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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 28, 29, & 30 2020
Atlanta, Georgia

Final - October 27, 2020

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
Atlanta, Georgia 30329
October 28-30, 2020

	AGENDA ITEM	PRESIDER/PRESENTER(s)
Wednesday, October 28, 2020		
10:00	**Welcome & Introductions**	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
10:30	**Immunization Schedules**	
	Introduction to combined immunization schedule work group	Dr. Hank Bernstein (ACIP, WG Co-Chair) Dr. Kevin Ault (ACIP, WG Co-Chair)
	Proposed changes to 2021 child/adolescent immunization schedule	Dr. Patricia Wodi (CDC/NCIRD)
	Proposed changes to 2021 adult immunization schedule	Dr. Mark Freedman (CDC/NCIRD)
11:30	***Break***	
11:45	**Seasonal Influenza Vaccines**	
	Introduction	Dr. Keipp Talbot (ACIP, WG Chair)
	Efficacy of cell-derived quadrivalent influenza vaccine (Flucelvax Quadrivalent) in children & adolescents ≥2 years to <18 years old	Dr. Gregg Sylvester (Seqirus)
	Influenza Disease Burden and Vaccine Impact Estimates, 2019-20 Season	Dr. Carrie Reed (CDC/NCIRD)
	End-of-Season Estimates of 2019–20 Seasonal Influenza Vaccine Effectiveness against Medically Attended Influenza from three U.S. Networks	Dr. Lisa Grohskopf (CDC/NCIRD)
	Updates and WG Considerations	Dr. Lisa Grohskopf (CDC/NCIRD)
12:30	***Lunch***	
1:15	**Orthopoxvirus Vaccine**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
	Orthopoxvirus work group background	Dr. Brett Petersen (CDC/NCEZID)
	JYNNEOS® (MVA-BN®) Smallpox and Monkeypox Vaccine	Dr. Heinz Weidenthaler (Bavarian Nordic)
	Variola virus plaque reduction neutralization assay for the Vaccinating against monkeypox in the Democratic Republic of the Congo with JYNNEOS®	Dr. Christina Hutson (CDC/NCEZID) Dr. Brett Petersen (CDC/NCEZID)
	Next Steps	Dr. Agam Rao (CDC/NCEZID)
2:45	***Break***	
2:55	**Dengue Vaccines**	
	Introduction	Dr. Robert Atmar (ACIP, WG Chair)
3:05	**Pneumococcal Vaccines**	
	Work group introduction	Dr. Katherine Poehling (ACIP, WG Chair) Dr. Miwako Kobayashi (CDC/NCIRD)
3:15	**Cholera Vaccines**	
	Work group introduction	Dr. Pablo Sanchez (ACIP, WG Chair)
3:25	***Break***	
3:30	**Public Comment**	
4:15	***Break***	
4:20	**Vote - Immunization Schedules**	Dr. Mark Freedman (CDC/NCIRD)
4:30	**Adjourn**	

Final - October 27, 2020

Thursday, October 29, 2020

10:00	**Unfinished Business and Agency Updates** CDC, CMS, FDA, HRSA, IHS, NIH, OIDP	
10:15	**Zoster Vaccine**	
	Introduction	Dr. Grace Lee (ACIP, WG Chair)
	Update on post-licensure safety monitoring of recombinant zoster vaccine (RZV, Shingrix) in the Vaccine Adverse Event Reporting System (VAERS)	Dr. John Su (CDC/NCEZID)
	Vaccine Safety Datalink (VSD) update on post-licensure safety monitoring of RZV	Dr. Jennifer Nelson (Kaiser Permanente)
	Risk of Guillain-Barré syndrome following herpes zoster	Dr. Tara Anderson (CDC/NCIRD)
	Summary and planned risk-benefit analysis regarding use of RZV in immunocompetent adults	Dr. Tara Anderson (CDC/NCIRD)
	Planned risk-benefit analysis regarding use of RZV in immunocompetent adults	Dr. Tara Anderson (CDC/NCIRD)
11:45	***Lunch***	
12:20	**Tick-borne Encephalitis Vaccine**	
	Introduction	Dr. Katherine Poehling (ACIP, WG Chair)
	Overview of tick-borne encephalitis (TBE) and TBE vaccine	Dr. Susan Hills (CDC/NCEZID)
	Immunogenicity and safety of Pfizer's TBE vaccine	Dr. Dr Heinz-Joseph Schmitt (Pfizer)
	Next steps for TBE vaccine work group	Dr. Susan Hills (CDC/NCEZID)
2:00	***Break***	
2:15	**Rabies Vaccine**	
	Introduction	Dr. Sharon Frey (ACIP, WG Chair)
	Minimum acceptable rabies antibody titer and implications on ACIP recommendations	Dr. Susan Moore (Kansas State University)
	Pertinent fundamentals of rabies immunology	Dr. Deborah Briggs (Kansas State University)
3:30	***Break***	
	Pre-exposure prophylaxis schedule: Grading of recommendations assessment, development, and evaluation (GRADE)	Dr. Agam Rao (CDC/NCEZID)
	Evidence to recommendation framework (EtR)	Dr. Agam Rao (CDC/NCEZID)
	Summary and next steps	Dr. Agam Rao (CDC/NCEZID)
4:50	**Adjourn**	

Final - October 27, 2020

Friday, October 30, 2020

10:00	**Coronavirus Disease 2019 (COVID-19) Vaccines**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
	Update from Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting	Dr. Doran Fink (FDA)
	NVX-CoV2373 Vaccine Candidate	Dr. Filip Dubovsky (Novavax)
	Janssen's SARS-CoV-2 Vaccine Program	Dr. Jerry Sadoff (Janssen)
11:45	***Break***	
12:00	Update on vaccine implementation planning	Dr. Janell Routh (CDC/NCIRD)
	Vaccinate with Confidence	Dr. Amanda Cohn (CDC/NCIRD)
12:30	***Lunch***	
1:15	FDA safety surveillance systems	Dr. Steven Anderson (FDA)
	Post-authorization safety monitoring plans	Dr. Tom Shimabukuro (CDC/NCEZID)
	Modeling strategies for the initial allocation of COVID-19 vaccines Discussion	Dr. Matthew Biggerstaff (CDC/NCIRD)
2:30	***Break***	
2:45	Updates to immunity and epidemiology to inform COVID-19	Dr. Megan Wallace (CDC/NCIRD)
	Ethical principles for early vaccine allocation	Dr. Mary Chamberland (CDC/NCIRD)
	Work Group interpretation of data	Dr. Sara Oliver (CDC/NCIRD)
	Policy questions, Evidence to Recommendation Framework, and Discussion	Dr. Kathleen Dooling (CDC/NCIRD)
4:45	**Adjourn**	

Acronyms

CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus Disease 2019
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]
NIAID	National Institute of Allergy and Infectious Diseases
OIDP	Office of Infectious Disease and HIV/AIDS Policy
RZV	Recombinant Zoster Vaccine
SAGE	Strategic Advisory Group of Experts
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
WG	Work Group
WHO	World Health Organization
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AECI	Adverse Events of Clinical Interest
AESI	Adverse Events of Special Interest
AFM	Acute Flaccid Myelitis
AGS	American Geriatrics Society
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
aIIV	Adjuvanted Inactivated Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
ANA	American Nurses Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APHL	Association of Public Health Laboratories
ARI	Acute Respiratory Infection
AS	American Samoa
ASA	Acetylsalicylic Acid
ASH	Assistant Secretary for Health
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
BSL-4	Biosafety Level 4
CBER	Center for Biologics Evaluation and Research
ccIIV	Cell Culture-Based Inactivated Influenza Vaccine
CDC	Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CEF	Chicken Embryo Fibroblast
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment
CLD	Chronic Liver Disease
CLI	COVID-Like Illness
CMS	Centers for Medicare and Medicaid Services
CMV	Cytomegalovirus
CNS	Central Nervous System
COI	Conflict of Interest
COU	Clinical Operations Unit
COVID-19	Coronavirus Disease 2019
COVID-NET	COVID-19-Associated Hospitalization Network
CoVPN	COVID-19 Prevention Network
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DRC	Democratic Republic of Congo

DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
EB	Empirical Bayesian
EBV	Epstein–Barr Virus
ECG	Electrocardiogram
ED	Emergency Department
EHR	Electronic Health Record
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
EV	Enteroviruses
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FFS	Fee-For-Service
FluSurv-NET	Influenza Hospitalization Surveillance Network
FQHC	Federally Qualified Health Center
FY	Fiscal Year
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GMPs	Good Manufacturing Practices
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HAIVEN	Hospitalized Adult Influenza Vaccine Effectiveness Network
HAN	Health Alert Network
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immune Globulin
HCoVs	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
Hib	Haemophilus Influenzae Type B
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSA	Human Serum Albumin
HZ	Herpes Zoster
HZWG	Herpes Zoster Work Group
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ID	Intradermal

IDCRP	Infectious Disease Clinical Research Program
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
IVIG	Intravenous Immunoglobulin
KAP	Knowledge, Attitudes, and Practices
KPSC	Kaiser Permanent Southern California
LAIV	Live Attenuated Influenza Vaccine
LRN	Laboratory Response Network
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal ACWY
MMWR	*Morbidity and Mortality Weekly Report*
MNT	Mouse Neutralization Test
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NACCHO	National Association of County and City Health Officials
NACHC	National Association of Community Health Centers
NACI	National Advisory Committee on Immunization Canada
NAIIS	National Adult and Influenza Immunization Summit
NAIP	National Adult Immunization Plan
NAM	National Academy of Medicine
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NGO	Non-Governmental Organizations
NHANES	National Health and Nutrition Examination Survey
NHIRD	National Health Insurance Research Database
NHIS	National Health Interview Survey
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIP	National Immunization Program
NIS	National Immunization Survey
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate

NOS	Newcastle-Ottawa Scale
NPRM	Notice of Proposed Rulemaking
NTV	Nerve Tissue Vaccine
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NVSN	New Vaccine Surveillance Network
OASH	Office of the Assistant Secretary for Health
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OMH	Office of Minority Health
PCECV	Purified Chick Embryo Cell Vaccine
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
Ph. Eur.	European Pharmacopoeia
PHAC	Public Health Agency Canada
PHN	Postherpetic Neuralgia
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PR	Puerto Rico
PrEP	Pre-Exposure Prophylaxis
PREVENT	Pregnancy Influenza Vaccine Effectiveness Network
PRNT	Plaque Reduction Neutralization Test
PRR	Proportionality Reporting Ratios
PT	Pertussis Toxin
PT	Preferred Terms (MedDRA)
PVRV	Purified Vero Rabies Vaccine
QALYs	Quality-Adjusted Life-Years
QC	Quality Control
QI	Quality Improvement
QIV	Quadrivalent Influenza Vaccine
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
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
RVNA	Rabies Virus Neutralizing Antibody
RVV	Rabies Virus Variants
RZV	Recombinant Zoster Vaccine
SAB	Spontaneous Abortion

SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBLA	Supplemental Biologics License Application
sBLA	Supplemental Biologics License Application
SCCS	Self-Controlled Case Series
SCR	Seroconversion Rate
SD-IIV3	Standard Dose Inactivated Influenza Vaccine
SHEA	Society for Healthcare Epidemiology of America
SLU	Saint Louis University
SME	Subject Matter Expert
TB	Tuberculosis
TBE	Tick-Borne Encephalitis
TIV	Trivalent Influenza Vaccine
UK	United Kingdom
US	United States
US Flu VE	US Influenza Vaccine Effectiveness Network
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
USG	US Government
USPHS	US Public Health Service
UTD	Up-To-Date
VA	(US Department of) Veteran's Affairs
VACV or VV	Vaccinia Virus
VACV-WR	Vaccinia Virus Western Reserve
VAERS	Vaccine Adverse Event Reporting System
VCD	Virologically Confirmed Dengue
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
VSD	Vaccine Safety Datalink
VTU	Vaccine Treatment Evaluation Unit
WG	Work Group
WHO	World Health Organization
WPV	Wild Poliovirus

Wednesday: October 28, 2021

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

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn called to order and welcomed everyone to the October 28-29, 2020 Advisory Committee on Immunization Practices (ACIP) meeting. She indicated that all of the meeting materials were available on the ACIP website, that this meeting was available by live webcast, and meeting participants had joined the meeting via Zoom. In addition, she indicated that the slides were made available through a ShareFile link for ACIP Voting, Liaison, and *Ex-Officio* members; videos of the live webcast would be posted on the ACIP website approximately 4 weeks after the meeting; and that meeting minutes also would be posted on the ACIP website, generally within 120 days of the meeting. She noted that slides to be presented during this meeting could be access by all participants via the ACIP website, but were not 508-compliant and would be taken down at the end of the meeting, made 508-compliant, and then reposted approximately 4 weeks following the meeting.

The next regular ACIP meeting will be convened on February 24-25, 2021 and will be virtual. It is not clear whether the June 23-24, 2021 meeting will be in-person or virtual, but a decision will be made in the Spring. The Fall meeting will be October 20-21, 2021. These meeting dates do not include emergency ACIP meetings. CDC anticipates that as COVID-19 vaccines are brought to the Food and Drug Administration for consideration for Emergency Use Authorization (EUA) as described during prior meetings, an ACIP meeting will be convened to deliberate recommendations for use for any COVID-19 vaccine product immediately after an EUA is issued. Additional meeting dates will be announced on the ACIP website. There also is a link at the bottom of the ACIP page to receive email announcements.

