/a	12	584
Chatchen, 2017	RCT	Asia, Children	PCEC-0.5IM [0,7,21/28] PCEC-ID [0,7,21/28]	PCEC-IM [0,7,21/28]	12	96	68
Endy, 2019	RCT	North America, general population	PCEC-ID [0,7,21/28] PCEC-ID [0,7] PCEC-IM [0,7]	PCEC-IM [0,7,21/28]	12	12+(7d)	42
Soentjens, 2019	RCT	Europe, military	HDCV-2xID [0,7]	HDCV-ID [0,7,21/28]	-18	-18+(7d)	411

1: Individual study arms were treated as observational cohorts for pooled analysis. 2: Serology data taken between day 14-28 (before 3rd dose administered in [0,7,21/28] cohorts) used as proxy of [0,7] schedule

Looking at this beginning with the response in individuals 1 year post-vaccination, there was no significant difference between the 2-dose and 3-dose schedules looking at the GMT 1 year out. However, looking at serology at 1 to 2 weeks after the booster dose (i.e., booster given 1 year after the 2 dose series) there was a significantly higher anamnestic response in the 3-dose

group versus the 2-dose 0,7 schedule. Again, both of these are high above the minimal 0.5 IU/mL. The difference is again somewhat questionable in terms of clinical significance. In terms of the SCR, the opposite scenario is observed in which for the individuals who received a booster 1-year post-vaccination, the 2-dose group experienced a more rapid decay in the number of individuals with an adequate immune response. About 60% of individuals who received 2 doses still had an adequate response at 1 year compared to 90% amongst those who had received 3 doses. However, there is a complete universal anamnestic response post-booster dose in all individuals boosting above the minimal level.

Dr. Blanton summarized these studies individually, looking at the two primary studies that provided information on the serological response. Soentjens et al. (n=183) was administered entirely ID, it was one of the larger sample sizes. They found that amongst the individuals who had pre-booster serology taken in a 1 to 3 year window, the 2-dose ID group had a significant higher GMT (3.4 IU/mL) compared to those who received 3-dose ID (2.0 IU/mL). Again, as seen with the other data, 100% of both groups had an adequate titer (>0.5 IU/mL) after booster. Endy et al. (n=22) presented data on both 2-dose and 3-dose by IM and ID administration and similarly found no significant difference in the GMT at day 365 for 2-dose IM or 2-dose ID. Of the recipients, 40% to 50% of 2-dose recipients had a titer of >0.5 IU/mL at day 365, but 100% of recipients had an adequate titer after receiving booster at 1 year.

In terms of the larger systematic review, given the time that the 3-dose, 3 to 4 week schedule has been utilized, there has been more time to assess the long-term kinetics of the antibody response with this series. This also has been found in shorter time periods with some other 2-dose 0,28 day schedules. Most studies evaluating the 3-dose (0,7,21/28) schedule (IM and ID) found that there is a rapid decay during the first 6 months post-vaccination that slows to plateau between 6 months to 1 year. The decay has been found to be more rapid when administered by ID route. More importantly, the studies have generally found that in situations where a booster dose is administered at around 1 year, there is a greater increase in titer than what was observed in the original primary response amongst individuals, and that there is a slower decay after booster is received [Banga et al. *Vaccine*. 2014; 32:979; Brown et al. *Vaccine*. 2008; 26:3909; Mansfield et al. *Vaccine*. 2016; 34:5959; Strady et al. *JID*. 1998; 177:1290].

This also could be seen with some of the systematic review meta-analyses in which individuals are assessed who do not receive a booster dose at 2 years. These generally found that only about 85% are reported with an adequate titer at that time period (seen largely in cohorts of veterinary students) compared to individuals who do receive a booster at 1 year and tend to maintain much higher adequate antibody rates in excess of 95% over long periods of up to 4 to 5 years in some of these studies conducted over longer time periods.

This is just some of the information the WG is assessing in relation to the 2-dose schedule and consideration of recommendations pertaining to boosters for higher risk groups, which will allow for the extension of serological monitoring periods for the various risk groups.

Discussion Points

Dr. Hunter asked whether the first dose of a PEP could be considered as the booster for a 2-dose PrEP series. The way he was thinking about this from a clinical and public health response was that first. Someone needs to be in a situation in which they should receive the PrEP due to having ongoing exposures. The individual would then need to recognize that there was an exposure, and be in place that is not in the bush and PEP can be obtained. The question regards what amount of time one has from the point of recognition of exposure to when the

amnestic response is needed, and whether enough will be achieved from the first dose of PEP in time for protection.

Dr. Frey responded that part of the question requires that one be aware of the exposure and then seek follow-up. The incubation period for rabies is complex and the estimates are rather broad. The idea is that once there is an exposure, immediate attention should be sought. That could be difficult in the bush because it could be weeks or longer before getting aid. The other issues regards whether product is available when aid is sought. Whether the PEP dose is sufficient to boost the PrEP depends upon the period of time since exposure and how quickly someone can acquire the PEP. Those who are going into such a situation have to think differently about their PrEP.

Dr Bell said she always found the deliberations about the schedule for a vaccine such as rabies in which the mortality is pretty much 100% and there is no way to evaluate efficacy to be very challenging. The idea of shortening the schedule is also challenging. Given the issue of boosters for those who have received PrEP and ensuring that they do not miss their boosters so that they maintain their titers in a safe zone, it perhaps becomes more important to continue to have this margin of safety for people who have ongoing exposure. This is like a coverage question about which there are probably no data. However, she expressed interest in hearing Dr. Blanton's anecdotal sense of the extent to which the populations that are covered with existing PrEP recommendations are compliant with getting the recommended booster doses.

Dr Blanton responded that it is difficult to determine who is getting the booster doses. There generally has not been great compliance with serological monitoring. Large segments of the veterinary population, who are probably the best tracked, are not getting serological monitoring over these time periods and have populations of 20% to 30% who no longer meet the minimum titer level such that they would be recommended to receive a booster dose. The anecdotal story of that is that there have never been reported cases of failure in those populations.

Dr. Talbot observed looking at Slide 14, it appears that this is really based on the study with 22 patients. That is concerning to her because that is a very small number and this is a fatal disease. This is an instance in which the vaccine is known to be safe and 200 people could be recruited, given 2 doses, and followed over time to collect some really nice data. This does not have to be an elaborate study. Along those lines, it is time to obtain the data on how many veterinarians in high risk settings are getting repeat vaccinations and serology. That is a study that could be done working with the veterinary associations and other groups. These data are needed for ACIP to make a decision, particularly since this is a 100% fatal disease.

Dr. Frey agreed that there are a lot of studies that could or should be done in this field to answers those types of questions. Laboratorians are routinely checked every 2 years, and their levels are maintained at above 0.5 IU/mL. Veterinarians are fairly good about having their titers checked. Those who are not as good about it are the ones who might be at risk also for unknown exposures like the laboratorians.

It seemed to Dr. Bernstein that after 50 years of literature, there appeared to be some instances in which one vaccine might be preferred over the other. It sounded like duration was better with the IM than the ID administration route. He wondered whether people would prefer to use an IM rather than an ID initially.

Dr. Blanton indicated that there has been quite a bit of research assessing that. Generally, the ID route tends to have a slower decay than the IM over long periods. However, the relative clinical implications of that are not clear. While statistically significant, the implication for protection is not well-understood. More is better depending upon the type of exposure and contact one has, and the difference between ID and IM is probably negligible in terms of the difference of decay. Both routes have a very solid anamnestic booster response for that reaction. The ID route has been used pretty extensively throughout the rest of the world, and there is no real difference in failure rates and such has ever been observed with the ID route. A lot of issues regard the practical side of having enough vaccine throughout in the clinics to be able to reasonably use vials in a timely manner.

Dr. Talbot emphasized the need to conduct the suggested studies, particularly if ACIP was being asked to reduce the number of doses. Real data are needed. She is not comfortable changing a schedule for a 100% fatal disease without the data.

Dr. Atmar agreed and also would be concerned about the paucity of data for the IM route, which is essentially what they would be addressing for the US in terms of the potential ACIP recommendations to be made. Although it is likely that the ID will translate over, the fact is that based on the data presented, it appears that there are considerably less than 100 persons from whom the data on primary responses were obtained. That did not instill confidence about what the actual rates may be in terms of seroresponse or GMTs.

Dr. Bell added that she also had a certain level of discomfort with the idea of shortening the schedule that saves a dose of vaccine for approximately 15,000 people a year. To say that it is probably okay in this type of situation in which it also seems like compliance with booster doses is not great does not seem judicious. She would like to understand the rationale for reducing the doses in a situation where the potential adverse consequences are large.

Dr. Hunter pointed out that ACIP is likely to be faced with the situation that occurred with meningococcal B vaccine, which is a very severe sequelae without much data because of the low frequency of the disease.

Dr. Frey indicated that the WG is talking about a 6-month to 12-month booster in some populations, which ACIP would hear more about.

Clinical Guidance and Next Steps

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 emphasized that the revised table she reviewed earlier represented a good amount of the clinical guidance the WG worked on. As previously mentioned, the “Disease Biogeography” and “Typical Population” columns were modified somewhat, mostly to improve clarity but also to align with CDC Traveler’s Health Guidance and to provide more examples so that a provider has more information and can extrapolate it to the specific situation of the patient in front of him or her. Other guidance is the change in the minimal acceptable antibody level to 0.5 IU/mL, and the repeated advice to contact local or state public health for advice if unsure which mammals circulate in a specific region. The last column of this table will be completed once the GRADE and EtR of the data Dr. Blanton presented earlier are presented to ACIP in June 2020.

Because those recommendations could be different for special populations, the WG looked at data about the effectiveness of rabies PrEP for special populations. Children, however, exhibited a robust response—even better than healthy adults. Therefore, the WG does not anticipate needing any special considerations for children. For persons with altered immunity, studies found varying immune responses. As mentioned in ACIP’s [“Altered Immunocompetence Guidelines,”](#) effectiveness, but not safety, is of concern for inactivated vaccines like the rabies vaccines. The 2008 ACIP recommendations specifically state, “Patients who are immunosuppressed by disease or medications should post-pone pre-exposure vaccinations and consider avoiding activities for which rabies Pre-exposure prophylaxis is indicated. When that is not possible, immunosuppressed persons who are at risk for exposure to rabies should be vaccinated and their virus neutralizing antibody titers checked.” That is different from healthy patients in whom titers are not routinely checked after completion of a PrEP series.

There are data about effectiveness of PEP, but not PrEP, in pregnant persons. The current ACIP recommendation states, “If the risk for exposure to rabies is substantial, PrEP might be indicated during pregnancy.” The WG’s preference was to state that there is no safety or effectiveness concerns for PEP administration in pregnancy, and that the decision to perform activities that would necessitate receiving PrEP during pregnancy is an individual decision.

A consideration for travelers was the co-administration of rabies vaccines with malaria prophylaxis. In the 1980s, there was a report of a Peace Corps worker who received ID PrEP + chloroquine, and was later bitten by a dog but did not receive PEP and ended up passing away from rabies. Her rabies antibody levels at the time of her eventual hospitalization were found to be low, raising the question of whether antimalarials interfere with immunity from rabies vaccine. The 2008 ACIP recommendations lumped antimalarials in a sentence with immunosuppressive agents by stating that, “Corticosteroids, immunosuppressive agents, antimalarials... can interfere with development of active immunity after vaccination.” While there was no specific guidance for what to do if this were the case with antimalarials, the paragraph did go on to make the statements about the immunocompromised states that Dr. Rao mentioned earlier.

The WG reviewed a 2019 study published in the ¹*Journal of Infectious Diseases* that compared ACIP’s PEP IM schedule after initiation of chloroquine, Malarone, and doxycycline and found that co-administration of Malarone resulted in high antibody titers. For the arm involving chloroquine, the antibody levels were lower but were still 4 times higher than the minimum antibody cut-off (i.e., the lower antibody levels are not clinically significant). The WG’s preference is to remove antimalarials from the sentence about immunocompromising conditions since all antimalarials do not have an effect on active immunity, and instead state that titers may be considered for persons vaccinated while concurrently taking chloroquine, regardless of whether the chloroquine is for antimalarial prophylaxis [¹Endy TP, Keiser PB, Cibula D et al. *J Infect Dis.* 2019 Nov 2].

In terms of next steps, some of these items may be revisited given the discussion that was raised during Dr. Blanton’s presentation during this session. For now, Dr. Rao presented what had been planned. The Rabies WG developed 2 policy questions for PrEP topics. The first is, “Should a 2 dose pre-exposure prophylaxis (PrEP) series involving HDCV or PCECV IM [0, 7 days] replace the 3 dose series IM [0, 7, 21/28 days] for all those for whom rabies vaccine PrEP is recommended?” The population is persons for whom rabies vaccine PrEP is recommended, the intervention is [0, 7 days] rabies vaccine PrEP schedule, and the comparison is [0, 7, 21/28 days] rabies vaccine PrEP schedule. There was only one outcome, which is immunogenicity.