Dr. Cohn indicated that there would be a public comment period during this meeting. ACIP's oral and written public comment processes are designed to ensure that the public has an opportunity to inform ACIP's considerations for immunization recommendations. Efforts are being made to maximize opportunities for comments and make the public comment process more transparent and efficient. Those 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. Written public comments may be made via regulations.gov using the Docket ID: CDC-2020-0100. Information on the written public comment process, including information about how to make a public comment, can be found on the ACIP website.

Members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure 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 reviewed logistics and emphasized that this would be a very long meeting, with many topics on various vaccine products. She expressed appreciation for everyone's time and effort to make this possible by joining the meeting virtually.

Dr. Romero conducted a roll call of ACIP members during which the following COIs were identified:

- Dr. Robert Atmar is serving as the Co-Director of the Clinical Operations Unit (COU) of the National Institutes of Health (NIH)-funded Infectious Diseases Clinical Research Consortium (IDCRC) that is working within the COVID-19 Prevention Network (CoVPN) to evaluate Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccine candidates in Phase 3 clinical trials, including those produced by Moderna, AstraZeneca, Janssen, Novavax, and Sanofi.

- Dr. Sharon Frey is employed by Saint Louis University (SLU), which has a Vaccine Treatment Evaluation Unit (VTU) that is part of the IDCRC. She is currently serving as the Site PI for the Moderna and Janssen Phase 3 COVID-19 vaccine clinical trials.

- Dr. Paul Hunter owns a small amount of stock in Pfizer and has received a small grant from Pfizer to conduct a quality improvement (QI) project on pneumococcal vaccines.

A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the October 28-29, 2020 ACIP meeting.

Combined Immunization Schedule Work Group

Introduction

Hank Bernstein, DO, MHCM, FAAP
Kevin Ault, MD, FACOG, FIDSA
ACIP Combined Immunization Work Group (WG) Co-Chairs
Advisory Committee on Immunization Practices

Dr. Bernstein introduced the Combined Immunization Schedule Work Group (WG), the goal of which is to better harmonize the child/adolescent and adult immunization schedules. These schedules are presented for votes every fall because ACIP's approval is necessary prior to publication of the schedule in February of the following year in the *Morbidity and Mortality Weekly Report* (*MMWR*). ACIP approval is also necessary before the schedules are submitted

to the following partner professional medical organizations for approval prior to the 2021 publications:

- ❑ American College of Physicians (ACP)
- ❑ American Academy of Family Physicians (AAFP)
- ❑ American Academy of Pediatrics (AAP)
- ❑ American Academy of Physician Assistants (AAPA)
- ❑ American Congress of Obstetricians and Gynecologists (ACOG)
- ❑ American College of Nurse Midwives (ACNM)
- ❑ National Association of Pediatric Nurse Practitioners (NAPNAP)

New policy is not established in the proposed child/adolescent and adult immunization schedules. Instead, these schedules reflect a summary of published ACIP recommendations.

Dr. Bernstein indicated that for the remainder of this session, Dr. Wodi would discuss the proposed edits for the 2021 child/adolescent schedule and Dr. Freedman would discuss the proposed edits for the 2021 adult immunization schedule. These edits are intended to incorporate ACIP recommendations and *MMWR* publications that have occurred since October 2019 and improve readability and utility of the schedules into language that is easy to interpret at point of care for the busy provider. In addition to harmonization, there are proposed edits to Tables 1 and 2. There also are content changes for the notes sections of both schedules to be shared. He concluded that a discussion of the proposed edits would be followed by a vote on the child/adolescent and adult immunization schedules, and emphasized that the use of vaccine trade names was for identification purposes only and did not imply endorsement by the CDC.

2021 Child and Adolescent Immunization Schedule

Patricia Wodi, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wodi presented the proposed edits for the 2021 Child and Adolescent Immunization Schedule to reflect the following recommendations voted upon and published since October 2019:

- ❑ Influenza vaccination published in August 2020 for the 2020–2021 influenza vaccine recommendations.

- ❑ Meningococcal A,C,W,Y vaccination published in September 2020 to reflect inclusion of MenACWY-TT (MenQuadfi®) as an option for preventing disease attributed to meningococcal serogroups A, C, W, and Y.

The table of abbreviations and trade names on the cover page has been updated to reflect MenQuadfi® to the list of meningococcal A,C,W,Y vaccines. Also, vaccines were added to the list of combination vaccines. The abbreviation for live, attenuated influenza vaccine was changed from LAIV to LAIV4 because only the quadrivalent formulation is currently available in the United States (US).

Table 1 is the graphical presentation of the routine immunization schedule. Minor edits have been proposed for this table. In the Hepatitis B (HepB) row, arrows have been added to the second dose to clarify the recommended age range for administering the second dose. As noted earlier, LAIV was updated to LAIV4. Table 2 is the catch-up immunization schedule for children and adolescents. No edits were proposed for this table.

Table 3 is the graphical presentation of recommended immunizations based on medical indications. In the human papillomavirus (HPV) vaccine row, the pregnancy column has been changed from pink, which indicated delayed vaccination until after pregnancy, to red that indicates not recommended or contraindicated and that vaccine should not be administered. In addition, an overline text that reads “Not Recommended” with an asterisk also has been included in that column. The asterisk links to a descriptive text in the red box within the legend indicating that HPV vaccine can be given after pregnancy. Similar to the HVP row, the pregnancy column for measles, mumps, rubella (MMR) and varicella vaccines have been updated to include the overline text “Not Recommended” with an asterisk that links to the descriptive text in the red box in the legend indicating that vaccine can be administered after pregnancy. Similar to Table 1, the line for LAIV has been changed to LAIV4 and a footnote has been added to reflect a contraindication in children 2 to 4 years of age with asthma or wheezing.

In terms of the edits to the “Notes” section of the schedule, the following changes have been made:

- Under “Additional Information,” the sentence on when to administer a repeat dose stating, “**The repeat dose should be spaced after the invalid dose by the recommended minimum interval**” has been made bold for emphasis. No changes were made to the language.

- Within the diphtheria, tetanus, and pertussis (DTaP) note, a section on “Special Situations” has been added with recommendations for the use of DTaP in children under 7 years of age that reads, “**Wound management** in children less than age 7 years with 3 or more doses of tetanus toxoid-containing vaccine: For all wounds besides clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.”

- A minor edit was made to the *Haemophiles influenzae* type b (HIB) note for catch-up vaccination to include a new bullet stating that no further doses are needed for children who receive 1 dose of vaccine at age 15 months of age or older.

- A minor change was made to the notes for hepatitis A (HepA) vaccination regarding the 4-dose series for combined HepA/HepB vaccine. This was to clarify that the 4th dose at 12 months is a booster dose.

- In the notes for HepB vaccination, the sentence pertaining to infants born at ≥2,000 grams has been updated with additional language. The sentence now reads, “Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).” This edit was made to provide further clarification regrading when to vaccinate infants weighing <2,000 grams.

- ❑ The notes on "Routine and Catch-Up Vaccination" for HPV vaccine was updated to include information on the recommendation for interrupted schedules reading, "**Interrupted schedules.** If vaccination schedule is interrupted, the series does not need to be restarted."

- ❑ The influenza note was updated to specify LAIV4 and RIV4. In the section on "Special Situations," the language for persons who have egg allergy with symptoms other than hives was revised to reflect ACIP's recommendations for the 2020-2021 influenza season. The bullet now reads, "if using an influenza vaccine other than Flublok or Flucelvax, administer the vaccine in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions." New bullets on severe allergic reaction also were added:

    - ➢ Severe allergic reactions to vaccines can occur even in the absence of a history of previous allergic reaction. All vaccine providers should be familiar with the office emergency plan and be certified in cardiopulmonary resuscitation.
    - ➢ A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of the vaccine.
    - ➢ **LAIV4 should not be used** in persons with the following conditions or situations:
        - Children less than age 2 years
        - Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days

- ❑ Within the notes for meningococcal serogroup A, C, W, Y vaccination, MenQuadfi® was added to the list of vaccines in the sections on "Routine Vaccination," "Catch-Up Vaccination," and "Special situations." The "Special Situations" section also was updated with language on the recommendations for the use of MenACWY-CRM (Menveo) in infants to receive Dose 1 at 3-6 months of age with special situations, including "Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, use of complement inhibitors (e.g., eculizumab, ravulizumab), or travel in countries with hyperendemic or epidemic meningococcal disease." These updates were made to reflect ACIP's current recommendations on meningococcal vaccination.

- ❑ Minor edits were made to the notes on pneumococcal vaccination. "High risk conditions" was changed to "Underlying conditions" and language was added to clarify PPSV23 should be administered after all recommended PCV13 doses have been completed.

- ❑ Similar to the DTaP note, a "Special Situations" section has been added to provide information on the use of tetanus, diphtheria, and pertussis (Tdap) for wound management in persons 7 years of age or older that reads, "**Wound management** in persons age 7 years or older with 3 or more doses of tetanus toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm."

Discussion Points

Regarding Slides 18 and 19, Dr. Atmar found it confusing that some of the red cells contain language and some do not when the footnote basically states that it is “Not recommended/ contraindicated.”

Dr. Wodi indicated that for the pregnancy column, the overline text was added because they wanted to indicate that some vaccines could be used after pregnancy. An option would be to include the asterisk and leave the overline text off. In addition, there was an effort to try to harmonize the adult and child/adolescent schedules. The adult scheduled includes “Not Recommended” in some of the boxes as well.

Referring to Slide 31 under “Routine Vaccination,” Dr. Hayes (ACNM) suggested combining the 2 bullets pertaining to pregnancy into one bullet with the 2 sentences since both pertain to pregnancy.

2021 Adult Immunization Schedule

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

Dr. Freedman indicated that the 2021 Adult Immunization Schedule was updated to reflect recommendations published or voted upon since the October 2019 meeting and editorial changes to clarify notes or harmonize the adult schedule with the child/adolescent schedule in the following areas:

Changes to Tables

- ❑ Cover Page
- ❑ Table 1
- ❑ Table 2

Changes to Notes

- ❑ Hepatitis A
- ❑ Hepatitis B
- ❑ Human Papillomavirus
- ❑ Influenza
- ❑ Meningococcal ACWY
- ❑ Meningococcal B
- ❑ Pneumococcal
- ❑ Tetanus, diphtheria and pertussis
- ❑ Zoster

Minor changes were made to the cover page. First, the abbreviations for LAIV and RIV were updated to reflect that those are both available as quadrivalent vaccines, LAIV4 and RIV4. MenQuadfi® was added to the list of MenACWY vaccines and abbreviations were added for all 3 types of meningococcal ACWY vaccines. Zoster vaccine live (ZVL) was removed from the table and the injury claims section since it is no longer available on the market. Under the “Helpful Information” section, a link was added to frequently asked questions (FAQs) regarding shared clinical decision-making recommendations. These FAQs were not available when the schedule was published last year, so they are now easily referenced for providers.

In terms of changes to Table 1, which is the recommended adult immunization schedule, LAIV and RIV are now LAIV4 and RIV4 in the influenza row to reflect the availability of quadrivalent vaccine only. The Tdap row was split into two rows with the upper half colored purple to indicate vaccination is recommended for adults with an initial risk factor such as pregnancy and wound management. The lower half remained yellow to indicate that vaccination is recommended for adults. In addition, text overlay was added to the purple half of the row that states, "1 dose Tdap each pregnancy: 1 dose Td/Tdap for wound management (see notes)." In the MMR row, the yellow color was extended to the 50-64 years age column to reflect the age of persons born in 1957 or later. In the varicella row, the line between the yellow color and the purple color was shifted to the left to reflect the age of persons born in 1980 or later. In the zoster row, the row that referenced ZVL (Zostavax) was removed since it is no longer available on the market. In addition, the language was removed that said RZV was preferred since that is now the only vaccine available for zoster. In the column for ≥65 years in the pneumococcal row for PCV13, the text overlay in the blue box was changed from "≥65 years" to "1 dose" to be consistent with the other overlays in this table that reference doses and not ages.