Safety was not included as an outcome given the review of safety data that Dr. Rao presented earlier.

The second policy question is, “Should an IM booster dose of rabies vaccine (PCECV or HDCV) be recommended 6-12 months after the 2 dose pre-exposure prophylaxis (PrEP) series IM [0, 7 days] for those in the continuous and frequent categories of people who receive PrEP?” The population is persons in the “Continuous” and “Frequent” categories for whom rabies vaccine PrEP is recommended. The Intervention is 6-12 months rabies vaccine booster after [0, 7 days rabies vaccine PrEP schedule. Here as well, the WG identified only one outcome—duration of effective immunogenicity.

For the June ACIP meeting, the WG will give the last PrEP presentation which will be the PrEP GRADE and EtR presentation. They also will be presenting data about PEP, with a plan to present the background about PEP considerations and data to inform recommendations and guidance about PEP including the PEP vaccine series, the newly licensed rabies immune globulin products, location of RIG administration, and PEP considerations for special populations.

For future meetings, the WG will present clinical guidance about handling deviations in PrEP and PEP and clinical guidance about managing completion of a PEP series after it is initiated internationally and with vaccines not available in the US. The WG also took the suggestion that the committee gave to them during the October 2019 meeting and plan to introduce a flow chart that depicts what has previously only been included in text about PEP. The flow chart will be a visual depiction of the various factors that providers should consider when deciding whether PEP is indicated for a specific patient. In addition to the clinical guidance, meetings in October 2020 and February 2021 might involve votes for the PrEP and PEP policy questions. All of this is subject to revision, given the questions raised during Dr. Blanton’s presentation.

Discussion Points

Dr. Atmar said he was always confused about the 2 levels of seroprotective titers, but his recollection was that 5 IU/mL was used previously and WHO used 0.5 IU/mL. While he understood the desire for alignment, the rationale for the higher level being used up to this change and the implications it might have for interpretation of the chloroquine data was not clear. He requested a reminder of the prior threshold used and what data there are other than the desire to align with WHO this many years later.

Dr. Rao indicated that the recommendation as it stands now is complete neutralization at less than 0.5 IU/mL. By adopting 0.5 IU/mL, it is actually a higher titer level and the populations who would be affected would be those in the highest risk category (laboratorians, animal care workers near terrestrial or bat rabies). It would not be a lot of people.

Dr. Hunter wondered what would occur if the policy question were 0,7 and then 21 days to a year/anywhere in that range, for the third vaccine. It seems that there would be clinical and timeline implications for the analysis.

Dr. Rao asked whether he was suggesting this for only the people in the highest risk categories or for people lower down the list, such as international travelers.

Dr. Hunter clarified that he was thinking of all of them.

Dr. Rao indicated that earlier in the WG's process, they thought about perhaps keeping the 0, 7, 21 regimen for the highest risk categories but dropping down to a 0,7 schedule for the lower risk categories. The reason being that it is known from the data that for someone with short-term summer volunteer work experience with animals, the duration of a high titer is less important and a 0,7 schedule would suffice. However, it was starting to get somewhat hairy. For example, if someone is in the lower risk category but then changes professions to a higher risk category, it was not clear what to recommend for them. Part of the thought process for this booster dose being okay is that for people in the highest risk categories, their occupational health clinics should be enforcing it (laboratorians, veterinarians, wildlife workers). This is similar to ensuring that they receive the third dose at 21/28 days to ensure that they get it 6 to 12 months later, which the WG did not think would be much of a problem and would not be needed for the lower category of people. However, they had not thought about 21 days to 1 year. For travelers, it is known that the 21-day issue creates problems because people do not think beforehand about getting the entire vaccine series.

Dr. Frey added that one of the problems with travelers is they wait until almost too late to get the full series in. One of the considerations with the 0,7 day vaccination schedule was that travelers could accomplish that better. Some data showed that 0, 7, 21/28 day antibody titer response was somewhat better than the 0,7, 28, but it was not significant. For the high risk continuous risk folks, the idea is to keep the measurable level at 0.05 IU. The lowest level of protection is unknown, but 0.05 IU is known to be protective. Any boost further out gives a nice increase in GMTs.

In terms of the rationale to reduce the number of doses so that travelers can get them in, Dr. Cohn pointed out that there are other traveler recommendations. Therefore, she cautioned them not to change the recommendation just so that travelers can complete the dose. It would be preferable to provide guidance for them.

Dr. Frey clarified that the WG was not suggesting changing the schedule because of that. It was just a consideration.

To summarize some of the concerns, Dr. Lee observed that it seemed like a better understanding of implementation considerations might be useful (adherence to serologic testing, booster doses). Thinking about private practitioners and veterinarians, if someone is part of a health system, clinic, or animal control, it seems like there should be more routine regulatory standards to make sure protection is enhanced for that population.

Dr. Bell said she would like to better understand the rationale for the proposed changes, given that it was unclear whether anything actually needed to be changed.

Dr. Poehling thought it would be helpful to know which categories the 15,000 doses administered fall into.

Dr. Frey called on their public health colleagues to share information about what happens in their practices or what concerns they have.

Dr. Bahta said that while she had not worked with their rabies team recently, most of their work is in PEP. Therefore, she did not think they could speak to PrEP.

Dr. Cohn asked whether anyone was present from the company who could speak to where doses are distributed.

Dr. Ritchey (Sanofi Pasteur) and Dr. Leonard (GSK) indicated that they did not have specific data readily available to provide on distribution, but would obtain details and report back to ACIP at a later time.

Dr. Finley (AIM) indicated that in their area, they are aware that veterinary technicians are often not covered. There are private clinics that administer ID three times to try to meet it, because it is one-third the price. Cost is a major issue and vaccination is not always occupationally covered. They know it is not ACIP-recommended, but it is the best they can do to be protected.

Dr. Rao observed that perhaps a 2-dose series administered IM would be better accepted by such groups versus maintaining a 3-dose series via an ID route, and could be a potential consideration.

Dr. Hahn (CSTE) mentioned anecdotally that in Idaho, there are often exposures in veterinary offices. They are treating ill dogs and cats, and she is surprised at how often the staff are not vaccinated. She does believe that cost is probably part of that consideration. She would have assumed vaccination to be routine, but that does not appear to be the case in Idaho where there are no terrestrial rabies.

Dengue Virus Vaccine

Introduction

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

Dr. Atmar reviewed the Dengue Virus WG discussions from November 2019-February 2020, which included the following:

- Dengue Vaccination in the Philippines: Unintended Consequences
- Review of October ACIP Dengue Vaccines Session
- ACIP Dengue Vaccines Work Group Informal Poll
- CYD 65, DENVAXIA® Efficacy Follow-Up Study
- Partnership for Dengue Control Pre-Vaccination Screening Workshop Update
- Puerto Rico Dengue Vaccine Knowledge and Attitudes

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

- Dengue Vaccine Knowledge and Attitudes in Puerto Rico
- WHO Global Recommendations on Dengue Vaccination
- Summary of WG Discussions and Next Steps

In terms of future WG plans, topics for the June 2020 meeting include a CDC assessment of laboratory tests for pre-vaccination screening, with a possible additional cost-effectiveness of CYD-TDV presentation during the June 2020 meeting. Plans for the October 2020 meeting are

to present the Evidence to Recommendations (EtR), and possibly draft CYD-TDV recommendations.

Dengue Vaccine Knowledge and Attitudes in Puerto Rico

Ines Esquilin, MD
University of Puerto Rico
School of Medical Sciences
Department of Pediatrics

Dr. Esquilin presented data on dengue vaccine knowledge and attitudes data from Puerto Rico. This information was obtained from 3 sources including the general population, physicians, and parents of children 9 through 16 years of age. The general population data come from a household survey conducted in Puerto Rico. The physician data collection was sponsored and guided by the Puerto Rico Academy of Pediatrics. The opinions of parents of children 9 through 16 years of age come from focus groups conducted by the Behavioral Science Team of the Centers for Disease Control and Prevention (CDC) Dengue Branch in San Juan.

The general population data were obtained from a community-based cohort study implemented in 2018 known as Communities Organized to Prevent Arboviruses (COPA). The participants were recruited from selected households in 38 cluster areas. A total of 1139 adults participated in COPA. When asked if they would receive the dengue vaccine for free, 73% said they would receive it for themselves and 75% said they would administer it to their children. Among the same adults, 63% said that they would pay for the vaccine for themselves and 68% said that they would pay for it for their children. When interest in the dengue vaccine among adult participants in COPA was explored, 59% said they would pay \$10 per dose, 37% would pay \$20 per dose, and 12% would pay up to \$50 per dose.

When asked for the reasons for not wanting the vaccine or for being unsure about it, only 1% were not worried about getting dengue. There was a lack of information about the vaccine since 22% of the participants could not state a reason and 9% needed more information. Of the participants, 38% were worried about side effects/reactions. When they were asked about the most important feature of a dengue vaccine, most participants were concerned about the high level of protection at 66% among participants who said they would receive the vaccine versus 50% of those who would not or were unsure if they would receive the vaccine. Concern about minimal side effects was more common in participants who were unsure or not willing to receive the vaccine at 33% versus 17% in those willing to receive it.

In terms of the survey conducted among physicians in Puerto Rico, 115 physicians completed the survey. Of those, 81% were practicing pediatricians or pediatricians with a sub-specialty. In terms of the methodology, a pediatrician from the CDC Dengue Branch gave presentations to the local pediatric associations during their Fall and Winter continuing education meetings from September 2019 through February 2020. Physicians were asked to complete the survey after the presentation. The survey included an informational bar graph on the risk of hospitalization and severe illness in vaccinated seronegatives, and the implications of pre-vaccination test specificity. Additional surveys were provided to pediatricians in the San Juan metropolitan area. The University of Puerto Rico School of Medicine Department of Pediatrics was provided with a copy of the CDC presentation, published literature on CYD-TDV, and available laboratory tests for pre-vaccination screening.

Regarding the results, only 31% of the 110 physicians who responded indicated that they administer vaccines in their office. Most vaccines are administered at private or public immunization clinics on the island. Of the responding physicians, 98% acknowledged that dengue is a significant public health problem in Puerto Rico. Only 58% of physicians knew that there was an FDA-approved dengue vaccine, 40% knew that the schedule requires 3 doses and 48% did not know. Only half (59%) of the physicians answered the question on the efficacy of the vaccine and 54% stated that they do not know the approximate efficacy. The answer to the question pertaining to the percent of false positive tests the physicians were willing to accept was distributed between 0% to 5% of false positives for 54% of physicians, while 35% were not sure. Assuming that a laboratory test with acceptable specificity were available, 73% of physicians said they would recommend the vaccine and 21% were not sure.

Of those who would recommend the vaccine, 96% think that dengue is an important public health problem in Puerto Rico and that a reasonably effective vaccine is available for seropositive persons and 40% think that laboratory testing sufficiently reduces the possibility of vaccinating subjects with a false positive laboratory result. Of those unsure or unwilling to recommend the vaccine to their pediatric patients, 71% had concerns about the risks of vaccinating persons with false positive dengue laboratory results and 75% needed more information.

For patients diagnosed with dengue, 43% of physicians have documentation of a positive laboratory test in the medical record for some of their patients and only 5% have this for all of their patients. Physicians established that the necessary steps to enable a vaccination program for children in Puerto Rico include the Vaccines for Children Program (VFC) and private insurance coverage for the vaccine, and insurance coverage of the laboratory test for detection of past dengue infection. If insurance coverage for vaccine and laboratory tests were not available, 54% of physicians would still recommend the vaccine for private patients whose parents could pay for an approved laboratory test and the vaccination. However, 30% were unsure. If a recommended rapid diagnostic test for past dengue infection were available, 66% of physicians would support changes in Puerto Rico laboratory regulations. This is to allow such a test to be performed in the medical office, so that the first dengue vaccination would not require two or more patient visits. Most physicians (76%) would favor a pilot project with a phased in approach of dengue vaccination before implementing a large-scale program on the island.

A total of 38 participants were involved in the focus groups with parents of children between 9 and 16 years of age, of which 87% were mothers. The objectives of the focus groups were to: 1) assess acceptability of the vaccine; 2) determine barriers to and motivators for a dengue vaccination program; and 3) identify knowledge, attitudes, and beliefs towards vaccines in general. In terms of the methods, focus group discussions were conducted in 3 municipalities with a high dengue incidence (San Juan, Carolina, and Ponce). The sample was comprised of parents of children between 9 and 16 years of age who were recruited from pediatrician offices, the WIC (Women, Infants, Children) Program, schools, and the Boys and Girls Clubs of Puerto Rico. It is important to note that 63% of those parents had at least one year of college education and 33% had completed a Bachelor's or Master's Degree.