Regarding edits to Table 2, the medical indications table, LAIV and RIV were changed to LAIV4 and RIV4. In the MMR row in the pregnancy column, an asterisk was added after the "Not Recommended" text overlay to indicate that MMR vaccine should be administered after pregnancy. In addition, a line was added between the pregnancy column and the immunocompromised column to clearly separate them. In the varicella row also in the pregnancy column, an asterisk was added to the text overlay to indicate that varicella vaccine should be administered after pregnancy. A line was added between the pregnancy and immunocompromised columns to clearly separate them. In the column for HIV infection with CD4 counts ≥200 cells per cubic millimeter, the color was changed to blue to indicate that vaccination should be based on shared clinical decision-making. This reflects the recommendation that vaccination "may" be considered for this group. If it is considered, it would be 2 doses administered 3 months apart. In the zoster row, references to ZVL (Zostavax) and the text stating that is was preferred were removed. In the pregnancy column for the zoster row, the pink color for delay until after pregnancy was replaced with the red color with the text overlay "Not Recommended" with an asterisk to indicate that it can be given after pregnancy. In the HPV row in the pregnancy column, the pink color was replaced with the red color and the text overlay "Not Recommended" was added with an asterisk to indicate that it can be given after pregnancy. For the asplenia, complement deficiencies column through men who have sex with men (MSM), the text overlay was modified to state, "2 or 3 doses through age 26 years depending on age at initial vaccination or condition." For the HepB row, the text overlay in the asplenia through chronic liver disease (CLD) now reads "2, 3, or 4 doses depending on vaccine or condition." This accounts for the accelerated Twinrix schedule and dosing HepB vaccine for persons undergoing dialysis. In the diabetes column, the cell was split into a top half of yellow for those <60 years of age and a bottom half of blue to indicate that shared clinical decision-making should be used for vaccinating persons ≥60 years of age who have diabetes.

In terms of the edits to the "Notes" section of the schedule, the following changes have been made:

- Within the HepA note under "Travel in countries with high or intermediate endemic HepA, text was added for the accelerated Twinrix schedule reading, "(HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

- With the HepB note under "Special Situations," a note was added reading, "Percutaneous or mucosal risk for exposure to blood e.g., Diabetes: hepB vaccination using shared clinical decision-making for persons age 60 years or older."

- Minor wording changes were made in the HPV vaccine note:

  - In the first bullet, HPV vaccination is now recommended for all persons through age 26 years; whereas, last year it was recommended for adults through age 26 years.
  - Under "Routine Vaccination" the first bullet about 15 years of age or older was reformatted to match the language in the child/adolescent schedule, given that the previous wording was confusing.
  - A bullet was added to state that "No additional dose recommended after completing series with recommended dosing intervals using any HPV vaccine."
  - In the "Shared Clinical Decision-Making" section, the text was modified slightly to state that "Some adults age 27-45 years" instead of "Adults." That was to clarify and more accurately reflect the recommendations.
  - Two bullets were added under "Special Situations" reading as follows:
    - Age ranges recommended above for routine and catch-up vaccination or shared clinical decision-making also apply in special situations.
    - Immunocompromising conditions, including HIV infection: 3-dose series as above, regardless of age at initial vaccination.

- In the influenza vaccine section, the following changes were made to the "Special Situations" section:

  - Regarding egg allergy: New language was added to the second sentence in the second bullet such that the second sentence now reads, "Egg allergy more severe than hives: If using an influenza vaccine other than Flublok or Flucelvax, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions." Two new bullets were added that read as follows:
    - Severe allergic reactions to vaccines can occur even in the absence of a history of previous allergic reaction. All vaccination providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation.
    - A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of the vaccine.

  - A bullet was added to the "LAIV4 should not be used section" that reads, "Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days."

- The following edits were made to the meningococcal vaccines section:

  - MenQuadfi (MenACWY-TT) was added in all sections as a potential meningococcal vaccine.
  - Language was added under "Special Situations" regarding booster doses for MenACWY and MenB reading, "Booster dose recommendations for groups listed under "Special Situations" and in an outbreak setting (e.g., in community or organizational settings, and among men who have sex with men) and additional meningococcal vaccine, see https://www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

- ❑ In the pneumococcal vaccination notes:
    - ➢ The link was updated for routine vaccination in persons age 65 years or older to reference a new publication: www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?_cid=mm6846a5+w
    - ➢ Under "Shared Clinical Decision-Making," the order of the bullets was changed though the language in the bullets did not change. The order is now:
        - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first
        - PCV13 and PPSV23 should be administered at least 1 year apart
        - PCV13 and PPSV23 should not be administered during the same visit

- ❑ In the Tdap notes, information was updated for wound management based on the most recent publication. The language states, "Persons with 3 or more doses of tetanus toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus toxoid-containing vaccine is indicated for a pregnant woman, use Tdap For detailed information, see https://www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm"

- ❑ In the zoster notes, references to prior ZVL dosing were removed for routine vaccination of persons ≥50 years old with RZV and the bullet was deleted that explained ZVL dosing for persons ≥60 years since ZVL is no longer available.

Discussion Points

Regarding pneumococcal vaccine, Dr. Poehling suggested that the third bullet did not seem necessary since the second bullet states that "PCV13 and PPSV23 should be administered at least 1 year apart."

Dr. Freedman said that while he understood the point, he thought it was important to emphasize that they should not be administered during the same visit based on some questions CDC receives through the vaccine questions email and instances in which they have been co-administered.

To contrast the pediatric versus adult schedules, Dr. Atmar observed that "Not Recommended" is in all of the cells on the adult schedule. For the pediatric schedule, that could be a problem because there are a couple of cells in which there is language to identify a specific subpopulation within a group that would make putting "Not Recommended" problematic. As an adult physician, he finds the text overlay on the adult schedule to be useful and would not propose changing that. Perhaps the question for the pediatric schedule regarded how to have the asterisks in the pregnancy column stand out.

Dr. Freedman indicated that historically, the adult schedule has always had the text overlay and the child schedule has not. In general, the table by medical condition for the adult schedule has a lot more text overlay. The suggestion from the Combined Immunization WG was to get rid of the pink color because it caused additional confusion. Because red now indicates not

recommended/contraindicated, the addition of the asterisk could address dosing for pregnancy. The WG is open for suggestion.

Dr. Wodi suggested that a possible option would be to remove the "Not Recommended" text and just have an asterisk on the child/adolescent schedule.

Dr. Bernstein suggested changing the line spacing under the red box so that the asterisk stands out more in terms of vaccinating after pregnancy. In terms of the routine vaccination for Tdap that was proposed in the child/adolescent schedule, that level of information is not included in the adult schedule. Perhaps the suggestion to administer Tdap regardless of the interval applies more broadly than just during pregnancy.

Dr. Goldman (ACP) said that as a practicing internist, he found the text overlay to be helpful. One thing that needs to be emphasized for practicing clinicians is the importance of reading the notes section. While the comprehensive, color-coded text overlay guide is very useful for a quick glance, it does not really encompass the full depth of recommendations within it.

Dr. Freedman pointed out that the cover pages in both schedules include a box that describes how to use the schedule and emphasizes that all of the tables and notes should be used.

Revisions to the 2021 Immunization Schedules

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

Dr. Freedman indicated that the WG took into consideration the ACIP members' input and presented the following revisions that were made based on that input:

- Table 3, Child/Adolescent Schedule: "Not Recommended" was removed and the asterisk remained.

- Table 2, Adult Schedule: "Not Recommended" was removed from HPV during pregnancy and an asterisk remained in order to indicate that HPV vaccine should be given after pregnancy.

- Regarding recombinant zoster vaccine in pregnancy, the WG proposed making the box gray with no asterisk instead of red with an asterisk because the actual note from the policy states that, "There are no available data to establish whether RZV is safe in pregnant or lactating women and there is currently no ACIP recommendation for RZV use in this population. Consider delaying vaccination with RZV in such circumstances." The gray color indicates that there is no ACIP recommendation. The red color was left over from when ZVL live was still available, which was contraindicated in pregnancy.

Discussion Points

Dr. Poehling asked whether the same approach with the red box with an asterisk should be used for MMR and varicella vaccine on the adult schedule as on the child schedule.

Dr. Freedman indicated that those are true contraindications because they are live vaccines. Historically, there has always been more text overlay on the adult schedule. However, he emphasize that if ACIP felt strongly, the WG would consider changing that one as well.

Dr. Fryhofer (AMA) thought it would be helpful to keep the "Not Recommended" as a reminder that these are live virus vaccines. Although pediatricians are wonderful at giving immunizations, those who immunize adults are still trying to rise to the occasion to meet the bar pediatricians have set for them. The overlays are very helpful, especially in terms of indicating which vaccines are live and which ones definitely should not be given because of the subsets listed on the medical conditions. She suggested that perhaps for the live virus vaccines (MMR, varicella, LAIV) the overlay could say "Contraindicated" and for HPV could say "Not Recommended."

Dr. Rockwell (AAFP) thought it should be all or nothing in terms of whether there is text overlay. Red means "no." It is more confusing to remove the text only in one box but leave it in the others. "Not Recommended" is different from "Contraindicated." Perhaps extra verbiage is needed with "Contraindicated" to ensure that people understand not to give the vaccine. It seemed like they were now making subsets within the red, which would be more confusing.

In terms of the adult schedule, there was considerable support for either returning the text overlay to all of the red boxes or leaving it out of all of them.

Dr. Hayes (ACNM) reminded everyone that there is a major difference in pregnancy between "Not Recommended" and "Contraindicated." Some of these vaccines can be given during pregnancy if there is a clinical indication and the vaccine is not live. Not only is a live vaccine not recommended, but also it is contraindicated. The red bar is different from the orange bar. Perhaps if "Not Recommended" is to be used and it is a dead vaccine, the orange bar should be used.

Dr. Atmar pointed out that while the two are different, in fact they are combined in the color coding legend. Red with an asterisk is probably appropriate. Perhaps the text language in the supporting document can address the differences.

Dr. Lee pointed out that the immunocompromised category is increasingly complex and that there is newer guidance from transplant societies in terms of considering live viral vaccines in certain sub-populations where sufficient data are available about the importance of its use. The red box will become messy pretty quickly. For the future, it might make sense to explore this further.

Dr. Maldonado (AAP) suggested leaving the pediatric schedule as it is now, given that AAP has not had time to think about it. AAP harmonizes closely with everything CDC does pertaining to the schedule. Since it was not under consideration at the outset, this should be taken up separately in order to give careful consideration to how this would impact pediatric providers' approach to the schedule.

Dr. Romero indicated that the meeting would adjourn at this time and the schedules and vote would be revisited the next morning.

Vote: 2021 Immunization Schedules

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

During the second day of the meeting, Dr. Freedman reviewed the pending issues and presented the revisions before the vote. The first issue that arose regarded the wording under the child/adolescent schedule in terms of the notes for Tdap vaccination. There was a comment about combining the second and third bullet. The WG wanted to emphasize that Tdap may be administered regardless of the interval since the last tetanus Tdap vaccine. It does apply to pregnancy, so there was a request to combine the two bullets. However, it also applies to some other situations. For example, if a child inadvertently was given Tdap between 7 to 9 years of age, they would still be recommended to receive a Tdap booster at 11 to 12 years of age. Therefore, the WG opted to keep the bullets separate.

Regarding Table 1 of the child/adolescent schedule, the asterisks alone were used without any text overlay in preparation for Table 3 comment from the previous day. “Not Recommended” was removed from the pregnancy column in Table 3 for MMR, varicella, and HPV. The asterisks remain and the key for the red color will explain that the asterisk indicates to vaccinate after pregnancy. A line space will be added between the word “administered” and *Vaccinate after pregnancy so that it stands out more.

On Table 2 in the adult schedule, “Not Recommended” with an asterisk will be left for MMR, VAR, and HPV because the adult schedule traditionally has used more text overlay. For the pregnancy column, zoster vaccine was changed from red with “Not Recommended” text overlay and an asterisk to gray, which means there is no recommendation. That means that there is no recommendation for pregnancy, immunocompromised, or HIV infection because that reflects the currently published guidance.

Dr. Freedman concluded that the language for the vote was to “Recommend the proposed edits to both the 2021 adult and child/adolescent immunization schedules.”

Motion/Vote: Adult and Child/Adolescent Immunization Schedules

Dr. Atmar made a motion to accept the Adult and Child/Adolescent Immunization Schedules as revised and presented. **Dr. Poehling** 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

Influenza

Introduction

H. Keipp Talbot, MD, MPH
Chair, Influenza Work Group
Associate Professor of Medicine
Vanderbilt University

Dr. Talbot reminded everyone that during the June 2020 ACIP meeting, there were presentations on 2019-2020 influenza activity, vaccine effectiveness (VE), safety updates, and WG considerations and proposed 2020-2021 recommendations.

WG activities since June 2020 have included finalization of the publication of the 2020-2021 ACIP Influenza Statement that was published in the *MMWR* on August 20, 2020; review and discussion of 2019-2020 estimates of influenza VE, influenza disease burden, and burden averted through vaccination; and discussion of data from a randomized controlled trial (RCT) of cell culture-based influenza vaccine, FLUCELVAX® Quadrivalent, among children aged ≥2 through <18 years.

The agenda for this session included the following presentations:

- ❑ Efficacy Results of FLUCELVAX® Quadrivalent Cell Culture-Based Inactivated Influenza Vaccine (ccIIV4) in Subjects Aged ≥2 to <18 Years
- ❑ Influenza Disease Burden and Vaccine Impact Estimates, 2019-2020 Season
- ❑ End-of-Season Estimates of 2019–2020 Seasonal Influenza Vaccine Effectiveness against Medically Attended Influenza from Three US Networks
- ❑ Updates and WG Considerations

Efficacy of Cell-Derived Quadrivalent Influenza Vaccine (Flucelvax Quadrivalent) in Children & Adolescents ≥2 Years to <18 Years Old

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

Dr. Sylvester presented the results of a recently completed Seqirus™ study in a pediatric population for its ccIIV4, FLUCELVAX®, including a brief background on the merits of cell-based manufacturing, an understanding of the objectives and design of this RCT, and the results and conclusions. While there was a subset of participants who were part of an immunogenicity study during the second and third season, he did not present those data during this session due to time. This immunogenicity data was presented to and discussed with the Influenza WG prior to this presentation. The presentation during this session focused on the efficacy and safety data.