Prior to asking the questions a script was read with information about the dengue vaccine and doubts about the script were clarified for the participants. In terms of general opinions about vaccines, most participants had questions about having a dengue vaccine. They had positive opinions about vaccines in general, but some of them decided not to receive the influenza vaccine and were concerned about issues such as the influenza vaccine changing every year and efficacy. Some distrust some of the new vaccines and others had concerns about allergic

reactions and autism as a result of vaccination. In terms of opinions about dengue vaccine, most participants have questions and a few had mixed opinions about this vaccine. Some would wait to see the effects on other children and others do not find it necessary to have a dengue vaccine at this time. Almost all participants did not know about the dengue vaccine. In terms of willingness to vaccinate, 38% of parents said they would vaccinate, 30% would not, and 32% were unsure.

The barriers to vaccine program participation identified within this group included lack of or inconsistent information, high cost and lack of insurance coverage, time-consuming laboratory tests, side effects, laboratory test results not being 100% reliable, approval for use only in US territories, sickness at the time of vaccination, and low effectiveness of the vaccine. The motivators for vaccine program participation identified included: provision of correct vaccine information, information about dengue and statistics in Puerto Rico, prevention of future dengue infections, support from the Puerto Rico Department of Health (PRDH), laboratory confirmation of previous dengue infection, an epidemic, educational forums. Most participants would pay a deductible for the vaccine, but would prefer it at no cost. An acceptable insurance deductible for insurance participants would range from \$5 to \$20 and an acceptable cost without insurance would be about \$50 to \$80.

All participants wanted more information about DENVAXIA[®] and about the test to confirm past dengue infection. They have multiple questions, including:

- Why is the vaccine specific for children between 9 to 16 years of age?
- Where have clinical trials taken place and what were the results?
- What does the process of approval involve and how long does it take?
- What type of vaccine is DENVAXIA[®] and what are the components?
- What is the dosage and how many times does it have to be administered?
- What is the percentage of effectiveness?
- What is the evidence of short- and long-term side effects and how to treat side effects?
- Are there any possible interactions with previous medical conditions or medications?
- How does the vaccine react if people get vaccinated and later have dengue again?
- What countries are using the vaccine?
- Why is it approved for US territories only?
- Does the Puerto Rico Department of Health require the vaccine?
- What dengue tests are required and how accurate they are?

Participants stated that a culturally appropriate informed consent should include information about:

- Vaccine safety and effectiveness
- Confidentiality
- Specify laboratory test requirements prior to vaccination
- Specify consequences if vaccinated without a previous dengue infection
- Benefits and risks of vaccination
- Specific short-term and long-term side effects of the vaccine (i.e., if it could cause fever, headaches)
- Results from previous clinical trial studies with number of participants in the trials and percentage of effectiveness
- Information related to consent to be written in plain language and to be clear and concise

They all recognize that the best sources of information will include doctors (specifically pediatricians), nurses, the Academy at the University of Puerto Rico (UPR) School of Medicine at the Medical Sciences Campus, and CDC.

In conclusion with regard to the general population, participants demonstrated interest in the dengue vaccine among most adult participants for themselves and their children. Side effects and possible adverse reactions were the most important reason for those not wanting to receive the dengue vaccine. Among adult participants willing to receive the dengue vaccine, a high level of protection and minimal side effects were the most important features.

The conclusions from the physician knowledge and attitudes survey, most participants were pediatricians and only 30% of them administer vaccines at their offices. Almost all physicians recognize that dengue is a significant public health problem in Puerto Rico, but 43% were not aware that there is an FDA-approved dengue vaccine. Further physician education is needed regarding DENVAXIA[®] vaccine, its schedule and efficacy, and safety. Most physicians would recommend the vaccine if a laboratory test with acceptable specificity were available to document prior dengue infection. Medical record documentation of past positive dengue laboratory diagnostic tests for patients is limited. Most physicians view the necessary steps to establish a vaccination program in Puerto Rico to include VFC and private insurance company coverage for the vaccine and the laboratory test.

Regarding the conclusions from the parental acceptability focus groups, most parents would agree to vaccinate if they have information on DENVAXIA[®]. The most important barrier for parental consent to vaccinate with the dengue vaccine is lack of detailed information. The most important motivators are having information about the vaccine's effectiveness; side effects; rationale for use in Puerto Rico; and current use in other countries; having the support of the UPR, PRDH, and CDC; and the disease prevention impact of the vaccine. The most important influencers will be pediatricians and the family.

Discussion Points

Dr. Romero inquired as to where the other 69% of vaccines are administered if only 31% of vaccines are administered in physician offices.

Dr. Esquilin indicated that the other 69% are administered at either private or public vaccine administration clinics on the island. The vaccines that are provided by the VFC program are given to the patients in clinics that are run by the PRDH. The patients who have medical insurance can get their vaccines from private clinics established in various private hospitals on the island.

Dr. Szilagyi said he thought a lot of this confirmed other studies of providers and patients that there is general interest in vaccines, but that these practical feasibility issues can either facilitate or get in the way. He asked what the level of insurance coverage is for the laboratory test or for the vaccines beyond VFC in Puerto Rico, and whether the public health clinics perform the laboratory tests.

Dr. Esquilin indicated that they do not have that information yet. They need to have the laboratory test approved and then submitted to the insurance companies to find out whether they will cover it. The laboratory test has to be done at a laboratory because in Puerto Rico, there are regulations that establish that physicians cannot do any laboratory testing in the office or in a clinic. It has to be done by a laboratory technician in the laboratory. They have not been able to do even HIV rapid tests in the labor room. There is no point-of-care testing in Puerto Rico at this time.

Dr. Bernstein said it sounded like pediatricians would be a large influence on acceptance of this vaccine and providing the important information that is necessary, and asked whether in the health centers pediatricians or other child health professionals are administering the vaccine to 69% of the children. If they are not going to see pediatricians, it will be difficult for pediatricians to be influencers. Plus, it adds additional steps to go to get the laboratory test and then the vaccination.

Dr. Esquilin responded that the pediatricians are not physically at the immunization clinics. They are depending on the information provided by the nurses on site. The pediatricians will see the patients in their offices and will recommend a vaccine, but most patients will still have to go to immunization clinics to get the vaccine. Then they will receive additional information from the nurses and the consent form from the administration clinic nurse. The pediatrician will recommend and order the laboratory test, receive the result, and approve the administration of the dengue vaccine.

Dr. Atmar pointed out that one of the issues the WG is struggling with, and ACIP also has struggled with during previous presentations, is the logistical nightmare of having to go through the additional step of getting the testing done. The child presents to the pediatrician's office, then has to go to the laboratory to get the testing done, then the pediatrician has to evaluate the results, and then send the patient to the public health clinic to get the vaccine. While the vaccine may be a benefit to the child, the logistics of doing that and the additional concern of paying for the cost of the laboratory test, which is not covered through the VFC, is a problem. That is a major concern. One of the possibilities would be to get a point-of-care test, but it would require a change in the law essentially to allow that point-of-care test to be done in the doctor's office—assuming a sensitive and specific point-of-care test could even be developed.

Dr. Bernstein asked whether there is a reasonably robust electronic health record (EHR) if the difficulties with the hurricanes wiped out that option.

Dr. Esquilin indicated that for most of the hospitals and private pediatric offices on the island, there are no EHRs. In the main academic center in San Juan, an EHR was implemented about 3 months ago. That is a major difficulty also for getting the results of the laboratory tests available. If an EHR is not available, patients will have to return to the pediatric office to deliver the results. It is difficult to determine past dengue infection because it must be filed in the paper medical record in the physician's office.

Dr. Hunter said that as a clinician and as a medical advisory to a local health department, this analysis sets the standard for future similar analyses for the purposes of ACIP voting when there are such complicated implementation issues. The 3 study groups selected were very appropriate, the questions asked were right on track for what public health and clinical practice need to know, and the speed with which it was done and the size of the samples were appropriate for how fast this was needed. He commended Dr. Esquilin for setting the standard for the future.

Dr. Lee asked whether there is an electronic immunization registry available and, if so, whether it would be possible to amend it to enable laboratory testing to be part of the record. She also inquired as to whether these children potentially would be eligible for the Vaccine Injury Compensation Program (VICP) if they experienced any adverse effects.

Dr. Esquilin indicated that they do have an electronic immunization record that was created through the VFC, which is available to the entire population, even from private clinics. They are going to work to change the registry to include the dengue vaccine and probably the laboratory result as well so that if a patient presents to a different clinic, they can easily find out whether the patient had the test done and qualifies to receive a first, second, or third dose of the vaccine.

Dr. Rubin (HRSA) responded that because Puerto Rico is a US territory, injuries alleged to be due to covered vaccines will be covered by the VICP. However, dengue vaccine is not covered at this time.

Dr. Goldman (ACP) observed that the study opened up a lot of possibilities, such as in South Florida. There is a very large population from Puerto Rico where he is in South Florida, so it would be interesting to expand this kind of work to determine whether there is any role for those who are not living in Puerto Rico and have moved to South Florida. Florida does have a registry, but the problem they have is implementation. While they do have electronic records, not everyone is fully integrated with the state registry. In terms of point-of-care testing, he has tested for dengue antibodies for patients of his who have traveled, had symptoms, and tested positive or negative. With the local and national laboratories, those tests can be done and the results communicated to the patients. It would be interesting to see some integration with the state vaccine registry and then be able to get the laboratory data.

Dr. Coyle (AIRA) pointed out that it is one thing to have an indicator indicating a positive or negative result, it is a different issue all together to incorporate laboratory results into an electronic immunization registry. Because of the considerations that need to be put in place and the interoperability between an EHH and an Immunization Information System (IIS), these are major shifts in the way this typically has been done. It is not impossible, but it does need to be considered.

Dr. Esquilin agreed that it is difficult, but expressed her hope that they can do it.

Dr. O'Leary (PIDS) recalled that 17% said they did not believe in vaccines and he wondered whether that level of vaccine confidence was common in Puerto Rico.

Dr. Esquilin responded that there is a high percentage of vaccination in Puerto Rico for most of the vaccines. What has helped significantly is incorporating vaccines as a requisite to enter school for school-aged children. The acceptability of vaccines on the island is actually very good. However, they do have groups who are against vaccines who are not willing to vaccinate their children.

Dr. Waterman clarified that the 17% represented 17% of those who did not want to use the vaccine. For the total surveyed population, it was much lower at about 3%.

WHO Global Position on Dengue Vaccination

Joachim Hombach, PhD, MPH
Executive Secretary, SAGE
World Health Organization

Dr. Hombach spoke on WHO's position and rationale on dengue vaccination, which has evolved and is important to understand. This vaccine has been used only in 2 very limited public programs, so the experience overall is not large. However, experience from other vaccines also can be drawn upon. WHO's mandate is to advise countries on the use of vaccines against diseases of public health importance. The first generation dengue vaccine, DENVAXIA[®], was licensed initially at the end of 2015 and then in a number of endemic countries in 2016. In 2016, WHO issued its first position on dengue vaccination.

Dengue is really a global public health priority. In 2019, WHO had listed dengue among the 10 biggest public health threats for the year. That was certainly done with the perspective that the environment is extremely favorable to further transmission and spread of dengue. This is combined with the situation that there are very few tools apart from environmental management and vector control, which is very difficult and very difficult to scale. The need for a vaccine is extremely important and unfortunately, the situation is that the vaccine is not very easy to implement. Dengue is not a high mortality disease if it is well-managed. Instead, it is a morbidity disease. It causes a lot of fear among populations, a lot of strain to the health system, and actually can have quite considerable economic costs. The survey just seen demonstrates that there is a high awareness around dengue.

In terms of the time scale of the 2 pivotal studies that were used for licensure of DENVAXIA[®], CYD-TDV 14 in Asia and CYD-TDV 15 in Latin America, had overlapping age groups. Asia was 2 to 4 years of age and Latin America was 9 to 16 years of age. WHO's position in 2016 took into account data that became available around Month 48. It is important to underline that the efficacy against symptomatic dengue was moderate, while the efficacy against hospitalized and severe dengue was actually very high. It is important to keep in mind that this vaccine has been performing very well against the more severe forms of the disease. The issue that occurred is that in the third year after the start of the trial, a safety signal occurred in the youngest group with an increase in hospitalized dengue. At that time, the evidence for what was causing this was not entirely conclusive. While there was a strong suspicion that it was tied and linked to serostatus, the way the trial was set up did not allow for a definitive conclusion of this.

A lot of supportive work was done through mathematical modeling for the first submission. WHO convened 8 mathematical modeling groups that essentially assessed the impact of the vaccine in different transmission settings. They way these models assumed that the vaccine would work was that essentially it was assumed that the vaccination acts like a primary silent infection, which then brings the person into a situation during which there is an increased susceptibility to the disease and secondary infection if they were naïve at the timepoint of the vaccination. Thereafter, the person should be in the secondary low disease risk base. If the person has already had a single infection, the vaccine to some extent would move it to the post-secondary phase where protection would be seen. This model structure fitted most nicely with the empiric data that was collected from the vaccine trial.

WHO's position in 2016 was essentially a position that was informed by trial data and extensively by mathematical modeling. It was a position of risk minimization in populations with a statement that basically, population-based recommendations should be done only if the seroprevalence of the entire population is high. The model predicts the highest effectiveness of the range of seroprevalence was about 70% at 9 years of age. There was a recommendation against using the vaccine in lower seroprevalence settings. When WHO issued the recommendation, they also issued a very strong call for the company or the global community to gather more data on the performance of the vaccine to understand the root causes of the safety signal and to be more specific in terms of risk minimization on the balance of risk when using this vaccine.

About 2 years later, the company performed an additional retrospective analysis. When they issued the first position, nobody actually knew that this was possible at that time to perform such an analysis that indirectly estimated the serostatus at baseline before the administration of the first dose. These data came out around Month 66. These were the data that resulted in a major outcry, particularly in the Philippines and other countries that started to use the vaccine in 2016. The study that was published in the *New England Journal of Medicine (NEJM)* used three different methods to assess serostatus at its baseline. It is important to understand whether the antibodies are actually derived from the vaccine, which has a Yellow Fever (YF) component, or from natural infection. Therefore, one approach involved testing a sample of vaccinees with a new dengue NS1 antibody test which is specific for antibody to wild dengue virus as opposed to vaccine induced antibody. Two independent statistical models also were used to impute the serostatus at baseline, and the results were pretty similar. Over the full duration of the 66 months, the model shows continuous and reasonably robust protection against hospitalized and severe illness in seropositive individuals. However, the hazard ratio does not look favorable in the seronegatives. In other figures that include the younger age groups, this ration becomes even less favorable.

While that figure to some extent cooperated with what was in the mathematical models and also quantitatively very much fitted with the mathematical models, it created a major crisis in the sense that now there was a situation that they could describe and say which individuals would not benefit from the vaccine or would be put at risk. That also required WHO to reconsider its position, which they swiftly did. Risk minimization in seronegatives could still be thought of in terms of two approaches. One is still the population seroprevalence criteria without screening, perhaps with some tweaking in terms of what seroprevalence level would be accepted as the minimal level. The other is the individual-level pre-vaccination screening, which is the way the label has been changed. Both have major implications and come with major problems. A validated rapid diagnostic test for past infection is not available at this time, but there is a lot of work being done on this. When SAGE developed the policy, they considered a number of dimensions, including the following:

- Benefits and harm (population, individual, eligible populations)
- Ethical considerations (harm of omission versus harm of commission)
- Risk perceptions and communication (DENVAXIA[®] crisis occurring in the Philippines)
- Screening tests versus serosurveys (feasibility, test limitations, costs)
- Implementation challenges
- Impact, age, cost-effectiveness

On balance, there was a very clear statement that this vaccine should be used only with individual-level pre-screening prior to vaccination, even though the door was left open somewhat for seroprevalence-based use of the vaccine.

The WHO dengue position was updated on 7 September 2018 and is as follows:

Countries should consider introduction of the dengue vaccine CYD-TDV **only if the minimization of risk** among seronegative individuals can be assured;

For countries considering vaccination as part of their dengue control programme, **pre-vaccination screening is the recommended strategy**;

Screening tests would need to be **highly specific** to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated.

Point-of-care tests, i.e. RDTs, would facilitate the implementation of the pre-vaccination screening strategy, but have **not yet been validated** for that purpose.

Decisions about implementing a pre-vaccination screening strategy with the currently available tests will require **careful assessment at the country level**, including consideration of the sensitivity and specificity of available tests.

The **age group** to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission.

The **optimal age group** to be targeted is the age before which severe dengue disease incidence is highest;

If pre-vaccination screening is not feasible, vaccination **without** individual screening could be considered in areas with recent documentation of seroprevalence rates conducted at **high resolution**;

Documented seroprevalence rates of **at least 80%** at age 9 years should be aimed at;

Communication needs to ensure appropriate and **full disclosure of the risks** of vaccination of persons with unknown serostatus (but also on false positives if prescreening with RDT is done).

The screening tests are a problem because high specificity is needed to avoid vaccinating seronegatives, but robust and high sensitivity also is needed to assure that the seropositives have really been vaccinated. Obviously, there is a lot of work that needs to be done and is going on in order to validate rapid diagnostic tests. The performance of the test depends upon the epidemiology of the setting, so it requires very careful assessment.

The age group for vaccination also is relatively tricky. It depends on the transmission intensity, as well as operation and programmatic considerations. From an epidemiological understanding of the vaccine performance point of view, the optimal age group is the one for which the most individuals have monotypic. That would be the age before the peak of severe disease as a proxy. The door was left open for a population-wide use of the vaccine with very high seroprevalence, even though this is not thought to be feasible. Most important is full disclosure and communication around the risks with this vaccine in relation to individuals with unknown serostatus, as well as communication around the risk that comes from false positives if pre-screening with rapid diagnostic tests.

There are a number of implementation considerations. It is very important to understand the local burden of disease and the age distribution to understand which group is best to target. The rapid diagnostic test must be assessed in the context of the specific epidemiological setting. It is clear that besides the vaccine, there will be the cost of the test and for the program operations. Program operations costs can be quite significant, which is known from other vaccines such as HPV delivered in schools. This is a relatively important cost factor that needs to be put into the equation. Implementation strategies depend upon the age group chosen, which might be of strong interest in school-based vaccination. It also is important to have the necessary follow-up and recordkeeping, including electronic records. There are communication issues as well. As for any vaccine, it is important to assess local priorities in relation to other alternative investments. It is extremely important to highlight that this is a vaccine that is partially effective, which means that vector control needs to continue and clinical management must be kept at a high level of support.

According to the way the vaccine works, the aim is to optimize and target the group that has the highest proportion of monotypic seroprevalence. This depends upon the force of infection and the transmission intensity. In higher transmission settings, the peak will be earlier and more distinct. There also will be less seronegatives, so even with the pre-screening approach there is more flexibility in terms of which transmission settings are targeted. It is certainly more effective and more cost-effective to go into settings with a pretty high burden of dengue.

The diagnostic tests are an area of active research. The positive predictive value (PPV) and negative predictive value (NPV) depend on the seroprevalence, so it is important to look at this in the context of the epidemiological setting. A group has conducted some surveys and interviews in Asia and Latin America in terms of acceptable level of sensitivity and specificity for rapid diagnostic tests. This is also something that needs to be brought into the equation if considering implementation of this vaccine.

Regarding communication, Heidi Larson surveyed the confidence in vaccines in general, vaccination in the Philippines, and after the dengue vaccine crisis. She found that a strong confidence in vaccine was completely shattered with the crisis, and now a very strong proportion of the population has a tendency to disagree with the importance and safety of the vaccine. This led to a decrease in vaccination coverage in general and provoked measles outbreaks, so the repercussions for an immunization program can be dramatic if the communications are not properly handled, as the Philippines situation has shown. The program in the Philippines was essentially abandoned after 800,000 doses had been administered. To Dr. Hombach's knowledge, no follow-up evaluation is being done, so there were children who received either 1, 2 or 3 doses. Some of his colleagues did an estimation to try to understand the proportion of exceeding cases of dengue in relation to those being prevented through the use of the vaccine. This was based on the data from the Sanofi clinical trial, which had a large subgroup in the Philippines with the assumptions of seroprevalence and performance of the vaccine, it was estimated that about 18 dengue hospitalizations are avoided among seropositive for 1 precipitated hospitalization in dengue-naïve vaccinees and 10:1 in relation to disease. So, the overall performance of the vaccine is most likely to be positive, but it has not even been assessed and things have just been left in limbo, which is very unfortunate for the population and understanding of the vaccine.

In terms of communication, tailored and targeted communication is extremely important. Communication must be proactive—it must happen before a program is being put in place. WHO's communication specialists tell them that once a perception has formed on a vaccine, it is very difficult to change it. It is very important to convey the facts and figures ahead of time.

Many things need to be communicated about this vaccine because it is very complicated. A recap of key communication topics for dengue includes:

- Clear communication on benefits and risks
- Rationale for pre-vaccination testing
- Risk of vaccinating seronegatives due to false-positive test
- Exclusion of tested persons from vaccination due to false-negative test
- Partial effectiveness of the vaccine and continued need for vector control measures
- Information on vaccine schedule
- Information on duration of immunity and possible needs for booster vaccination, which is still under investigation

Key considerations in developing a communication strategy are as follows:

- Communication needs to be anticipated from the outset and must be proactive; avoid reactive communication
- The strategy needs to segment to different audiences (medical professional associations, general HCW's, teachers, parents, adolescents, journalists...)
- Messaging and materials need to be targeted to different audience groups
- Communications is not enough—there needs to be opportunities for actual dialogue to build understanding and support.

In conclusion, dengue is a high public health priority in many countries. The current vaccine has shortcomings, but offers significant clinical benefit in a seropositive target population. Any use of the vaccine must be accompanied with a risk minimization strategy. Pre-vaccination screening is the method of choice to minimize risk. Vaccine performance is expected to be best in individuals with a history of monotypic infection. This population can most easily be targeted and identified in high-transmission settings. Rapid diagnostic test characteristics must be assessed in the context of the epidemiological setting. Significant investments are needed in relation to programmatic implementation, monitoring and communication. Failure to do so can have dramatic consequences for public health confidence. Surveillance, vector control, environmental management, and case management must be emphasized in the dengue endemic setting, irrespective of whether a vaccination program is implemented.

Discussion Points

Dr. Poehling requested clarity about whether the estimations on Slide 18 were for the entire population, and whether they have separated the estimation of those preventions to those precipitated by age group for the children 9 to 16 years of age in particular.

Dr. Hombach said the assumption here regarded whether the vaccine performs the same if 1, 2, or 3 doses are given. Because this is not known, they had to assume.

Dr. Lee found it incredibly helpful to hear WHO's experience and what went into their decisions. She found it interesting because she was realizing that in a way, the way this was framed is the way value in healthcare in general is thought of. One of the things in addition to considering population benefits/risks and individual benefits/risks is that the way WHO evaluated the impact of its recommendation and subsequent implementation also takes into consideration the impact on providers and patients. She was particularly struck by the vaccine confidence slide, which was interesting and offered a good way for ACIP to think about the impact of its

recommendations in that how they make them and how they communicate them can make a major difference in public health efforts to help the population.

Summary of WG Considerations

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 latest considerations. As Dr. Atmar mentioned, the WG does not expect to make recommendations until an independent evaluation of the specificity of available laboratory screening tests for past dengue infection is available for presentation to ACIP. This contingency makes it likely that the WG would not make a preliminary recommendation until the October 2020 ACIP meeting at the earliest.

First, Dr. Waterman summarized what he thought the WG considered the key points and take-homes from Dr. Esquilin's presentation on community, pediatrician, and parent knowledge and sentiments about DENGIVAXIA® in Puerto Rico. The key survey results showed that 73% of pediatricians would use DENGIVAXIA® given an acceptable pre-vaccination screening laboratory test. The majority (84%) of pediatricians would like to see a screening test with a specificity of at least 95% and preferably 99%. About 76% of pediatricians supported a pilot project. Over 80% of pediatricians felt the vaccine and laboratory test insurance coverage were necessary steps for implementation. Clearly, parents and physicians need more education about the vaccine. There is a need to explain the rationale for vaccinating in dengue endemic areas such as Puerto Rico. There were relatively few negative perceptions about the vaccine in the surveys that were conducted.

The Dengue Vaccines WG conducted an informal poll of its formal members last December. The WG members were asked to comment on what information is needed to make a recommendation on DENGIVAXIA®. By far, the biggest and most often mentioned concern was having an acceptably specific pre-vaccination screening laboratory test for past dengue infection, and the sense that there is not yet enough information about available tests. The logistical challenges of pre-vaccination screening and the cost of the laboratory test also were frequently mentioned. Dr. Hombach's presentation echoes the WG's concerns about unintended consequences and the importance of community engagement to assure the perception of transparency. A number of WG members felt that a pilot vaccination program could be implemented in children with documentation of previous dengue infection in the medical record, and Dr. Esquilin's presentation on the Puerto Rico survey suggests support for such an approach among Puerto Rico pediatricians. A pilot vaccination program might enable logistical issues to be worked on and solved. With regard to a pilot, one WG member commented that an anticipatory recommendation would allow for insurance coverage for the laboratory test to be put in place as testing technology improves, and argued for the advantage of having a recommendation in place in advance of possible dengue outbreaks. A number of WG members expressed skepticism about a shared decision-making recommendation. Comments included that shared decision-making passes off the decision making to the clinician, and that such decision-making would be complex and could depend on the level of education of the family.