FLUCELVAX® is a cell-based influenza vaccine that is manufactured in a mammalian cell line instead of in chicken eggs. This process avoids the possibility of egg adaptation, which can occur in egg-based manufacturing. The cell-based vaccine is a closer match to the FDA-selected strains, and it has the potential for improved effectiveness compared to egg-based

vaccines. FLUCELVAX® is the only cell-based inactivated vaccine licensed by the FDA[1]. The original licensure occurred in 2012 for adults. In 2016, Seqirus™ was granted a new indication for ≥4 years of age based on immunogenicity and safety data. This is the first efficacy study with a quadrivalent cell-based influenza vaccine in a pediatric population, and it is a post-approval requirement by the FDA [[1]Pérez Rubio A & Eiros JM. *Hum Vaccin Immunother*. 2018;14:1874–1882].

The primary objective was to demonstrate VE of ccIIV4 in preventing polymerase chain reaction (PCR)-confirmed influenza versus non-influenza in a pediatric population. Given that this is an absolute efficacy study, FLUCELVAX® was compared to a non-influenza vaccine. The study would be deemed a success if a pre-defined criterion was met. The study was designed and powered to assess the lower limit of a 2-sided 95% confidence interval for VE to be above 20%. This was negotiated with the FDA prior to the start of the study. The secondary objective was to demonstrate VE of ccIIV4 in preventing culture-confirmed influenza due to any and vaccine-matched strains as well as vaccine-matched strains. As mentioned earlier, a subject participated in an immunogenicity study and FLUCELVAX® demonstrated a robust immune response against all 4 strains over the 2 seasons as assessed by seroconversion rates. The safety and tolerability of FLUCELVAX® also was evaluated in this population.

This study was a double blinded placebo controlled randomized clinical trial with randomization occurring in a 1:1 fashion. The study occurred over 3 influenza seasons. The study vaccine was manufactured containing the 4 influenza strains selected by the World Health Organization (WHO) for each one of those seasons. Menveo® was selected as a comparator vaccine. Menveo® is a conjugated meningococcal ACWY (MenACWY) vaccine. This comparator was chosen because it was licensed for children ≥2 years of age, it has a dosing regimen comparable to FLUCELVAX® and does not interfere with existing national immunization programs in the participating countries or the sites within those countries. Standard vaccine protocol inclusion and exclusion criteria were used during the enrollment phase and 2 cohorts were studied. Participants were divided into a previously vaccinated group and a previously not vaccinated group. Approximately two-thirds (N=3000) subjects were considered previously vaccinated. This meant that any subject ≥9 years of age or any subject younger than 9 years of age who had received 2 or more influenza vaccines prior to enrollment were considered previously vaccinated. Approximately 1500 were categorized as previously not vaccinated. These subjects were 2 to 9 years of age who had not receive 2 or more doses of influenza vaccine. This cohort received 2 doses of vaccine at least 28 days apart. All study participants received a 0.5 mL of FLUCELVAX® or a non-influenza comparator.

There were 39 clinical sites located in 8 participating countries, with a total of 4514 participants. There are no sites in the US because of the trial design. The ACIP has recommended a routine annual influenza vaccine for all persons ≥6 months of age who do not have a contraindication. However, the study sites did not enroll subjects with similar race demographics to the US population. Both study groups are similar in age, gender, race, prior vaccine status, and season in which the study participants were enrolled. The participants were Asian and White. Diversity and inclusion is important in clinical trials. Seqirus™ is currently finishing a US immunogenicity trial with FLUCELVAX® in infants and young children. In that study, African Americans and Hispanics comprise more than 25% of the study population. Dr. Sylvester said that he would be happy to present those results during a future ACIP meeting.

In terms of the results of the primary efficacy objective, there were 175 subjects with confirmed influenza by PCR in the FLUCELVAX® and 364 subjects with PCR-confirmed influenza in the control group. This calculates to a VE point estimate of 54.5% with 95% confidence intervals of 46% to 62%. The lower bound of the confidence interval is well above the pre-specified endpoint of 20% and thus, the success criterion was met. To summarize the secondary efficacy results for FLUCELVAX® against culture-confirmed influenza, efficacy for FLUCELVAX® to prevent culture-confirmed influenza due to any A or B type of influenza strain regardless of antigenic shift was nearly 61%. The highest efficacy was against influenza A/H1N1 followed by any B influenza strain and then influenza A/H3N1. The efficacy against matched strains was slightly higher, with the majority of H1N1 and B/Yamagata strains being matched.

Regarding the percentage of study participants reporting at least one solicited local or systemic AE, solicited AEs are reported from 6 hours after vaccination all the way through Day 7. Unsolicited local and systemic AEs were collected from Day 8 all the way to 180 days or to the end of the influenza season, whichever period was longer. The most commonly reported solicited local AE in both the FLUCELVAX® and the comparator vaccine groups was tenderness at 28.7% and 25.4%, respectively. Pain was 23.8% in the FLUCELVAX® group and 19% in the comparator group, and erythema was 19.3% in the FLUCELVAX® group and 21.2% in the comparator group. Except for a slightly higher rate of pain and tenderness in the FLUCELVAX® group, no notable differences in rate of solicited local AEs were observed between the two groups.

Severe solicited local AEs were uncommon at ≤1.4% in both vaccine groups. The majority of solicited local AEs resolved spontaneously within a few days after vaccination. Headache and fatigue were the most common solicited AEs. These 2 symptoms were collected from study participants who were ≥6 years of age. The symptoms of sleepiness and irritability were collected from parent diaries for children up to 6 years of age. Severe solicited systemic AEs were uncommon and generally less than 1%. There was 1 death that occurred within the control group. The child died of cerebral edema caused by diabetic ketoacidosis. This death was carefully reviewed and deemed not related to the vaccine in the control group. The reported unsolicited AEs for local and systemic were also similar amongst the two groups. This study's safety profile is similar to the previous Seqirus™ immunogenicity FLUCELVAX® in children ≥4 years of age.

In conclusion, this is the first efficacy study in a pediatric and adolescent population with a cell-culture-based quadrivalent influenza vaccine. The overall VE was 54.6% with high confidence intervals (95% CI 45.7, 62.1). FLUCELVAX® was well-tolerated, with similar rates of solicited and unsolicited AEs the two vaccination groups.

Discussion Points

Dr. Szilagyi asked whether Dr. Sylvester could provide information about VE across influenza seasons, and whether any subgroup analyses were done by smaller age groups.

Dr. Sylvester referred to back-up slide 13 of absolute VE by season. Season 1 is the Southern Hemisphere 2017, Season 2 is the Northern Hemisphere 2017-2018, and Season 3 is the Northern Hemisphere 2018-2019. Season 1 was 56.5% for any strain, for Season 2 was 44%, and Season 3 was 59%. These data are also broken down by whether the strain was H1N1, H3N2, or one of the B strains. Subgroup analyses were done by age and they looked to see whether there was a difference between the previously vaccinated and non-previously vaccinated groups, and no difference was seen.

Dr. Kimberlin (AAP Redbook) asked whether this was a stratified study in that the randomization within each of the two-thirds vaccinated and one-third not vaccinated was evenly spaced between active influenza recipients and placebo recipients.

Dr. Sylvester indicated that the previously vaccinated group of about 3000 participants were relegated to receive either the comparator or FLUCELVAX®. Within the 1500 not vaccinated group, 750 received FLUCELVAX® and the rest received the comparator.

Dr. Whitley-Williams (NMA) asked when data would be available for the ACIP to review from the US immunogenicity trial with FLUCELVAX® in infants and young children that includes over 25% African American and Hispanic participants.

Dr. Sylvester indicated that the trial he just shared has been submitted to the FDA under a supplemental biologics license application (sBLA) down to ≥2 years of age, with the hope that they will hear from the FDA whether this trial is approved by January 2021. In terms of the data he referenced, the hope is to submit the sBLA in March 2021. Once that is submitted, he would be happy to share the data with the WG prior to June and then in June 2021 to present the data to the entire ACIP. That age range is ≥6 months of age up to ≥4 years of age and it is an immunogenicity study.

Dr. Poehling asked whether the 2 doses 1 month apart was used for the previously not vaccinated group of children.

Dr. Sylvester clarified that the previously non-vaccinated group received 2 doses of the 0.5 mL vaccine on Day 1 and again on Day 28. If they were in the non-comparator, they received Menveo® as their first vaccine and then a saline solution placebo for their second vaccine.

Influenza Disease Burden and Vaccine Impact Estimates, 2019-2020 Season

Carrie Reed, DSc, MPH
Lead, Applied Research and Modeling Team
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Reed reminded everyone that CDC tracks influenza activity in the US in collaboration with state and local health departments using multiple surveillance systems in different surveillance categories. Together, these systems are designed to provide a national picture of influenza activity, including how much influenza-like illness (ILI) there is; determine the distribution of the virus types and subtypes circulating; and measure trends in influenza-related outpatient illness, hospitalizations, and deaths.

To provide context to the rest of the presentation, Dr. Reed shared data from influenza testing in clinical laboratories for the 2019-2020 influenza season. Influenza began to increase in early November of 2019, peaked in Week 6 in February 2020, and then declined rapidly in March 2020 similar to recent seasons. Stratifying by positivity for influenza A and influenza B viruses separately illustrates that the early season activity was influenza B and later season activity experienced increases in influenzas A activity. Comparing influenza types for the 2019-2020 season to recent prior seasons based on influenza testing done and reported to CDC by public health laboratories, the 2019-2020 season was predominated by influenza A/H1N1 and

influenza B/Victoria viruses and there was very little H3N2 virus activity [https://www.cdc.gov/flu/weekly/fluviewinteractive.htm].

For a number of reasons, these surveillance systems that CDC uses to monitor influenza activity do not capture every influenza-related illness, medical visit, hospitalization, or death in the US. CDC feels like it is important to convey the full burden of seasonal influenza and the reductions in disease burden that occur because influenza vaccination in the US. Therefore, Dr. Reed presented on two additional activities that use the surveillance data collected through CDC's routine systems and other key influenza platforms to answer some key questions about influenza disease burden and the impact of vaccination in the population.

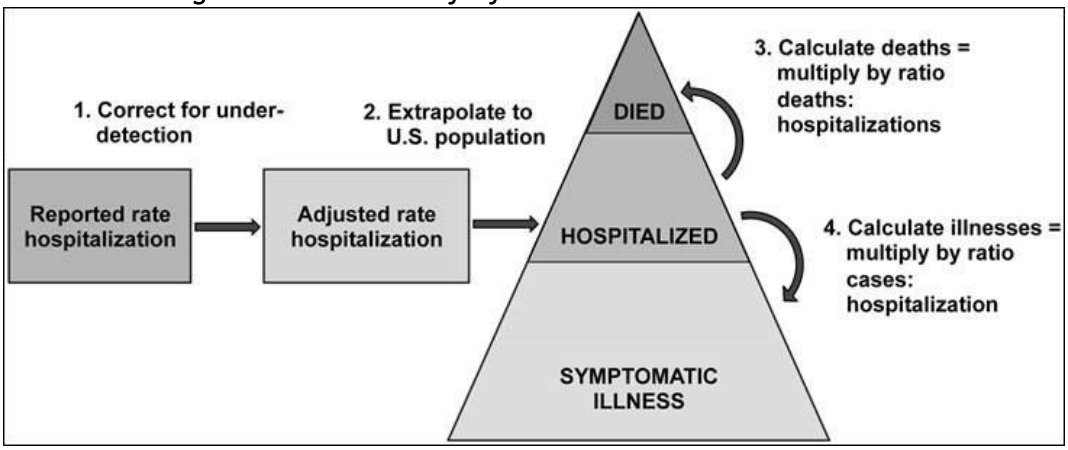
One of the key questions that is not measured directly in surveillance is, "How do people get influenza every year?" and by extension, "How many people are hospitalized and how many people die?" Measuring this directly in surveillance presents major challenges and cases, hospitalizations, and deaths are considered that are confirmed to be influenza and reported to public health agencies and CDC to be the "tip of the iceberg." This can be for a number of reasons, some of which include the following:

- ❑ Not all people seek medical attention for their illness
- ❑ Symptoms can be similar among respiratory pathogens
- ❑ Illnesses often are not confirmed with laboratory testing
- ❑ Many adults are no longer shedding virus by the time that they are tested
- ❑ Complications may be broader than respiratory illness and not thought to be influenza and not tested
- ❑ Even when confirmed, influenza many not be recorded on a death certificate
- ❑ Surveillance is not conducted everywhere

Thinking about why not all cases are detected and how that impacts what is known, someone who is hospitalized with influenza may or may not be tested for influenza when they present for care. If someone is tested for influenza, there are a variety of tests that could be used and there is a variation in the sensitivity between tests. Some people who are tested may test positive, but there may be some people who are falsely negative on their test results. What is know about in the surveillance systems are the positive influenza tests. In order to know total number of hospitalizations, CDC collects information on some additional factors such as test sensitivity, distribution of test types that are used, and the percent of patients in settings such as hospitals that test for influenza. Using these additional pieces of information, it is possible to map out and work back to the total number of influenza hospitalizations.

The method used to estimate the disease burden of illness, hospitalizations, and deaths observed during an influenza season was developed originally during the 2009 pandemic. This model has been refined over the last several years to be able to monitor the disease burden during a season based on routine surveillance. The key system in this process is the Influenza Hospitalization Surveillance Network (FluSurv-NET), with several other steps utilized to extrapolate this to the US population and estimate illness, deaths, and medical visits/hospitalizations as depicted in this illustration:

Figure 1: Illustration of Influenza Burden Estimates Model

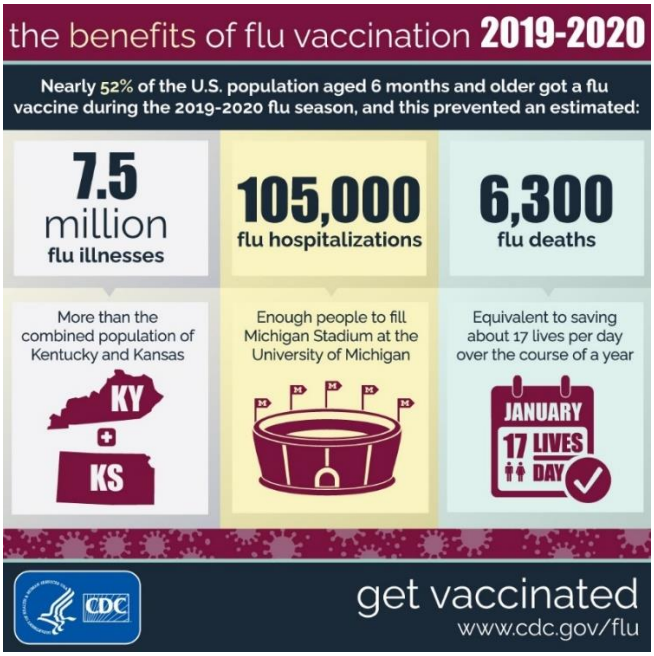


To correct for under-detection, data are collected on influenza testing in hospitals. To calculate deaths, the risk of dying in a hospital setting from influenza is monitored in FluSurv-NET. Because some people die outside of the hospital, additional information is collected from death certificates on the proportion of deaths that have occurred outside of the hospital to capture the full number of deaths inside/outside of the hospital. To calculate illness, CDC has data from previous studies on the risk of hospitalizations to estimate how many symptomatic illnesses were in the population given the estimates of hospitalization and then some additional information on medical care seeking behaviors to estimate medical visits. As mentioned, these methods have been refined over time and have been published in the scientific literature [Reed et al. PLoS One. 2015; Rolfes et al. IoRV. 2018].

Following that methodology, the estimates overall for all ages for the 2019-2020 influenza season are 38.2 million Illnesses, 17.5 million medical visits, 400,000 hospitalizations, and 22,000 deaths. This also is estimated by 5 age groups: 0-4, 5-17, 18-49, 50-64, 65+ years. The detailed estimates for this past season as well as estimates for all seasons since 2010-2011 can be found at https://www.cdc.gov/flu/about/burden/index.html. Of note, these estimates are considered to be preliminary because some of the data inputs mentioned with respect to the model can be lagged in time. Data are used from previous seasons until those can be finalized and estimates can be updated when more complete data are available. The website was updated a few years ago to present a lot more information. High-level information is included on how/why CDC estimates burden, a link is provided to the tables with the detailed estimates by age group and by season for all past seasons, and there is a link to the preliminary in-season estimates that are updated weekly throughout the influenza season.

The second question that is not directly estimated in any of CDC's platforms is, "what impact can our interventions have, specifically vaccination, in terms of reducing disease burden in the population?" Influenza vaccination is the primary strategy available to prevent influenza illness and its complications. Vaccine coverage, VE, and rates of influenza can all vary between seasons, between age groups, and between different types and subtypes of influenza viruses. A few years ago, CDC began a process to use the data available on those factors from that season to estimate the burden of influenza prevented by vaccination to better describe the population impact of influenza vaccination [Tokars et al. Vaccine. 2018; Rolfes et al. CID. 2019; Chung et al. CID. 2020].

For the 2019-2020 season, the components that went into that analysis included: 1) **disease burden** (38 million illnesses; 22,000 deaths; 400,000 hospitalizations) estimated by age group and influenza type/subtype; 2) **vaccine coverage** (38% to 75%, varying by age group) from CDC's FluVaxView; and 3) **VE** (22% to 57%, varying by age group and influenza type) from the US Flu VE Network. Assembling those pieces of information, the estimated influenza averted burden from the 2019-2020 influenza season is illustrated in this infographic:



A few years ago, CDC's Communications Group started using analogies such as those presented in the infographic above to try to communicate the magnitude of these estimates. In addition to influenza illness estimates, CDC also calculates the prevented fraction or proportion of potential influenza cases that were prevented because of vaccination. For example in this case, it was estimated that 21% (N=105,000) of all influenza hospitalizations were prevented or 1 in 5 influenza hospitalizations did not occur because vaccination. This fraction was highest this year for children 6 months to 4 years of age, with 28% or over one-fourth of hospitalizations prevented by influenza vaccine.

To summarize, during the 2019–2020 season an estimated 38 million people were sick with influenza. This resulted in 18 million visits to a health care provider; 400,000 hospitalizations; and 22,000 deaths. The estimated influenza illnesses, hospitalizations, and deaths were lower than some recent seasons and similar to other seasons where influenza A(H1N1)pdm09 viruses dominated. Persons aged <50 years had rates of illnesses, hospitalizations, and deaths similar to or greater than during the 2017-2018 season, a recent season with high severity. Vaccination prevented the greatest proportion of outcomes among children aged 6 months to 4 years of age, an age group with high vaccine uptake and the greatest vaccine effectiveness.

Discussion Points

Dr. Szilagyi noted that he has been pointing out for several years that it would be great to show data about disease averted by vaccine, and found this to be a wonderful way to do this. He did not think the analysis accounted for herd immunity and wondered whether there may be some additional analyses that could account for this. With FluVENET, the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), and New Vaccine Surveillance Network (NVSN) it may be good to hone in on the actual VE that are specific to outpatients, emergency departments (EDs), or hospitalizations from these 3 networks that are now available. Assessing ED visits would be very good.

Dr. Reed confirmed that this analysis did not include any indirect effects, or herd immunity, from reduced susceptibility in the population. This is directly from people being vaccinated and not from herd protection in the population, thought this is a question that they are examining with some modeling colleagues with the hope of refining the analysis to include the additional benefits. In terms of the comment regarding VE, a single VE is included from the US Flu VE Network. The assumption in the analysis is that if influenza is prevented, downstream consequences from influenza are prevented. They do not have separate VE for hospitalizations or deaths. However, there is additional attenuation from vaccine that could be included in the future and they have discussed examination of ED visits as well.

Dr. Frey asked Dr. Reed to share her thoughts about the effect that COVID-19 infection and mask wearing may have for the 2020-2021 influenza season on the ability to effectively estimate influenza burden.

Dr. Reed indicated that there have been discussions about this and observed that at the end of last season, influenza activity decreased faster than it had in previous seasons likely in part due to COVID-19 interventions and restrictions that were in place in March. There has been discussion about how to monitor influenza burden this season. The plan is to continue to rely on the hospitalization platform and continuing to do case finding for influenza this season. One of the key factors will be how influenza testing in the clinical setting is influenced and whether influenza is being detected at the same rate as usual. There is some ongoing work to better monitor how influenza rates, hospitalizations, testing practices, and detection of influenza is changing during this coming season. It is likely to be a challenge, but efforts are being made to assess influenza detection.

Dr. Romero asked whether the availability of combined COVID-19 and influenza testing would offer a better idea or confound the evaluation in the coming season.

Dr. Reed said that through various platforms, they are trying to collect information about influenza testing overall and COVID-19 testing rates overall, and combined testing and whether these are more likely to be positive for one or the other and the factors associated with that.

Dr. Bernstein asked whether the model which has been published is used by other countries, particularly in the Southern Hemisphere where SARS-CoV-2 and influenza have already co-circulated. This could be beneficial given the current pandemic.

Dr. Reed indicated that CDC has worked closely with its international colleagues in the past on applying the averted burden model. Many colleagues in the Southern Hemisphere have been using similar methods to estimate averted burden for influenza. They have not worked with them specifically during this past influenza season. In many parts of the world and the Southern

Hemisphere, influenza activity was relatively low during this season, but this method has been used elsewhere in past seasons.

Dr. Lee was glad to see the information presented this way in terms of disease burden and preventable burden, and expressed her hope that the same could be done for COVID-19 vaccines. Given that the estimates on detection are dependent upon people getting tested, she wondered whether consideration had been given to ways to account for disparities in testing and vaccination and how that might impact disparities in the estimates for disease burden. A lot is being learned from COVID-19 and thinking about how to account for that might be very important. It also would be extremely helpful to understand the burden of disease and the preventable burden in pregnant women through vaccines. She encouraged the team to try to capture those estimates for influenza vaccine and potential future COVID-19 vaccines.

Dr. Reed indicated that they have an analysis to the one she presented for pregnant women specifically. Though this was sidelined somewhat due to the COVID-19 response began, it is in progress and the hope is to have it out soon. They do recognize the disparities in COVID-19 burden estimates, especially racial and ethnic disparities. They have stratified the hospitalization rates she mentioned by race and ethnicity and are thinking about what other inputs would be needed to better understand, especially in terms of how race/ethnicity testing practices could help to better understand disparities in burden.

Ms. Bahta noted that the data Dr. Reed shared are used at the state level for messaging about the importance of influenza, and agreed that the same type of messaging would be helpful in terms of how vaccination could help mitigate COVID-19.

Dr. Ault asked whether the proposed modeling for pregnancy would include pre-term delivery and other obstetrical complications of influenza infection in pregnant women.

Dr. Reed indicated that while they have had these discussions, right now it is similar to what she presented earlier in terms of illnesses, medical visits, hospitalizations, and deaths in pregnant women and their infants who potentially would have residual protection from vaccination. They have not yet gotten into some of the other specific pregnancy outcomes.

Given the situation in clinical practice with the current influenza season of differentiating between COVID-19 and influenza, Dr. Hunter asked if there would be a recommendation or guidance on a national level to perform more influenza testing this year than would be done in most years and if so, how that would tie into the availability of supplies since influenza testing would use similar reagents as COVID-19 testing.

Dr. Reed said they have heard comments from surveillance sites that are having similar questions about how to prioritize testing since supplies are currently limited. While she could not speak to the current status of discussions about recommendations, but perhaps others could report back to ACIP on that.

Ms. Stinchfield (NAPNAP) indicated that testing of COVID-19 to date has mostly been single antigen tests, which will be going away in her area in a couple of weeks when they begin using a 4-plex test that includes influenza A, influenza B, respiratory syncytial virus (RSV), and COVID. They are certainly planning to have more data than usually because of the need to rule out COVID versus influenza in children. They will be happy to share this information later.

Dr. Goldman (ACP) asked whether there are any modeling data or studies suggesting VE in preventing disease and the timing of when the vaccine is administered, early or late, in the season.

Dr. Reed indicated that their group recently published an analysis by Ferdinands et al that assessed this to some extent and there is ongoing interest in refining models related to that as well.

Dr. Schaffner (NFID) commented that due to the increasing number of COVID-19 cases, the 2020-2021 influenza season is likely to be very challenging. Many of the same individuals who are most vulnerable to serious complications of COVID-19 (e.g., older adults, members of minority groups, and those with certain chronic health conditions) also are at greater risk for the complications from influenza. To address this public health issue, NFID convened a multidisciplinary round table to explore the potential impact of influenza and COVID-19 on adults with chronic health conditions. Outcomes from the round table are summarized in the NFID "Call to Action: The Dangers of Influenza and COVID-19 in Adults with Chronic Health Conditions (October 2020)," which is available on the NFID website at https://www.nfid.org/wp-content/uploads/2020/10/NFID-Call-to-Action-Dangers-of-Influenza-and-COVID-19-in-Adults-with-Chronic-Health-Conditions.pdf. All healthcare professionals are encouraged to use the strategies in this publication to save lives, decrease hospitalizations, and reduce the overall burden on the healthcare system. Let's just vaccinate!