The CDC Dengue Branch Laboratory is in the process of evaluating available and newly developed dengue IgG laboratory tests. The process involves three steps, the first of which is the WHO and CDC landscape analysis that has been mentioned previously. As a result of that first step, 14 laboratory tests will be evaluated. CDC has recently procured a number of these tests and is in the process of procuring the others. Two stages of evaluation are planned, with the first being evaluation for the intended use of many of these tests for diagnosis of acute dengue infection, and the second evaluation based upon performance of long-term samples for past infection. All of the tests will be evaluated head-to-head with a curated set of PCR-positive samples CDC has selected, with the hope of completion of the process by the next ACIP meeting.

As a reminder, Dr. Perkins presented data from the University of Notre Dame's modeling of the cost-effectiveness of DENGIVAXIA® in Puerto Rico during the October 2020 ACIP meeting, but did not have an opportunity to share these tables at that time:

	Baseline	Baseline	Averted	Averted	
Prior Exposure in 9 Year Olds	Symptomatic	Hospitalizations	Symptomatic	Hospitalizations	Additional Hospitalizations
0.3	225,460	51,790	1,886	1,662	214
0.5	262,852	62,113	4,652	3,415	184
0.6	275,317	64,571	6,377	4,664	164

The table provides the estimated population impact of DENGIVAXIA® vaccination in Puerto Rico over a 10-year timeframe for vaccinating 9-year-olds screened by a laboratory test with 95% specificity and 80% sensitivity at different seroprevalence levels. With a 50% dengue seroprevalence, which is what preliminary data show for Ponce, Puerto Rico, about 3400 hospitalizations would be averted among seropositives, and 184 additional hospitalizations would be seen among vaccinated dengue naïves who tested seropositive—a ratio of over 18.6:1.

Regarding one of the questions raised about where laboratory testing would be performed in Puerto Rico, Dr. Waterman indicated that there are currently 2 laboratory tests that are Clinical Laboratory Improvement Amendments (CLIA-approved) that Sanofi has evaluated in publications. Their evaluation showed 99% specificity. These tests are available at private laboratories. There have been discussions with the health department regarding whether they could perform these tests, but that is completely up in the air.

In conclusion, Dr. Waterman invited feedback on whether there were other specific data ACIP would like to see and/or other considerations ACIP would like the WG to address.

Discussion Questions

Dr. Wharton asked if the primary side effect of concern is severe dengue, that hopefully most patients would fully recover from without sequelae, whether that would be covered by the VICP. While she understood that dengue vaccine is not covered at this time, if it were recommended and the vaccine was included in the VFC program, she thought that the program was designed

to address adverse events that have long-term sequelae rather than something like an illness that might result in hospitalization from which the patient would recover.

Dr. Rubin (HRSA) responded that there is a severity requirement. In terms of being eligible for compensation, symptoms have to last more than 6 months or there should be inpatient hospitalization for intervention or death.

Dr. Poehling asked if VICP coverage would be impacted by whether the recommendation is for shared decision-making versus being fully recommended.

Dr. Rubin (HRSA) replied that what is currently covered in the VICP program are vaccines that ACIP has routinely recommended for children that are in the immunization tables, not necessarily clinical decision-making.

Dr. Cohn said she thought it was similar to VFC and private insurance coverage in that, if it is on the immunization schedule, it will be included in the VICP. It can be either routine in that all children in a group should receive a vaccine or children should receive a vaccine based on shared clinical decision-making. This is in general how this has been done.

Dr. Rubin (HRSA) added that for example, meningitis is covered for age groups versus specific populations at this time. To be covered, ACIP has to recommend a vaccine for routine administration to children, but there also are other procedures before the coverage goes through.

Dr. Lee emphasized the importance of being mindful of potential disparities in access to testing or care that may result, and that her question derives from the fact that she is worried about families who may not have the ability to pay for hospitalizations out-of-pocket if that were the case and/or other sequelae.

Dr. Waterman said he thought Dr. Esquilin would be in the best position to answer that question, but his impression was that access to care in Puerto Rico is quite good. A large percentage of the population is covered by the indigent healthcare system. While the healthcare system has been compromised by the public debt, overall access is good in general. He believes that children who have severe illness have access to hospitalization. Dr. Esquilin concurred with Dr. Waterman's response.

Dr. Szilagyi said he was intrigued by the concept of a pilot project. Often in system or practice improvement, a pilot is conducted to work out feasibility issues. He wondered what the goal would be for the pilot and what would be learned that then would allow it to be scaled up in a meaningful way.

Dr. Waterman stressed that this is a complex logistical process to undertake. Most of the discussions regarding pilots is that there is not a large population, but a significant number of persons who already have documented dengue infection in their medical record and that they could start to vaccinate those persons. Simultaneously the education process could continue along with work to resolve some of the logistical and insurance issues that have been raised. The argument could be made that this would be a symbolic gesture that might not have much population impact, but it would get some children vaccinated and perhaps could generate momentum toward figuring out how to make this a programmatic process if that was the will of the health department and the pediatric community. It would not be a pilot of the 2- or 3-step laboratory process, though that might be piloted eventually as well.

Dr. Cohn asked whether the WG had discussed whether an ACIP recommendation would be needed for the specific group of individuals who have documented previous dengue before conducting a pilot, from an economic perspective.

Dr. Waterman responded that they had not done so from an economic perspective. While there is individual benefit to the vaccine, the WG would want to see some type of ACIP recommendation before commencing a pilot. Further discussion is needed on that.

Dr. Atmar added that the WG has not specifically addressed that, but the discussions thus far have been in the context of an ACIP recommendation. Part of the rationale for that pertains to covering the cost of the vaccine, which potentially is a major consideration.

Dr. Maldonado (AAP) said she thought they had come a long way since the original discussions. She does want to revisit the issue of a pilot at some point and what that actually means, given that there are complex scientific, functional, and operational issues. It would be helpful to try to pilot the building of a screening test into public and private sector settings. There will be a series of steps depending upon the sensitivity/specificity of the test, informed consent, who will pay, et cetera. A pilot may be beneficial in helping to answer some of these complicated issues. For example, rapid testing was rolled out for HIV through a series of implementation demonstration projects in the US. It took a while to acquire community input, engaging healthcare personnel, et cetera. It took a while to get that all aligned before legislation could take place. Now it is generally seamless, but it took a lot of work to get there.

Dr. Waterman emphasized that consent is a very important issue. While it may not be informed consent as in a clinical trial, behavioral scientists will need to develop culturally appropriate language to ensure that the community understands the risks and benefits and have that thoroughly researched ahead of time. Even for a pilot, there would need to be considerable education of physicians in the community.

Dr. Hunter thinks one of the major advantages of conducting a pilot would be increasing the confidence of the general public, pediatricians, and parents that they will be heard and implementation will be done correctly. If he were in Puerto Rico in the local or territorial health department, he would want to be the ones deciding whether a pilot would be conducted. While he would consider CDC guidance, a pilot would need to be implemented by the local folks with a lot of support. Therefore, they should have the authority to do that.

Dr. Waterman responded that the PRDH is the spokesperson for immunizations in Puerto Rico, so that clearly would have to occur.

Dr. Atmar said that his understanding of the way that the childhood immunization program has worked in Puerto Rico, particularly with respect to the high compliance because of the school requirements, one of the challenges with shared decision-making would be that if dengue vaccine was added to the schedule, it would be handled like other childhood vaccinations assuming a child is seropositive. While there would be information presented to the family, whether it would be required as part of attending school to increase compliance and make the system work has not been fully decided. That would be the usual means by which such vaccinations would be implemented. There was some concern in the WG that this could cause problems in the future.

Polio Informational Session

Introductions

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

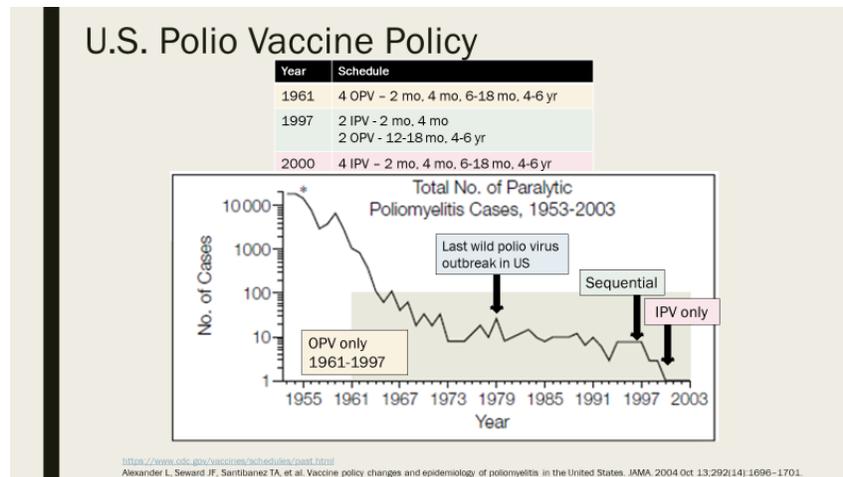
Dr. Shimabukuro indicated that during this session, Dr. Walt Ornstein would provide a historical perspective on the US transition from oral polio vaccine (OPV) to the all inactivated polio vaccine (IPV) schedule. Dr. Ornstein is with Emory University and was the Director of CDC's National Immunization Program (NIP) during the switch. Dr. Ornstein would be followed by Mr. John Salamone, a former consumer representative member of the ACIP and former member of the Advisory Commission on Childhood Vaccines (ACCV). Mr. Salamone was accompanied by his wife, Kathy. Their son, David, contracted vaccine-associated paralytic polio (VAPP) from an OPV vaccine he received as a child. The Salamones' public advocacy for switching to an all-IPV schedule was a key factor in accelerating the change. Mr. Salamone would be followed by, Dr. Stephen Cochi from CDC's Global Immunization Division (GID) who would provide an update on progress and prospects for global polio eradication.

Polio and Polio Policy in the US: The OPV to IPV Switch

Walter A. Ornstein, MD
Professor of Medicine, Global Health, Pediatrics, and Epidemiology
Emory University

Dr. Ornstein indicated that it had been 20 years since the US embarked on an all-IPV schedule in 2000. It was a difficult decision to abandon OPV because of fears that there could be polio outbreaks. The fact that OPV crippled people for life when there was a perfectly safe alternative IPV, led to the decision to move to an all-IPV schedule. There was medical consensus that this was causally related, albeit very rare. Dr. Ornstein said that his goal for this session was to explain why the decision was difficult and what led to making the decision to move to an all-IPV schedule, which he discussed in the context of three eras.

Polio vaccination began with IPV in 1955. In 1961, there was a switch to OPV that lasted until 1997 when a sequential schedule of IPV followed by OPV was adopted. The present era of IPV has spanned from 2000 to the present. This is a graph of polio in the US. It is important to note that this is a log scale and should be interpreted with caution:



In 1961, the US went to an all OPV schedule administered at 2 months, 4 months, 6-18 months, and 4-6 years. The sequential schedule that began in 1997 included 2 doses of IPV at 2 and 4 months and then 2 doses of OPV to get the benefits of both vaccines. That was followed in 2000 by the 4 IPV doses administered at 2 months, 4 months, 6-18 months, and 4-6 years. There was a marked reduction in polio with IPV, but some problems were still being observed with it at that time. Switching to OPV, there was a marked reduction. The last outbreak of polio in the US was in 1979. While there was no wild polio virus (WPV) after that, there still were about 8 to 10 cases a year of VAPP. The switch to sequential resulted in a reduction of cases, but did not eliminate poliovirus. Subsequent to the switch to all-IPV, there has been no polio.

The OPV era lasted from 1961-1997, Albert Sabin pioneered the live-attenuated weakened viruses. These were preferred for a variety of reasons. First, it was substantially less expensive than the IPV. In addition, it was substantially easier to administer. Non-technical individuals could be trained to administer it because it was oral as opposed to requiring injections. A major issue was that it was far better at inducing intestinal immunity than IPV. IPV and OPV both induced great individual systemic immunity, so they protected the central nervous system (CNS). However, IPV could be inferior in terms of the intestinal side and the extent that fecal-oral spread was important or not. Another advantage of the OPV at the time, before the detection of circulating vaccine-derived poliovirus (VDPV), was that passive spread of the vaccine viruses permitted immunization of individuals who were not being reached in the immunization program who would have been completely susceptible with a switch to IPV.