End-of-Season Estimates of 2019–2020 Seasonal Influenza VE Against Medically Attended Influenza from Three US Networks

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

Dr. Grohskopf reported preliminary results from three networks (US Flu VE, HAIVEN, and NVSN) to evaluate VE against laboratory-confirmed, medically-attended influenza in a variety of settings and for a variety of ages. The US Flu VE enrolls children and adults ages ≥6 months from ambulatory settings with acute respiratory illness (ARI), including cough. This network consists of sites located in Washington (Mike Jackson, Lisa Jackson), Wisconsin (Ed Belongia, Huong McClean), Michigan (Arnold Monto, Emily Martin), Pennsylvania (Rick Zimmerman, Tricia Nowalk), and Texas (Manju Gaglani) with the Principal Investigators (PIs) shown in parentheses. The HAIVEN sites enroll adults ≥18 years of age with ARI, including cough or worsening cough or sputum production, from inpatient settings. This network consists of sties in Michigan (Arnold Monto, Emily Martin), Pennsylvania (Rick Zimmerman, Donald Middleton, Fernanda Silveira), Tennessee (H. Keipp Talbot), and Texas (Manju Gaglani). Three of these sites overlap with the US Flu VE sites. The NSVN enrolls children aged 6 months–17 years in inpatient settings. This network consists of sites in Washington (Janet Englund, Eileen Klein), New York (Geoffrey Weinberg, Peter Szilagyi), Ohio (Mary Staat), Pennsylvania (John Williams, Marian Michaels), and Texas (Julie Boom).

The methods overall for these networks are similar. They use a test-negative study design to estimate VE by comparing the odds of influenza vaccination among patients with laboratory-confirmed influenza by reverse transcriptase polymerase chain reaction (RT-PCR) vs. patients testing influenza-negative who serve as the test-negative controls. Vaccination status is defined by receipt of any licensed 2019–2020 seasonal influenza vaccine at least 14 days prior to illness

onset. Vaccination status was ascertained using a variety of sources, including medical records, immunization registries, and/or self-report. VE is estimated as 1 – adjusted odds ratio of receipt of current seasonal influenza vaccination in cases compared to controls x 100%. These analyses are adjusted for a number of potential confounders such as study site, age, calendar time, and baseline health status.

The US Flu VE Network enrolled 8845 patients between November 2019 and March 2020, with 31% testing positive for influenza. HAIVEN enrolled 3116 patients between October 2019 and March 2020, with 18% testing positive for influenza, NVSN-Hospital enrolled 2029 patients between September 2019 and May 2020, with 17% testing positive for influenza. NVSN-ED enrolled 2102 patients between September 2019 and May 2020, with 32% testing positive for influenza.

In terms of the relative distributions of the different types and subtypes of influenza viruses in the networks, the VE analysis included participants enrolled during each site's specific influenza season. The season was defined as the dates of the first through the last influenza-positive case among the enrolled patients at each site. The season for NVSN was characterized by early circulation of B/Victoria viruses and A(H1N1)pdm09 viruses that came to a peak later and circulating throughout the season. For HAIVEN, there were relatively few influenza B cases. This is typical of disease patterns in adults and most of the B cases were observed early in the season. A(H1N1)pdm09 viruses represented the overall majority of infections in this network. In NSVN, which includes both children and adults, most early season influenza cases were from B/Victoria viruses, followed by a predominance of A(H1N1)pdm09 viruses during the second half of the season. Of note, there was very little A(H3N2) activity observed in any of the VE networks for this season.

In terms of VE results for the US Flu VE Network, preliminary estimates were initially presented during the ACIP meeting in June 2020. Final end-of-season estimates are pretty similar to these previous estimates. Overall VE against medically-attended A and B influenza viruses was 39%, with B slightly lower than expected. A/H1N1pdm09 was 30% and B/Victoria was slightly higher than expected at 45%, particularly since most of the B viruses were antigenically drifted from the vaccine components. For VE by age group, point estimates overall were fairly similar across age groups, with overlapping confidence intervals. For A/H1N1pdm09 viruses, VE was relatively low across all age groups compared with prior seasons. There was some suggestion of some variability between different age groups, with VE ranging from 22% to 42% and being the lowest in children. Again, confidence intervals overlap.

For NVSN, VE in children by virus type and further stratified by inpatient versus ED setting, overall VE in children was relatively high at 62% against hospitalized influenza-associated illness and 56% against medically-attended illness in the ED setting. For A/H1N1pdm09 viruses, this was 64% against hospitalized illness and 53% in the ED setting. Estimates were similar for B/Victoria viruses in inpatient and ED settings at 54% and 55%, respectively. Comparing VE estimates from children from the ambulatory US Flu VE Network to the inpatient and ED estimates for NVSN. Higher VE was observed in the inpatient and ED settings compared with the ambulatory settings, which was most noticeable for A/H1N1pdm09 viruses. The group plans to assess geographically overlapping sites to see if they can still observe the same trends restricted to similar geographic areas. In terms of further inpatient, ED, and outpatient estimates for children within the more restricted pediatric age categories (6 months to 16 years, 6 months to 4 years, and 5 to 17 years) similar trends were observed, with overall lower VE seen in the ambulatory network.

For VE against hospitalization by virus type in HAIVEN compared to Flu VE, estimates were similar between the inpatient and ambulatory networks. In hospitalized adults, an overall VE of 41% was seen for A and B viruses. VE for A/H1N1pdm09 was 40% and VE for B viruses was 33%, but with wide confidence intervals due to the small number of B cases among hospitalized adults. For VE against influenza hospitalized and outpatient visits in HAIVEN and US Flu VE respectively among adults 3 non-overlapping age groups, within each age group, confidence intervals for VE estimates in the inpatient and ambulatory settings overlapped. For hospitalized adults, VE surprisingly was highest among adults ≥65 years of age with a point estimate of 54% and lowest and not significant in young adults 18 to 49 years of age with a non-significant VE of 16%.

VE networks are subject to a number of limitations. In particular, networks are limited in their ability to assess estimates of VE by specific vaccine types and there were a number of them for the 2019-2020 season. Notably, there was limited use of LAIV4 among children as well as the existence of site-specific difference in use of vaccine types offered to patients when the different sites are compared. Some results, including VE for partial versus full vaccination status among children under 9 years of age is pending confirmation of final vaccine receipt data.

In summary, 2019–2020 influenza vaccination significantly reduced laboratory-confirmed medically-attended influenza across all VE networks as followed:

- 39% (95%CI: 32, 44) against outpatient illness aged ≥6 months (Flu VE)
- 62% (95%CI: 52, 71) against pediatric hospitalizations (NVSN)
- 56% (95%CI: 46, 65) against pediatric ED visits (NVSN)
- 41% (95%CI: 27, 52) against adult hospitalizations (HAIVEN)

Despite vaccine mismatch, vaccination offered important protection against B viruses in children for whom B viruses tend to be associated with severe disease. In children, VE trended lower for ambulatory compared to inpatients and ED settings, which warrants additional analysis. For adults, outpatient and inpatient VE were similar.

Discussion Points

Dr. Kimberlin (AAP Red Book) noted that several slides had “NVSN/Flu VE” and requested clarity regarding whether that was the Flu VE Network or influenza VE from the NVSN.

Dr. Grohskopf clarified that these were comparisons between the two networks, NVSN and US Flu VE Network, to compare hospitalized/ED within NVSN to outpatients in the US Flu VE Network.

Dr. Lee asked whether any information could be provided about background rates of community vaccination in the communities in which these individuals are coming from, and whether there are any differences in distribution of communities by outpatient versus hospitalized ED status. This relates to the question from the prior presentation about how much herd immunity can be accounted for, realizing that these studies are focused on direct protection.

Dr. Flannery indicated that in the US Flu VE Network, many of the sites have a population that is enrolled in a health system who are likely to be more vaccinated than the general population in those areas. That is also true because of the overlapping sites with the inpatient adult network. The NVSN network enrolls in children’s hospitals where not all of them are drawing from source populations and may be more reflective of vaccine coverage in children. When the

US Flu VE Network is compared to some of the other network data in the control group, or influenza-negative group, vaccination coverage in the US Flu VE Network tends to be higher than survey-based estimates for those areas. However, that may not be the case with the NVSN hospital and ED networks and they will have to look into this further with that group.

From the consumer perspective, Ms. McNally asked whether there has been any discussion regarding potential ways to evaluate VE for LAIV4.

Dr. Grohskopf indicated that uptake of LAIV4 has not been terribly high in the last couple of seasons, which does somewhat limit the ability to detect VE.

Dr. Flannery added that CDC is tracking VE from other networks. The best are from the UK. Several years ago when comparisons were done between the US and UK, data showed discordant results. CDC does not have data from other networks at this point for LAIV effectiveness against H1N1. As Dr. Grohskopf indicated, intake has been low in both the NVSN and the US Flu VE network, so it has not been positive to have an estimate for LIAV either overall or for H1N1.

Dr. Hunter if an influenza vaccine is preventing hospitalization more than all medically-attended infections, it meant that some vaccinated people having mild symptoms might be continuing their social interactions that result in some transmission. If so, he wondered what the role of physical distancing and masking might be in future influenza seasons.

Dr. Grohskopf said that while she did not have a specific answer to that, it is conceivable that people may have relatively milder sub-clinical illness. Some people do get infected with influenza and do not have many symptoms at all; however, that does not mean that they are not contagious. It remains to be seen what sort of effect the current measures being applied to mitigate the spread of COVID-19 will have on influenza as well. It is difficult to speculate on whether it would be desirable to apply those measures specifically to prevent transmission of influenza at this point.

Ms. Hayes (ACNM) said that anecdotally, she knows a couple of people who had a prescription called in for treatment for influenza without ever getting testing. This made her curious as to whether CDC is monitoring prescriptions in addition to monitoring testing.

Dr. Grohskopf said that at least within this activity, they are not monitoring prescriptions. The recommendations for the use of antivirals for influenza generally state that if the clinician believes that it is influenza and the person falls into a category for which the antiviral would be indicated (e.g., people who are at high risk of severe illness), testing is not required or the clinician does not have to wait for positive test results before prescribing antivirals. She was not aware of the proportion of individuals who do not get tested but receive a prescription. While she was not aware of whether CDC is actively monitoring the sale and number of anti-influenza medications as a way of monitoring the cases.

Dr. Cohn added that CDC does monitor prescription medications, but more so from the perspective of monitoring them for potential shortages. They have not used that as a way to assess potential influenza disease. They definitely can take this into further consideration.

Updates and WG Considerations

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

Dr. Grohskopf expressed gratitude to Dr. Atmar for his leadership as Chair of the Influenza WG during this demanding period of time and welcomed Dr. Talbot.

She reported that there have not been any policy changes. For pertinent updates, it is projected that approximately 194 to 198 million doses of influenza vaccine will be distributed this seasons. Approximately 154.6 doses had been distributed as of October 16, 2020. Influenza activity in the US is currently low. Based on the virologic surveillance results from FluView, the percent of specimens positive is about 0.3%. Data from the Influenza-like Illness Surveillance Network (ILINet) as of Week 42 ending October 17, 2020 show very little ILI activity being reported through this network even relative to other recent seasons.

Regarding WG discussions and considerations, the Influenza WG had the opportunity to hear and discuss the presentations of burden, averted burden, and VE that were presented during this session. In addition, they heard the data for the trial of FLUCELVAX® Quadrivalent vaccine among children ≥2 through <18 years of age. While some clarifying questions were raised during the discussion about the design of the study population, no specific concerns were raised by the WG.

Discussion Points

Dr. Hunter said his impression was that if the very low rates of influenza currently occurring are representative of what is occurring in clinical practice, there is not a strong reason for clinicians, health systems, and public health to spend a lot of resources for influenza testing or diverting resources from COVID-19 testing to influenza at this point.

Dr. Grohskopf said that with influenza, it is known that one thing that can be anticipated is being surprised and not necessarily being able to predict. It is unknown what will happen with the remainder of the season.

Orthopoxvirus Vaccine

Introduction

Beth Bell, MD, MPH
ACIP, Orthopoxvirus Vaccine WG Chair
Clinical Professor, Department of Global Health
School of Public Health, University of Washington

Dr. Bell explained that the purpose of the Orthopoxvirus WG is to update the ACIP recommendations to include the use of JYNNEOS® to prevent orthopoxviruses in persons at risk for occupational exposure. WG activities have been to: 1) review and evaluate available data

about the safety and effectiveness of the newly licensed vaccine JYNNEOS®; 2) consider consolidating US recommendations for vaccination of persons who may have occupational exposures to orthopoxviruses; and 3) identify areas in need of further research for informing future vaccine recommendations to prevent Orthopoxvirus infection.

In terms of WG accomplishments since announcing its formation during the October 2019 ACIP meeting, the WG began meeting in February 2020. The WG has heard 3 background presentations and assessed the scope of work, and has deliberated data about use of the newly licensed orthopoxvirus vaccine, JYNNEOS® (also known as MVA-BN®, IMVAMUNE®, and IMVANEX®) for persons at risk for occupational exposure to orthopoxviruses. They reviewed the ACIP recommendations published over the last approximately 20 years about orthopoxviruses. They heard a presentation by the manufacturer about data that contributed to licensure of JYNNEOS® and evaluated data presented by CDC about variola plaque reduction neutralization test (PRNT) data and preliminary immunogenicity data from a monkeypox vaccine study in the Democratic Republic of Congo (DRC) using JYNNEOS®.

In addition, the WG drafted PICO (Population, Intervention, Comparison, Outcomes) questions after reviewing examples from previous ACIP WGs and identified outcomes that were considered “critical” or “important” and which should therefore be included in the GRADE (Grading of Recommendation Assessment, Development and Evaluation) and the Evidence to Recommendation (EtR) Framework. The WG also confirmed that considerations will be limited to those at occupational risk pre-event and began discussions about which occupations (e.g., laboratorians) should be included in this update. Previous recommendations have included broad occupational groups. Finally, the WG determined search terms for a systematic review of the published literature and began that review. The goal for this session is to begin detailed presentations to ACIP, provide background information and the proposed PICO question in preparation for GRADE and EtR presentations during the next meeting, and answer questions about the WG’s progress and the day’s presentations. The presentations for this session included the following:

- ❑ Background
- ❑ Variola Virus PRNT Assay for the Assessment of JYNNEOS® Vaccinee Sera
- ❑ JYNNEOS® (MVA-BN) Smallpox and Monkeypox Vaccine
- ❑ Vaccinating Against Monkeypox in the DRC with JYNNEOS®
- ❑ Summary and Next Steps

Background

Brett Petersen, MD, MPH
Orthopoxvirus WG Team Lead
United States Public Health Service
Epidemiology Team Lead, Poxvirus and Rabies Branch
NCEZID National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Petersen provided background on the orthopoxviruses, introduced the currently licensed orthopoxvirus vaccine, and provided a brief overview of the current ACIP recommendations.

The poxviridae are a family of deoxyribonucleic Acid (DNA) viruses that infect a broad range of hosts. The orthopoxvirus genus within this family includes several species that cause disease in humans that can lead to isolated lesions to systemic rash illness. Variola virus is the most

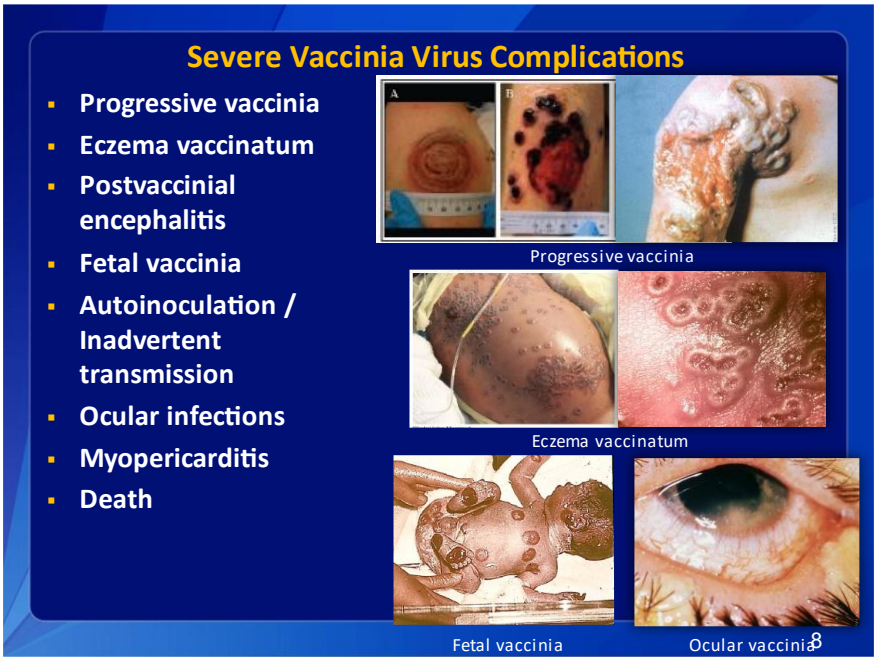
commonly known orthopox virus. It is the causative agent of smallpox. Vaccinia virus is the principal source of smallpox vaccine, causes zoonotic infections in South America, and is used fairly widely in biological research. Monkeypox virus causes both endemic and epidemic disease in Africa as well as imported cases to other countries, including the US. Cowpox virus is endemic in Europe. There are even newly discovered species orthopoxvirus species, including Akhmeta virus that was discovered in the Country of Georgia and Alaskapox virus that has occurred in the US.

It is the ability of orthopoxviruses to induce cross-protective immunity that has led to the use of vaccinia virus (VACV or VV) as a smallpox vaccine. The traditional smallpox vaccines contain live virus and they are replication competent. They are administered in a single dose via multiple puncture technique using a bifurcated needle. This produces a major cutaneous reaction or "take" that is actually evidence of a successful vaccination. However, these vaccine site lesions are infectious and can be spread to other parts of the body of the vaccinee and to other persons through inadvertent inoculation.

ACAM2000® is the currently available smallpox vaccine. It was licensed by FDA in August 2007. It replaced the previous smallpox vaccine, Dryvax®. The Dryvax® license was withdrawn by the manufacturer and remaining vaccine destroyed. ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high-risk for smallpox infection [https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5708a6.htm; https://www.fda.gov/media/75792/download].

The ACAM2000® package insert does have contraindications and recommends that individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000®. It further describes these individuals as those who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation. The package insert also includes a number of warnings and precautions, including a "black box warning" for a series of AEs, including: myocarditis and pericarditis (suspect cases observed at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stephanes-Johnson Syndrome), eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness and fetal death that have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines. The label notes that these risks are increased in certain individuals and may result in severe disability, permanent neurological sequelae, and/or death. However, it does go on to further note that persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk for death from smallpox or other orthopoxvirus infections. Consequently, the risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox or other orthopoxvirus infection [https://www.fda.gov/media/75792/download].

Examples of severe vaccinia virus complications are illustrated in the following images:



Progressive vaccinia is seen in the first image. This is a complication that occurs in persons with immunosuppression and leads to uncontrolled replication of the virus and often death. Eczema vaccinatum is seen in the second image is another complication resulting in uncontrolled replication of the virus, which is often seen in persons with atopic dermatitis. This also can have high mortality. Postvaccinial encephalitis occurs most commonly in the pediatric population. Fetal vaccinia has been observed with vaccinia virus vaccines in which there is vertical transmission of the virus to the fetus, resulting in fetal loss. Autoinoculation and inadvertent transmission can be significant problems when the virus is spread to areas on the body with high risk of severe sequelae, including ocular infections that often result in blindness. Myopericarditis is also associated with ACAM2000®. Although the mechanism of action of the AE is not completely understood, it continues to be a problem.

In an effort to improve smallpox vaccine, there have been many advances made in vaccine technology. The first generation vaccines were those used in the smallpox eradication campaign that were propagated in animals, most commonly calf skin. The second generation vaccines are now propagated in tissue culture and produced using modern Good Manufacturing Practices (GMPs). However, they are almost equivalent as they are clonally derived from the first generation vaccines and are expected to have similar efficacy and safety. In contrast, the third generation vaccines are those that have been attenuated through propagation in tissue culture. However, these also are still produced using modern GMPs. Fourth generation vaccines also have been developed (e.g., protein subunit vaccines, DNA vaccines), but they are still experimental and not yet available.

JYNNEOS® is an example of the third generation vaccines. It is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN®). It is an attenuated, non-replicating orthopoxvirus that has a number of other names as Dr. Bell mentioned (IMVAMUNE®, IMVANEX®, MVA®). MVA-BN is grown in primary chicken embryo fibroblast (CEF) cells. Its multiple passages through these cells leaves it unable to replicate in mammalian cells. This vaccine was approved by the FDA in September 2019. JYNNEOS® is indicated for the prevention of smallpox and monkeypox disease in adults ≥18 years of age determined to be

at high-risk for smallpox or monkeypox infection. It is administered via subcutaneous injection and is given in two doses (0.5 mL each) 4 weeks apart. Each dose (0.5 mL) is supplied in a single-dose vial.

The rates of solicited adverse reactions, including injection site reactions, and systemic AEs are similar to other modern vaccines. Of note, this vaccine has been studied in populations at high-risk for severe vaccine complications, including persons with HIV infection and adults with atopic dermatitis. None of the severe vaccine complications described earlier were seen in these populations. The frequency of AEs also were similar to those observed in healthy adults. Overall, the 4 SAEs for which a causal relationship to JYNNEOS® could not be excluded were not fatal. The 6 cases of cardiac adverse events of special interest (AESI) were considered to be causally related to JYNNEOS® vaccination, though none were considered serious and no cases of myopericarditis were identified. VE against smallpox was inferred by comparing the immunogenicity of JYNNEOS® to the currently licensed ACAM2000® smallpox vaccine using a Plaque Reduction Neutralization Test (PRNT) and also was supported by efficacy data from animal challenge studies. Similarly, the VE against monkeypox also was inferred from immunogenicity and efficacy data from animal challenge studies [https://www.fda.gov/vaccines-blood-biologics/jynneos]. Solicited AEs, severe AEs, cardiac AEs of special interest, and VE are listed on the package insert as follows:

Solicited Adverse Reactions

- In smallpox vaccine-naïve healthy adults, the most common (> 10%) solicited injection site reactions were pain (84.9%), redness (60.8%), swelling (51.6%), induration (45.4%), and itching (43.1%); the most common solicited systemic adverse reactions were muscle pain (42.8%), headache (34.8%), fatigue (30.4%), nausea (17.3%) and chills (10.4%)
- In healthy adults previously vaccinated with a smallpox vaccine, the most common (> 10%) solicited injection site reactions were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%); the most common solicited systemic adverse reactions were fatigue (33.5%), headache (27.6%), and muscle pain (21.5%)
- The frequencies of solicited local and systemic adverse reactions among adults with HIV-infection and adults with atopic dermatitis were generally similar to those observed in healthy adults

Severe Adverse Events

- Across all studies, a causal relationship to JYNNEOS could not be excluded for 4 SAEs, all non-fatal, which included Crohn's disease, sarcoidosis, extraocular muscle paresis and throat tightness
- Cardiac Adverse Events of Special Interest
- Among the cardiac AESIs reported, 6 cases (0.08%) were considered to be causally related to JYNNEOS vaccination and included tachycardia, electrocardiogram T wave inversion, electrocardiogram abnormal, electrocardiogram ST segment elevation, electrocardiogram T wave abnormal, and palpitations
    - None of the cardiac AESIs considered causally related to study vaccination were considered serious
    - No myopericarditis

Cardiac Adverse Events of Special Interest

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    - None of the cardiac AESIs considered causally related to study vaccination were considered serious
    - No myopericarditis

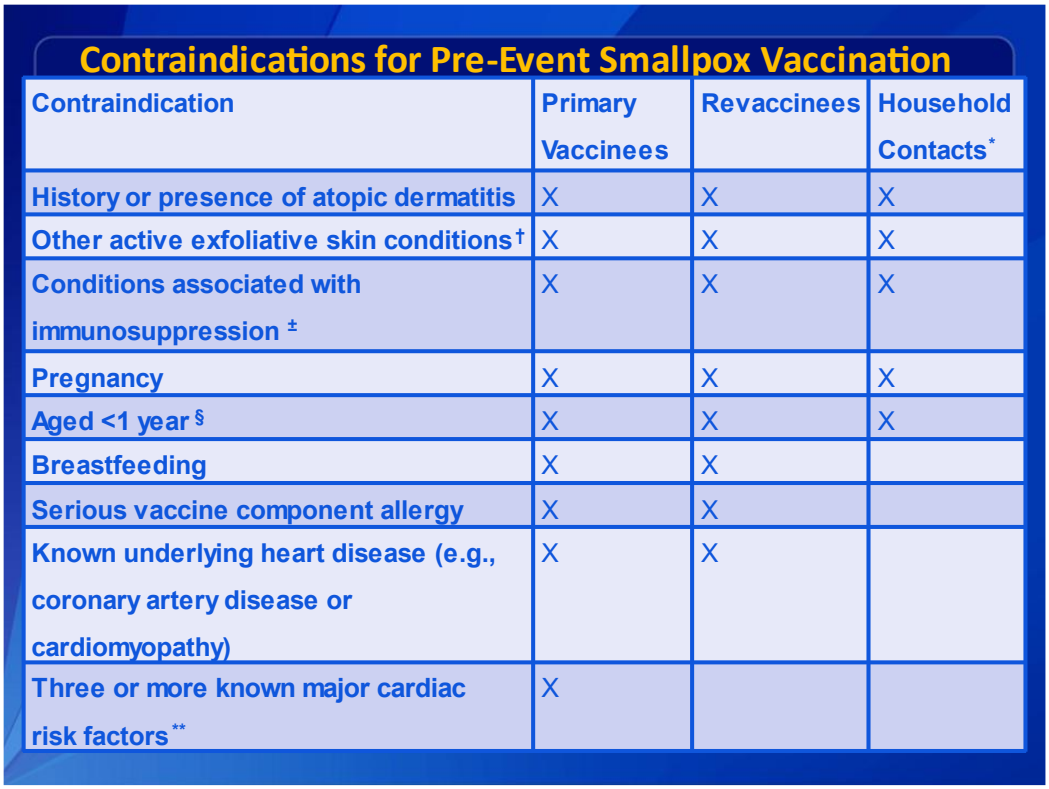
Vaccine Effectiveness

- Vaccine effectiveness against smallpox was inferred by comparing the immunogenicity of JYNNEOS to a licensed smallpox vaccine (ACAM2000) based on a PRNT using the Western Reserve strain of vaccinia virus and was supported by efficacy data from animal challenge studies
- Vaccine effectiveness against monkeypox was inferred from the immunogenicity of JYNNEOS in a clinical study and from efficacy data from animal challenge studies

Moving on to describe the current ACIP recommendations for orthopoxviruses, the latest recommendations are from 2015 and describe the use of vaccinia virus smallpox vaccine in the laboratory and HCP at risk for occupational exposure to orthopoxviruses. As mentioned previously, vaccinia virus is used as a tool in biological research, as well as a viral vector for recombinant vaccine. Laboratory exposures and resulting infections do occur in this population. To prevent these infections, ACIP does recommend routine vaccination with ACAM2000® for laboratory workers who directly handle a) cultures or b) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola).