Roland Sutter assembled some data pertaining to intestinal immunity and shedding in two studies. One study was by Ghendon and Sanakoyeva many years ago in which he studied 4 groups of patients: Susceptible Control Subjects, IPV-Vaccinated, OPV-Vaccinated, and Naturally Immune. He challenged them with a Type 1 oral vaccine virus and then assessed the proportion of shedding, the duration, and the mean titer of virus excreted to calculate an excretion index. With regard to fecal shedding, the IPV group was not very different from the OPV group. They shed for a somewhat shorter period, but substantially more than the OPV group and at a substantial 2-log increase titer and about a 1-log difference from the completely susceptible individuals. IPV was 95% better than nothing, but 5 times worse than OPV.

At that time, it was unclear what that meant. The other data are from Onorato and McBean looking at children who received a complete schedule of IPV or a complete schedule of OPV and then were challenged with 2 doses of OPV. With regard to oral transmission, which would be dependent upon a pharyngeal setting, there was no real difference in IPV or OPV. They were equivalent. Where IPV was clearly inferior was in intestinal shedding. One of the issues that was not clear was the major mode of transmission in the US at the time.

The other advantage of the oral vaccine regards the spread. Chen and others led a study in 1996 of children in Detroit and Houston who were documented to be completely unvaccinated. High proportions of them were found to have antibody to polio, suggesting that passive spread of the oral vaccine virus was good because it was reaching people who were not being reached by the program. At this point, nothing was known about circulating VDPV polio outbreaks.

In 1960 when the switch was made from IPV to OPV, there were still between 2500 and 3000 cases still occurring. Even though there was IPV at that time, it was not as potent as the current IPV. After the switch, there was a dramatic reduction, but there remained a constant level of polio occurring. One of the things that made everyone feel better, but in retrospect was not adequate was that there was a Vaccine Injury Compensation Program (VICP). For the 8 to 10 people who were paralyzed a year due to the OPV, at least there was financial remuneration that began in October 1988. It applied not only to recipients, but also to passive contacts of recipients who developed VAPP.

Moving to the sequential schedule era that began in 1997, the doses of IPV were administered at 2 and 4 months and the age was raised for the third dose at that time to 12 months. That was in part because one of the major risk groups for paralytic polio from OPV were those with immune deficiencies. Waiting to administer the OPV gave more time to diagnose those immune deficiencies. The hope was to achieve the benefits of both vaccines. Overall, there was about one case of VAPP per about 2 million doses of trivalent OPV (tOPV) distributed. The risk was highest after the first dose at 1 per 750,000 doses compared to subsequent doses at 1 per 5.1 million doses. The case categories included: Recipients, Contacts, Community-Acquired, and Immunologically Abnormal. The immunologically abnormal group was large, particularly those with B-cell immunity defects. As this period occurred, less and less risk was observed of wild virus. This called into question continued use of this vaccine, given the lower risk.

The Americas were certified as being WPV-free in 1994, with the last case occurring in Peru in 1991. In a meeting in June 1996, parents and children with VAPP attended the ACIP meeting and had a major impact on the thinking. Dr. Ornstein read a passage from the ACIP minutes that were recorded at the time, "They described the parents' emotional and financial burdens, though significant, as inconsequential compared to their children's probable lifelong struggle to have a normal life. Repeatedly, they stressed that these tragedies need not have happened. They agreed that OPV's risk was not adequately conveyed." This was not about polio vaccine versus no vaccine, but instead was about a polio vaccine versus a polio vaccine and one which was completely safe. This was very different from having only OPV, in which case OPV use would have continued.

The reasons for adopting a sequential schedule were that: 1) a sequential schedule was expected to reduce recipient VAPP by more than 90%; 2) a sequential schedule may reduce contact VAPP; 3) continued use of OPV induces high levels of intestinal immunity; 4) maintaining OPV in the schedule results in fewer injections than going to an all-IPV schedule; 5) and stocking of both vaccines facilitates choice for providers. The ACIP recommendation published in the *Morbidity and Mortality Weekly Report (MMWR)* on January 24, 1997 read:

“ACIP recommends a transition policy that will increase use of IPV and decrease use of OPV during the next 3–5 years.”

- ❑ “...The risk-benefit ratio associated with the exclusive use of OPV for routine immunization has changed because of rapid progress in global polio eradication efforts.”
- ❑ “The relative benefits of OPV to the U.S. population have diminished because of the elimination of wild-virus–associated poliomyelitis in the Western Hemisphere and the reduced threat of poliovirus importation into the United States.”
- ❑ “The risk for vaccine-associated poliomyelitis caused by OPV is now judged less acceptable because of the diminished risk for wild-virus–associated disease (indigenous or imported).”

This is the summary table depicting the advantages and disadvantages of the three vaccination options:

Attribute	OPV*	IPV [†]	IPV-OPV [‡]
Occurrence of VAPP [§]	8–9 cases/year	None	2–5 cases/year**
Other serious adverse events	None known	None known	None known
Systemic immunity	High	High	High
Immunity of GI mucosa	High	Low	High
Secondary transmission of vaccine virus	Yes	No	Some
Extra injections or visits needed	No	Yes	Yes
Compliance with immunization schedule	High	Possibly reduced	Possibly reduced
Future combination vaccines	Unlikely	Likely	Likely (IPV)
Current cost	Low	Higher	Intermediate

* Oral poliovirus vaccine.
[†]Inactivated poliovirus vaccine.
[‡]Sequential vaccination with IPV and OPV.
[§]Vaccine-associated paralytic poliomyelitis.
 ** Estimated.

Poliomyelitis prevention in the United States: introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 1997 Jan 24;46(RR-3):1–25.

A very important study was conducted by Mark Miller, who was at CDC at the time, taking into account the higher costs of IPV showing that changing to an IPV-only or a sequential schedule would cost \$28.1 million and \$14.7 million, respectively. The bottom line is that the costs per case of VAPP prevented were estimated as \$3.0 million and \$3.1 million for each option, respectively. Despite that, the need was felt to switch due to moral and ethical reasons.

Moving to the IPV-only era, Dr. Ornstein called out Dr. Paul Offit, who played a major role having chaired the ACIP WG on Polio during this period that led to the all-IPV recommendation. With the change to a sequential schedule, VAPP was reduced but was not eliminated. It was not that the IPV failed, but was the fact that many providers having OPV in their stock were still administering OPV first without IPV. Therefore, the problem was still occurring with the sequential schedule. During 1997–1999, 13 VAPP cases occurred, 7 in 1997 and 3 each in 1998 and 1999. None of these cases occurred in persons who had followed the sequential IPV-OPV or all-IPV schedules. Of the cases, 9 occurred in OPV recipients, 6 of which were associated with a first OPV dose; 2 occurred among contacts of OPV recipients who had not followed the

sequential schedule; and 2 were among immunologically abnormal OPV recipients, both associated with a second dose. There have been no cases of polio since 2000.

In terms of key issues, continued VAPP cases were seen. There were no declines in childhood immunization coverage seen after adoption of the sequential schedule. No indigenous WPV has been seen in the US since 1979. Further progress was made by the Global Polio Eradication Initiative (GPEI) toward eradication (i.e., decreased risk of importation). No declines in immunization coverage were observed, despite the need for additional injections. ¹CDC investigated the impact of the change to a sequential IPV-OPV vaccination schedule at two large West coast health maintenance organizations (HMOs), which found that children receiving IPV as their first polio vaccination were as likely to be up-to-date at age 12 months as children receiving OPV. ²CDC's National Immunization Survey (NIS) provides ongoing estimates of vaccination coverage in the United States. National vaccination coverage achieved was greater than or equal to 90% each for three doses of poliovirus vaccine [¹Impact of the Sequential IPV/OPV Schedule on Vaccination Coverage Levels -- United States, 1997 [Internet]. [cited 2017 Jan 4]. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/00055785.htm> ²Centers for Disease Control and Prevention (CDC). National vaccination coverage levels among children aged 19-35 months--United States, 1998. MMWR Morb Mortal Wkly Rep. 1999 Sep 24;48(37):829–30].

In June 1999, the ACIP recommended an all-IPV schedule:

“ACIP recommends an all-IPV schedule for routine childhood polio vaccination in the United States to eliminate the risk for VAPP.”

- ❑ “Since 1997, the global polio eradication initiative has progressed rapidly, and the likelihood of poliovirus importation into the United States has decreased substantially.”
- ❑ “The sequential schedule has been well accepted, and no declines in childhood immunization coverage have been observed.”

Regarding the take-home messages, science is critical in making recommendations. There were unknowns and it is difficult because decisions must be made without all of the information sometimes. Epidemiologic and implementation science alone are not the only inputs into policy. Moral and ethical issues need to be considered. Cost-effectiveness can be superseded. Had the concerns about the lack of intestinal immunity and decreased coverage with IPV turned out to be correct, ACIP would have been severely criticized. However, it was necessary to make that decision based on what was known and this was the most appropriate decision. It has turned out to be the right decision as there has been no polio in the US since 2000.

Discussion Points

Dr. Hunter emphasized that this is a great example of what history can teach us, and it demonstrates how ACIP needs to balance difficult issues, safety, and other issues with the need to make a decision in the absence of all of the information.

Dr. Kimberlin (AAP) recalled that there was perhaps an enhanced IPV product and wondered when that was developed and how it factored in with the decision-making, and whether the sequential approach was an option from the beginning and who thought of it.

Dr. Ornstein indicated that the enhanced IPV was licensed in the 1980s. It did play a role because in essence, the IPV used in the 1950s was not as potent and not as immunogenic as that IPV. The enhanced potency IPV was the only vaccine at the time these decisions were undertaken. Regarding the sequential approach, he thought the initial debate was one or the other. The sequential approach consideration regarded the notion of getting the benefits of both of the vaccines. There were data from Hungary in which IPV preceding OPV caused a major reduction in VAPP. The sequential approach was a “no lose” option until they found out that you did lose. It was thought to be the best schedule to begin with and clearly, there were no cases of VAPP between 1997 and 2000 in people who had received the sequential schedule.

Dr. Romero observed that presentations such as this allow ACIP to look back at the efforts the committee has made and allows them to focus past efforts on current problems and projects.

Parent/First ACIP Consumer Representative

Mr. John Salamone

**Past Consumer Representative, CDC Advisory Committee on Immunization Practices
Past Member, HHS Advisory Commission on Childhood Vaccines**

Mr. Salamone expressed his gratitude for the opportunity to appear before ACIP. He noted that it had been 17 years since he served on ACIP, and that it was nice to be back among familiar and friendly faces. He found himself thrust into the polio vaccine debate because his son, David, was born with Bruton’s Disease Syndrome, an immunodeficiency disorder that prevented him from making B-cells. Because of that genetic disorder, David, like dozens of other US children at the time, contracted polio from the oral vaccine as an infant in 1990. It left him with an atrophied leg, but with the help of physical therapy, a brace, and a supportive family, he lived a somewhat normal life.

After dealing with the initial grief of seeing their only son disabled, he and his wife Kathy were determined to find out why a seemingly healthy baby would suddenly lose the use of his leg overnight. They discovered that other children experienced similar adverse reactions each year from OPV, even though there was a safer and just as effective IPV. While removing an entrenched vaccine from the market that had been a mainstay in immunization history for 40 years was not easy, it had to be done. OPV did its job and did it well, but any vaccine needs to undergo a periodic benefit/risk evaluation. In the case of OPV, the only cases of polio in the US for decades stemmed from the very vaccine meant to eliminate the disease. Changing to a safer IPV schedule was critical and overdue.

With his background in journalism, Mr. Salamone knew he could write—so that was what he did. He reached out to magazines, newspapers, and broadcast media to tell David’s story and the need for a safer all-IPV immunization schedule to replace the current all-OPV schedule. To his surprise, he started to get calls and stories on David began to appear in newspapers like the *Washington Post* and the *New York Times*, as well as magazines such as *Good Housekeeping* and *Family Circle*. Since he had worked in Congress in the 1970s, he contacted some old friends, and even the White House since President Clinton’s Chief of Staff, Leon Panetta, was a friend for 20 years.

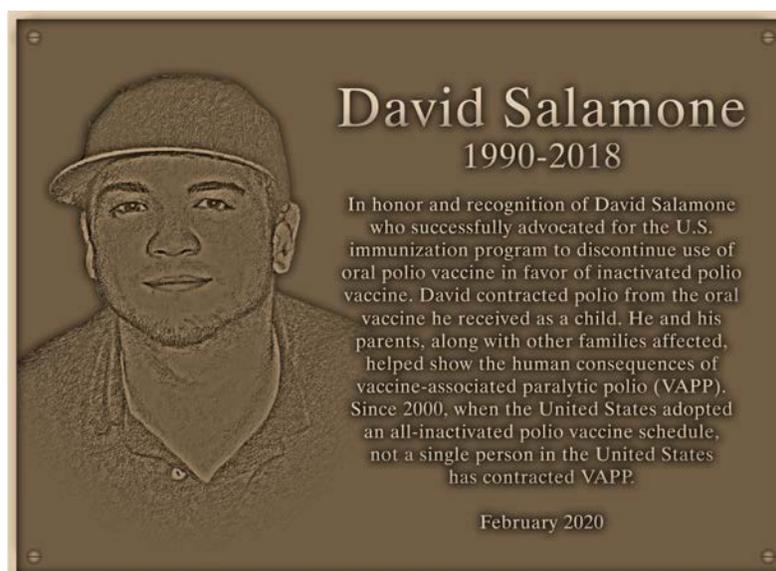
They felt that they were getting out the world, but nothing was changing. They desperately wanted a safer polio vaccine, but they knew they could not get it with just press and politicians. They made their case to the media and Congress, and now they needed to focus on the decision-makers and work within the system at the CDC. It was time to go to Atlanta. Mr.

Salamone researched and discovered other VAPP families throughout the US. They shared their stories and their pain. He convinced many of them to join him and Kathy at a meeting of the ACIP in June 1996 in a room much smaller than the one in the Global Communication Center (GCC) and located in another building. This was clearly a turning point. He thinks they spoke to the hearts and minds of ACIP members who, for the first time, saw the faces and braces of those behind the statistics. It helped those children, and especially his David, feel they could make a difference and help others. Their sacrifice was not in vein. While it took several more years, ACIP transitioned to an all-IPV schedule in 2000. Since that date, there have been no cases of VAPP in the US. The US can now truly be said say that since the year 2000, polio has been eradicated in the US.

In conclusion, Mr. Salamone said that he learned several things from this experience. He learned that the professionals who work at the CDC and who serve on important committees like ACIP are dedicated, intelligent, caring individuals who take seriously their responsibility to create a world where people are not injured and die from preventable diseases. Because of their work, many of those diseases such as smallpox, measles, rubella, tetanus, diphtheria, and polio have been virtually eradicated in the US. Today, the CDC and ACIP are on the frontlines of protecting Americans from the growing concern of coronavirus. They have saved too many lives to count, and he expressed gratitude to them for the decisions they have made based on science and not rumors and unwarranted fears.

Mr. Salamone said he wished David were there on the 20th year since VAPP-free America. He passed away on September 7, 2018. On his last ambulance ride to Georgetown Hospital, he said to his mom, "I wanted to do something good for people. I know I could help." David did good and he helped. He and Kathy are grateful that CDC and ACIP recognized his contributions and those of others for a safer US immunization program.

Dr. Shimabukuro requested that Kathy Salamone and Dr. Ornstein join him and John Salamone on the stage. Through the generosity of the CDC Foundation, Dr. Shimabukuro presented the following plaque honoring David Salamone, his parents John and Kathy, and other families who advocated for switching from OPV to IPV. Immediately following this session, the plaque was to go on display in front of the CDC library:



Dr. Romero pointed out that Mr. Salamone was the first Consumer Representative on the ACIP. His work continues today through each subsequent generation of Consumer Representatives ACIP has. He has a living legacy on this committee.

Global Polio Eradication: Progress and Prospects

Stephen L. Cochi, MD
Senior Advisor to the Director
Global Immunization Division, Center for Global Health
Centers for Disease Control and Prevention

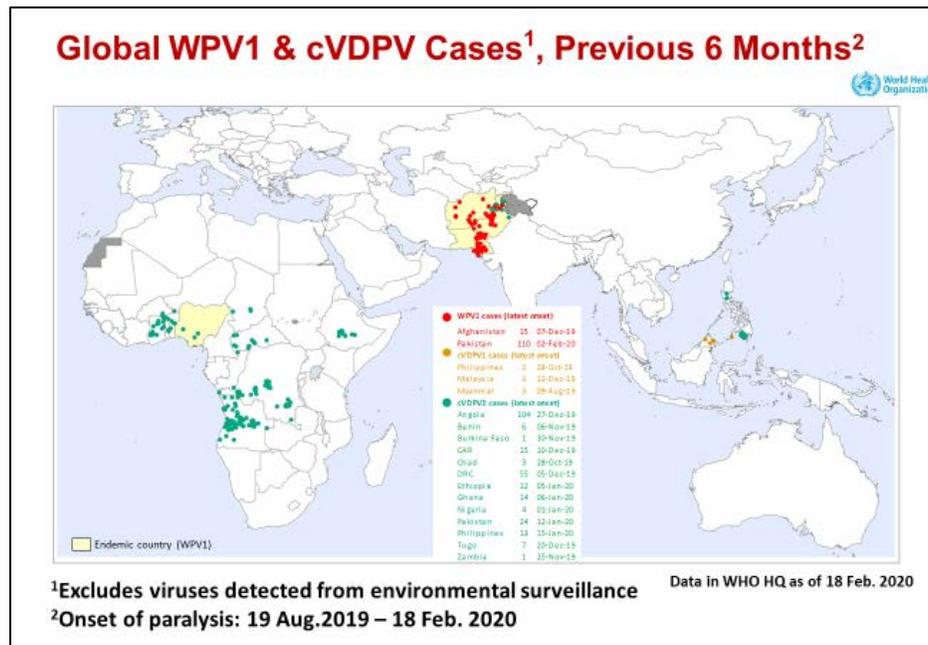
Dr. Cochi provided an update on global polio eradication and the effort to eliminate all poliovirus disease, WPV and VAPP, pointing out that he had good and bad news to share. The four primary strategies being followed in the polio eradication and endgame strategy include:

1. Poliovirus Detection and Interruption
2. OPV2 Withdrawal, IPV Introduction, Immunization System Strengthening
3. Containment and Global Certification
4. Transition Planning

During this session, Dr. Cochi focused on Strategy 1—poliovirus detection and interruption. Before the Global Polio Eradication Initiative (GPEI) began, polio was endemic in 125 countries and paralyzed over 350,000 children every year. As of the end of 2019, there were only 3 polio-endemic countries: Afghanistan, Nigeria, and Pakistan. While Nigeria is still considered to be an endemic country, it has not had WPV in over 3 years and soon may come off of the list of endemic countries. In terms of major milestones, the last WPV Type 2 (WPV2) occurred in India in 1999. India had the last WPV case in 2011, which was a major milestone in the world. In 2015, the Global Certification Commission (GCC) formally certified the world as free of WPV2. The same occurred for WPV Type 3 (WPV3) in 2019. WPV3 has not been seen anywhere in the world since 2012 in Nigeria. Given the accelerated global effort, since 1988 the number of polio cases averted on an annual basis globally has increased tremendously. Cumulatively, nearly 19 million polio cases have been prevented in the world through polio vaccination. The certificate showing that the world is free of WPV3 was signed on October 17, 2019 by the GCC headed by Professor David Salisbury of Great Britain.

To summarize the good news, more than 7 years have passed without detection of WPV3. The GCC certified WPV3 eradication last Fall. The number of inaccessible children in formerly Boko Haram-controlled areas in Borno State, Nigeria has been drastically reduced from about 500,000 children inaccessible in 2016 to a current estimate of about 30,000 children who remain inaccessible. These estimates are determined by satellite photography that is done on a regular basis to look at villages and towns that are still in existence or have been burned or otherwise destroyed by Boko Haram. More than 3 years have passed without detection of any WPV in Africa. The African RCC will convene in June 2020 in Nigeria on a preliminary basis to determine regional certification of all WPV disappearance in the African Region. IPV supplies are now sufficient for routine immunization, and catch-up of missed cohorts is in progress. There was a major problem with the supply when IPV was added to OPV-only using countries. There is a cohort of about 40 million children who need to be caught up since 2016. The Europe Regional Office (EURO), Pan American Health Organization (PAHO), and South East Asia Regional Office (SEARO) of WHO all remain polio-free, including from circulating vaccine-derived poliovirus type 2 (cVDPV2). Gavi (the Vaccine Alliance) has joined GPEI.

Now for the bad news. This is a graphic of the WPV1 and cVDPV cases for the previous 6 Months in the world as of February 18, 2020:



The red dots represent cases if WPV1 is limited to Afghanistan and Pakistan, with the bulk of cases occurring in Pakistan. The green dots reflect cases of cVDPV2, while the small number of yellow dots represent an outbreak of cVDPV1 in Malaysia and the Philippines.

To summarize the bad news, WPV1 cases increased from 33 cases in 2018 to 173 cases in 2019. Of those, 144 were in Pakistan where there was a major surge in polio cases. The Taliban ban on house-to-house vaccination in Afghanistan is severely affecting the ability of the program to carry out campaigns. In Pakistan, a new government is starting to provide national leadership. However, over 6 months passed in the second half of 2019 without large-scale vaccination campaigns and WPV cases surged. WHO's Africa Regional Office (AFRO), Eastern Mediterranean Region Office (EMRO), and Western Pacific Regional Office (WPRO) all battle outbreaks of cVDPV2.

To further explain cVDPV, polioviruses can rarely regain the ability to cause paralysis and tOPV has attenuated WPVs. That attenuation results in markedly less ability to cause paralysis than WPV, less capacity to pass from person-to-person than WPV, and a similar induction of antibodies as WPV. OPV polioviruses in areas with low polio vaccine coverage can rarely mutate during prolonged circulation and become VDPVs. That mutation consists of back-mutations to make the vaccine neurovirulent, as well as recombination events with non-polio enteroviruses (EVs) to make the vaccine viruses better able to transmit and cause paralysis. These viruses become VDPVs, which is the scientific name given to these viruses. They are able to spread and cause paralysis and outbreaks rather than just isolated cases of VIPP. Those viruses are the result of back-mutations toward neurovirulence.

Approximately 700 paralytic cases cVPDV2 polioviruses cases were confirmed during the 15-year period from 2001-2015, while there were no WPV in the world. This prompted the strategic decision to withdraw OPV2 use in all routine and supplementary immunization activities going from a trivalent to a bivalent 1 and 3 serotype vaccine. In 2016, the policy was implemented to remove the Type 2 component and go to a bivalent vaccine in 155 OPV-using countries in the world. This switch took place over the course of about 1 month. This was a massive effort because it involved taking back and destroying every vial of tOPV, ceasing further distribution of this vaccine, and adding IPV in order to benefit from both vaccines.

The rationale for introducing IPV was that IPV complements tOPV by increasing immunity to all three types of polioviruses. This is part of a transition to withdraw all OPV from the world. After the switch, IPV will provide protection against paralysis from Type 2 polioviruses and boost immunity against Types 1 and 3. In previous OPV2 recipients, IPV will boost intestinal immunity to infections with Type 2 polioviruses. There was strategic use of IPV in response to Type 2 poliovirus outbreaks alongside monovalent OPV2 (mOPV2) mass campaigns to increase population protection from paralysis.

In terms of the results, there were fewer cVDPVs in 2016 than in over a decade. There was a Type 1 cVDPV outbreak on the island of Hispaniola. There was a predominance during the period of time from 2000-2016 of cVDPV2, which peaked in 2009. The majority of these were occurring in Nigeria. The switch occurred in 2016, at which time a nadir of cVDPV was reached.

Then, some bad news ensued. After reaching that nadir in 2016, the number of cVDPV2 cases and outbreaks increased dramatically. This represented an unprecedented phenomenon that had to be dealt with. Several outbreaks have been terminated after successful implementation of at least two mOPV2 rounds. However, many responses required over 4 rounds of mOPV2 to stop outbreaks. Many new emergences are occurring across the African region due to low quality responses with mOPV2. This is characterized by many countries with weak immunization systems, low routine immunization coverage, and low population immunity against the Type 2 virus as a result. Increasingly, outbreaks are occurring in areas where mOPV2 has not been used in a mass campaign. These outbreaks tend to occur in low-performing countries around the edges just outside the targeted geographic area for the OPV2 mass campaigns. These outbreaks are being caused by decreasing population mucosal and systemic immunity since OPV2 was withdrawn in 2016 and through population movement from the geographic areas where mOPV2 is being used to areas adjacent to that where it was not used.

Thus, there is an evolving new challenge that has never been faced previously. The program is battling many outbreaks of cVDPV2 in Sub-Saharan Africa, and is at risk of re-establishing poliovirus Type 2 endemicity in Africa with the cVDPV-derived virus. There is now detection of cVDPV2 outbreaks in Asia in China, Pakistan, and the Philippines that may herald a global emerging problem. There is a limited supply of global mOPV2 in the stockpile, which requires balancing its use with the availability of new shipments and the need for more production.

Dr. Cochi shared an article published last Fall by Helen Branswell, a well-known journalist and science writer who has followed the polio eradication situation for many years. The article was titled, *'The Switch' was supposed to be a major step toward eradicating polio. Now it's a quandary.* He pointed out that the dictionary definition of "quandary" is "a state of perplexity or uncertainty over what to do in a difficult situation." In terms of where to go from here, efforts are being made to improve the quality of mOPV2 campaigns by more rapid deployment of mOPV2 supplies, revised strategy guidance for control of cVDPV2 that is more aggressive (finalized in January 2020), and increased scope and quality of mOPV2 of mass campaigns with a surge in

technical support. Work is also underway to accelerate the development and regulatory review and use of novel OPV2 through the Emergency Use Listing (EUL).

mOPV2 is a genetic modification of the existing OPV2. For the past several years, the Gates Foundation has invested heavily in the development of this new vaccine, as well as nOPV1 and nOPV3 that are not as far along in the development stage. The two candidate vaccines have multiple changes in the genome on the 5' and 3' ends. One of the vaccines also has multiple changes in the nucleotide sequence in the P1 region, which is the capsular protein. The belief is that these re-designed vaccines will decrease the risk of seeding new cVDPVs and the risk of VAPP when deployed under cVDPV2 outbreak control circumstances.

The regulatory approval process for this new vaccine is being accelerated through an EUL. The owner of the EUL is the WHO Essential Medicine Department (EMP). The goal is to make "experimental" health products available for emergency response. The EUL is very new and as such, no products have been listed under the EUL thus far. The eligibility criteria for an EUL is that it has to be a product that deals with controlling the spread of a disease that already has been deemed a Public Health Emergency of International Concern (PHEIC), which falls under the International Health Regulations (IHRs) governed by the WHO. Coronavirus recently has been declared a PHEIC. There are very few such instances in which this has been used. This is the fastest way to obtain regulatory review and approval.

Dr. Cochi briefly described the process that will be necessary for ramp-up of nOPV2 clinical development and production to align with EUL approval. Many studies already have been conducted in adults, and more recently in children, to develop the database on immunogenicity and safety and shedding of these viruses in children 1 to 5 years of age. Genetic stability already has occurred in adults and is in the process of being studied in young children. A pilot production scale facility in Indonesia has been identified. The WHO process is anticipated to take the next 3 months. During that period of time, approximately 4 to 8 million pilot doses of vaccine are being developed by the Indonesia manufacturer. Further studies will then be conducted on the genetic stability, updated stability data, and further examination of the production facility on a commercial scale through a 1-month review. By July to August of 2020, the hope is to have 100 million doses commercially available for use in the field. By the end of the 2020, another 100 million doses are anticipated to be ready for commercial availability/use. It is anticipated that these 200 million doses of vaccine will be utilized in a transition period as a replacement for the current mOPV2.

In summary, polio eradication made some progress in 2019, but encountered serious challenges. WPV eradication requires access in Afghanistan and vaccination quality improvements and accountability in Pakistan. Several cVDPV2 outbreaks threaten the success of "the switch" and may lead to re-establishment of Type 2 endemicity. mOPV2 needs to be replaced as soon as feasible by nOPV2, which is more stable genetically. A second dose of IPV in routine immunization is under discussion when supplies allow. It is anticipated that supplies will grow with entering into the market of a number of developing country manufacturers, so this could take place in the near future. Securing the funds to run the program is a very high priority, and has been emphasized by having to respond to all of these VDPV outbreaks.

Discussion Points

Dr. Jean Smith indicated that she retired from CDC in 2018. She said she was fortunate for CDC to second her to WHO in India, Nepal, and the Southeast Asia Region from 1995-2005 thanks to Dr. Cochi. She requested that Dr. Cochi say something about the situation in VAPP in countries still using OPV, whether the incidence is known, and the awareness and reaction if there is VAPP in these countries.

Dr. Cochi replied that there continues to be VAPP in the OVP-using countries. However, it is very difficult to define what is/is not a VAPP case in these developing country situations because they do not have the technology available like industrialized countries such as the US has to make those distinctions. The incidence of VAPP has decreased substantially, given that the OPV2 that was causing about 90% of all of the DVPD cases was responsible for about 40% overall of all of the VAPP cases. In a general sense, it can be said that the incidence of VAPP is down. However, the goal is for the incidence of VAPP to go to 0 by withdrawing all OPV, including the use of bivalent OPV (bOPV). The problems with the cVDPVs outbreaks have delayed the transition toward an all-IPV future.

Hepatitis B Vaccines

Sharon Frey, MD
Chair, Hepatitis Vaccines Work Group
Saint Louis University Medical School

Dr. Frey indicated that the Hepatitis B Work Group (WG) is continuing its work. The current term of reference for this group is to update the recommendations for hepatitis B vaccination among US adults. The current recommendations for hepatitis B have been updated twice since 2008. This included new recommendations plus several updates, as well as the recommendation for use for adjuvanted Hepatitis B vaccine:

- ❑ Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. *MMWR* April 20, 2018;67:455–458.
- ❑ Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR*, January 12, 2018;67(No. RR-1):1–31.

The WG has been busy. From September 2019 through November 2019, the WG developed a PICO question and estimated denominators of risk groups. In January 2020, the WG gave a presentation of interim results of a post-marketing surveillance study that was done by the Principal Investigator (PI) at Kaiser Permanent Southern California (KPSC). The WG discussion in Spring 2020 will include discussion of the cost-effectiveness analysis (CEA), which is currently under ACIP technical review in an external WG.

The policy question under discussion for the next round is, “Should a routine universal HepB-vaccination strategy (2-dose and 3-dose schedules) be utilized vs. the current risk-based vaccination strategy (2-dose and 3-dose) for adults?” The outcomes of interest include: Mortality, Morbidity, Incidence, Vaccine Uptake, Seroprotection, and Adverse Events (Mild and Serious).

The next steps are to continue deliberations on updates to adult hepatitis B vaccination. That will include completion of the CEA review process and presentation of the CEA to the WG; discussion of the final results of the post-marketing surveillance study for HEPLISAV-B®, when available; and initiation of the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) and Evaluation to Recommendation (EtR) framework for universal adult hepatitis B vaccination.

General Best Practices

Overview

Paul Hunter, MD
Chair, ACIP General Best Practices Work Group
Associate Professor of Family Medicine and Community Health
University of Wisconsin School of Medicine and Public Health
Associate Medical Director, City of Milwaukee Health Department

Dr. Hunter noted that he is the outgoing Chair for the Best Practices WG and that Dr. Bahta is the incoming Chair and Dr. Sanchez is the other ACIP member serving on the WG.

The terms of reference for the General Best Practices WG are to: 1) Revise the ACIP [General Best Practice Guidelines for Immunization](#). The last revision was in 2019, sections of which are to be revised every two years; 2) Address issues related to general best practices for vaccines and immunization programs; and 3) Work on emergent issues that do not clearly belong to another specific pre-existing WG.

The adult and child adolescent schedules summarize the ACIP vaccine-specific recommendations for implementing those recommendations in clinical and public health practice. The *General Best Practice Guidelines for Immunizations* help clinicians, nurses, pharmacists, and other vaccinators answer practical questions that are not or cannot be directly addressed by vaccine-specific recommendations.

The *General Best Practice Guidelines for Immunizations* are CDC guidance with input from the WG. Major changes require discussion by the ACIP, but rarely would this require a vote. Updates are uploaded to the ACIP website on a rolling schedule, primarily in order to maintain accreditation for continuing education credit.

Update on Recent Postings

Andrew Kroger, MD MPH

Medical Officer

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Kroger pointed out that this informational session would complete a loop with ACIP that began during the October 2018 meeting involving content that was added to the *General Best Practice Guidelines for Immunizations*, as well as supply additional updates that have been posted in the past year that represent harmonizing with voted, cleared ACIP recommendations.

On the landing page for the HTML versions of the *General Best Practice Guidelines for Immunizations* documents, each of the light gray banners in the center of the page represents a separate listing of all of the general topics:

- Introduction
- Methods
- Timing and Spacing of Immunobiologics
- Contraindications and Precautions
- Preventing and Managing Adverse Reactions
- Reporting Adverse Events After Vaccination
- Vaccine Administration
- Storage and Handling of Immunobiologics
- Altered Immunocompetence
- Special Situations
- Vaccination Records
- Vaccination Programs
- Vaccine Information Sources

On the right side of the landing page is the link for information on how to obtain continuing education credit. The most recent renewing of the credit was in April 2019. That followed the October 2018 discussion. The new cover page reflects the new authorship, with Dr. Kroger and all of the ACIP Chairs of the General Best Practices WG since the previous revision of the document in 2017. One can access the PDF of the entire document or individual PDFs of all of the separate chapters. Because revisions occur constantly to this on-line document, it is not likely that a PDF of the entire document will remain timely for long.

Each revision is indexed by the date, in order of the most recent changes, with links to the appropriate areas of the document. Under May 14, 2019, Dr. Kroger inserted a notification that an entire section of the document, Vaccination Administration, was revised following the focused ACIP discussion and the clearance of the section through CDC eClearance. This is the section that was discussed and now added to the document. It reads:

Health Care Provider Exposure to Vaccine Components

Providers are sometimes concerned when they have the same contraindications or precautions as their patients from whom they withhold or defer vaccine. For administration of routinely recommended vaccines, there is no evidence of risk of exposure of vaccine components to the health care provider, so conditions in the provider labeled as contraindications and precautions to vaccine components are not a reason to withdraw from this function of administering the vaccine to someone else. Historic concerns about exposure to vaccine components are limited to non-parenteral vaccines in which some degree of environmental exposure is unavoidable (5, 6), or situations in which self-inoculation is likely due to the nature of the vaccine microbe [e.g. reduced attenuation of smallpox vaccine virus (7)]. Persons administering ACAM 2000 smallpox vaccine to laboratory and health care personnel at risk for occupational exposure to orthopoxviruses can decrease the risk for inadvertent infection through recommended infection prevention measures. However, because of a theoretical risk for infection, vaccination with ACAM2000 can be offered to health care personnel administering this vaccine, provided individual persons have no specified contraindications to vaccination (8).

There have been 6 other updates since October 2018 to the on-line document, which reflect harmonization with existing CDC content. It is important to note that all of this is content that is already in an *MMWR* vaccine-specific statement, so none of this is new. The first is the addition of the 2-dose series of HPV vaccine, which was added to the Timing and Spacing interval table. It accompanies the 3-dose series, which remains on the table. Also in Timing and Spacing, HIV was added to conditions for which PREVNAR 13[®] and Menactra[®] should be spaced by 4 weeks. Providers are recommended to administer PREVNAR 13[®] and then Menactra[®] 4 weeks later. There are three additions to the Contraindications and Precautions section. One is that an exception was carved out for recombinant zoster vaccine. There is no need for an interval between recombinant zoster vaccine and anti-herpes antivirals. This is a non-live vaccine, so the concern about interference does not exist with recombinant zoster vaccine.

Some changes were made to some of the listings in the table because of components that were identified. Yeast is acknowledged as a component of PCV13, which is relevant when discussing allergies. Pregnancy was added as a reason not to administer HPV vaccine. The language that states that “HPV vaccine is not recommended in pregnancy” follows the removal of HPV vaccine as a column listing for Precautions because pregnancy is not a precaution to HPV vaccine. It is that HPV vaccine is not recommended in pregnancy. The last change is under Storage and Handling. Content was removed from the previous published *MMWR* version of the *General Best Practices* regarding information about when to repeat doses of vaccine that are administered and then later found to be expired. This information had to be added back in. There are some interesting nuances here. Non-live vaccines generally would not require an interval from the vaccine that is invalidated because it is expired. The dose would just be repeated as soon as possible. The exception to that is SHINGRIX, which is not live but does require a 4-week interval because of safety considerations.

Vaccine Supply

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
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During this session, Dr. Santoli presented an update on the pediatric and adult HepB vaccine supply. She reported that Merck will begin distributing its pediatric monovalent HepB vaccine in the private sector effective March 9, 2020. As a reminder, Merck's limited supply previously was targeted toward the public sector using CDC's vaccine contracts. Now it will be available in the private sector as well. In addition, Merck projects that its available supply of monovalent vaccine will be sufficient to meet historical demand for this vaccine in both the public and private sectors.

Merck will not be distributing its adult HepB vaccine or the dialysis formulation through at least the first half of 2020. Dynavax and GSK have sufficient supplies of adult HepB vaccines 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. Hunter requested clarity that the Merck adult HepB vaccine shortage was not new.

Dr. Santoli clarified that the shortage has been ongoing for a couple of years. What is new information is that in October 2019, she reported that there would not be distribution through the end of 2020, but Merck is now saying it will not be distributing its adult HepB vaccine or dialysis formulation through the first half of 2020. That foreshadows what is to come and they are hoping to have another update the next time they talk.



Certification

Upon reviewing the foregoing version of the February 26-27, 2020 ACIP meeting minutes, Dr. Jose 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.

ACIP Membership Roster

October 2019
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Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2019 – June 30, 2020

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