The recommendation goes on to define replication-competent vaccinia viruses that are capable of causing clinical infection and producing infectious virus in humans. Vaccination with ACAM2000® is not recommended for persons who work only with replication-deficient strains of vaccinia virus (e.g., MVA, NYVAC, TROVAC, and ALVAC). MVA is the strain used for JYNNEOS®. In terms of healthcare workers, those whose contact with replication-competent vaccinia viruses is limited to contaminated materials (e.g., dressings) and persons administering ACAM2000® smallpox vaccine who adhere to appropriate infection prevention measures can be offered vaccination with ACAM2000®.

ACIP lists a number of contraindications in order to prevent severe vaccine complications. The high-risk populations that are contraindicated are listed in the following table. Of note, even potential vaccinees who have household contacts among these several high-risk populations also are contraindicated:



Contraindications for Pre-Event Smallpox Vaccination

Contraindication	Primary Vaccinees	Revaccinees	Household Contacts*
History or presence of atopic dermatitis	X	X	X
Other active exfoliative skin conditions†	X	X	X
Conditions associated with immunosuppression ±	X	X	X
Pregnancy	X	X	X
Aged <1 year §	X	X	X
Breastfeeding	X	X	
Serious vaccine component allergy	X	X	
Known underlying heart disease (e.g., coronary artery disease or cardiomyopathy)	X	X	
Three or more known major cardiac risk factors**	X		

https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/smallpox.html

* Household contacts include persons with prolonged intimate contact with the potential vaccinee (e.g., sexual contacts) and others who might have direct contact with the vaccination site or with potentially contaminated materials (e.g., dressings or clothing).
† Conditions include eczema, burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis).
§ Conditions include human immunodeficiency virus/acquired immune deficiency syndrome infection, leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, being a recipient with hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component.
¶ Vaccination of infants aged <1 year is contraindicated. Additionally, the Advisory Committee on Immunization Practices does not recommend vaccinating children and adolescents aged <18 years.
** Major cardiac risk factors include hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking.

ACIP also has recommendations for revaccination of laboratory and HCP. For those individuals working with vaccinia viruses, the recommendation is that they be revaccinated at least every 10 years. Those working with more virulent orthopoxviruses like variole or monkeypox should be vaccinated every 3 years.

There also is a 2003[1] recommendation document describing the use of smallpox vaccine in a pre-event vaccination program. These recommendations do recommend smallpox vaccination for both Smallpox Response Teams and Smallpox Health-Care Teams with a goal of having a cadre of vaccinated individuals who are able to investigate in the event of a possible smallpox outbreak and to provide care for any initial smallpox cases. The 2003 recommendations do not provide recommendations, advice, or guidance for revaccination. A memo was produced in October 2008 to address this issue[2]. In this memo, it was recommended that individuals vaccinated under this pre-event smallpox program would only be re-vaccinated on an “as needed” or “out-the-door basis” in the event of an emergency [[1]https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/smallpox.html; [2]https://www.cdc.gov/smallpox/pdfs/revaccination-memo.pdf].

With respect to how much vaccine is actually being distributed, all of the ACAM2000® is provided by CDC's Drug Services. They receive approximately 100 requests for ACAM2000® per year. Vaccine is distributed as 100-dose vials. This number of requests is believed to represent approximately 100 to 200 individual vaccinated per year. Of these requests, about 5 are for Smallpox Response Teams, which may represent 5 to 10 individuals per year. The vast majority of vaccine that is currently being administered is for laboratory and healthcare worker populations.

Discussion Points

Dr. Lee asked whether other than nurses and physicians there are HCP who might be exposed to potentially contaminated materials who would be important to consider as well. For example, is there any concern about environmental service workers handling contaminated dressings from wound care.

For ACAM2000®, Dr. Petersen indicated that those who they expect may be exposed would be those who are administering ACAM2000®, those making follow-up visits to evaluate vaccine site lesions, or those who are taking care of people who are receiving experimental recombinant vaccinia virus vaccine. It is not a large population and is anticipated to be comprised largely of nurses or physicians. That is who the HCP recommendation is really directed toward. If contaminated dressings are taken care of according to recommendations, they should be placed in biohazard bags with the addition of bleach or another viricidal agent. If those precautions are being followed, there is very little risk that there would be any potential exposures to others in environmental services or other sectors.

JYNNEOS® (MVA-BN®) Smallpox and Monkeypox Vaccine

Heinz Weidenthaler, MD
Vice President, Clinical Strategy
Bavarian Nordic

Dr. Weidenthaler provided: 1) background on smallpox orthopoxvirus vaccines and JYNNEOS® (MVA-BN®); 2) a summary of the safety data and FDA approved label of JYNNEOS®; and 3) an overview of clinical data supporting JYNNEOS® approval in terms of the Phase 3 non-inferiority trial versus replicating smallpox vaccine, immunocompromised subjects, and durability data.

In terms of why Bavarian Nordic developed a vaccine knowing that smallpox has been eradicated since the late 1970s, smallpox may remain a biosecurity threat especially taking into account that de novo synthesis of orthopoxviruses is technically feasible. In 2018, Noyce et al reported on an infectious horsepox virus from commercially available DNA fragments. There is waning population immunity after cessation of smallpox vaccinations. Given that there are no longer routine vaccinations, the younger half of the population has never received a poxvirus-based vaccine. This makes the population a lot more vulnerable to poxvirus infections. Natural disease remains including monkeypox, camelpox, and other animal reservoirs for orthoxpoxes. There also is the potential for accidental releases of othropoxviruses in laboratories or research, or resurface of old samples. In 2014, live smallpox was discovered in storage in the US.

Monkeypox is a global threat beyond the African-endemic countries. Some recent cases of travelers who have brought infection into other countries, including secondary transmissions to healthcare workers in the UK. The complications of replicating smallpox vaccines also can be an issue. The more recent complication identified was myopericarditis, which was identified only after a smallpox eradication campaign when the vaccines were used in the post-911 setting in a large-scale vaccination campaign. Based on that experience, there has been a very close focus on cardiac adverse events during the development program of JYNNEOS®. This product was finaly developed as a safe alternative smallpox vaccine to the previous replicating vaccines. They also had in mind that there ware a number of populations who cannot receive replicating smallpox vaccines, so Bavarian Nordic wanted to create someting that is suitable for all populations.

JYNNEOS® is a live, attenuated, non-replicating strain of Modified Vaccinia Ankara (MVA), indicated for prevention of smallpox and monkeypox disease. It has been FDA-approved since September 24, 2019 for adults ≥18 years of age determined to be at high-risk for smallpox or monkeypox infection. In terms of the safety profile, it is important to note that there has been no signal of inflammatory cardiac disorders. It is suitable for all populations, including immuno-compromised persons. The standard dose regimen per the approved label is subcutaneous injection of 2 doses 4 weeks apart.

This table offers a high-level overview of the development program Bavarian Nordic has been running over the past 2 decades, which has included the enrollment of a variety of populations (e.g., healthy, atopic dermatitis, immunocompromised, elderly, vaccinia-naïve, or vaccinia-experienced populations):

Time	N (studies)	Objectives	N (subjects)
2001 - 2002	1	First clinical trial (Phase 1) initiated	86
2003 - 2006	4	Dose-finding, comparison to Dryvax®, first studies in AD and HIV populations	450
2007 - 2010	8	Healthy,AD, HIV and elderly populations (1 dose vs. 2 doses, vaccinianaïve/-experienced, booster)	2281
2011 - 2012	3	Healthy (various schedules, freezedried [FD] vs. liquidfrozen [LF], high dose); post stem cell transplant patients	635
Since 2013	2	Lot-consistency and safety Non-inferiority FD vs. LF	3655
	1	Condensed schedule (FD formulation)	435
	1	Special access program	22
	1	Additional data in immunocompromised subjects (HIV)	87
	1	Efficacy/non-inferiority to ACAM2000®	220
TOTAL	22		7871

To summarize the safety data based on these 22 completed trials with 7871 subjects, the vast majority of AEs have been local injection site reactions that were mild to moderate and resolved rapidly without intervention. No trends or clusters have been observed for unexpected or serious adverse reactions. There were 6 cases of cardiac AESIs (0.08%) that were considered to be causally related to vaccination. None of these were considered serious and there have been no signals for cardiac inflammatory disorders in any MVA-BN clinical trial or in the development program as a whole. There is no clinically relevant difference between vaccinia-naïve and experienced populations or healthy and at-risk populations, including subjects with atopic dermatitis and HIV. The safety profile of MVA-BN has been confirmed in approximately 40,000 subjects exposed to MVA-BN-Filo as part of Janssen's heterologous Ebola vaccination regimen [References: JYNNEOS® Prescribing Information, Janssen MVA-BN-Filo data on file Volkmann (2020), *Vaccine*. 2020 Oct 17;S0264-410X(20)31091-4. doi: 10.1016/j.vaccine.2020.08.050].

Because of the experience with the replication vaccines in terms of myopericarditis, the development program included active cardiac monitoring of all subjects that included targeted physical examinations, electrocardiograms (ECGs), and Troponin testing. The inclusion criteria included Troponin <2xULN, ECG without clinically significant findings, and no previous cardiac diseases history. Among the cardiac AESIs reported, 6 cases (0.08%) were considered to be causally related to JYNNEOS® vaccination and included tachycardia, electrocardiogram T wave inversion, electrocardiogram abnormal, electrocardiogram ST segment elevation, electrocardiogram T wave abnormal, and palpitations. None of the cardiac AESIs considered causally related to the study vaccination were considered serious. There were no cases of myocarditis in in over 7800 vaccinated subjects [JYNNEOS Prescribing Information Zitzmann-Roth (2015), PLoS One, 16-Apr-2015, DOI:10.1371/journal.pone.0122653 Elizaga (2013), PLoS One, 17-Jan-2013, DOI:10.1371/journal.pone.0054407 Volkmann (2020), Vaccine. 2020 Oct 17;S0264-410X(20)31091-4. doi: 10.1016/j.vaccine.2020.08.050].

In terms of special populations, the cardiac safety of JYNNEOS® also was investigated in HIV-positive (n=696), atopic dermatitis (n=381), and elderly (n=120) subjects. Elderly subjects in the trial had less stringent inclusion/exclusion criteria. This allowed for a previous history of myocardial infarction >2 year previously; up to a 25% risk of major cardiac events using cardiac risk calculator; allowing subjects on chronic, stable medication such as low-dose acetylsalicylic acid (ASA) to participate. The trial with older subjects using MVA-BN was in 120 subjects aged 56+ among whom 42 subjects were aged 65+. No differences were observed in the cardiac safety profile as compared to healthy populations, and there were no cases of ischemic or inflammatory cardiac disorders in special, vulnerable populations [Elderly: Greenberg (2016). PLoS One. 2016 Jun 21;11(6):e0157335. doi: 10.1371/journal.pone.0157335. HIV-positive: Greenberg (2013). J Infect Dis. 2013 Mar 1;207(5):749-58. doi: 10.1093/infdis/jis753 Overton (2015). Open Forum Infect Dis. 2015 May 5;2(2):ofv040. doi:0.1093/ofid/ofv040 Overton (2020). Vaccine. 2020 Mar 4;38(11):2600-2607. doi: 10.1016/j.vaccine.2020.01.058. Atopic dermatitis: von Sonnenburg (2014). Vaccine. 2014 Sep 29;32(43):5696-702. doi:10.1016/j.vaccine. 2014.08.022 Greenberg (2015). PLoS One. 2015 Oct 6;10(10):e0138348. doi: 10.1371/journal. pone.0138348].

This table summarizes the comparison of the traditional smallpox vaccine to the JYNNEOS® (MVA-BN) vaccine:

Replicating Smallpox Vaccines	**Non-Replicating JYNNEOS® (MVA-BN)**
❑ Based on replicating virus strains ❑ Single dose by scarification using a special bifurcated needle ❑ Cause a major cutaneous reaction ("take"); only historical measure of efficacy (protection) ❑ Vaccines associated with autoinoculation and accidental infection of others ❑ Not suitable for immune compromised or people in close contact with risk populations ❑ Myocarditis in up to 1 in 200 vaccinees	❑ Non-replicating in human cells ❑ Administered subcutaneously, 2 doses 4 weeks apart ❑ No vaccine take is induced ❑ Cannot cause transmission to self or others ❑ Designed for the general population including immune compromised ❑ No myocarditis cases in >10,000 subjects dosed (>50,000 with the MVA-BN vector platform)

To summarize the clinical data, the co-primary objectives of the JYNNEOS® (MVA-BN) Phase 3 head-to-head non-inferiority trial vs. ACAM2000® were immunogenicity and efficacy:

Immunogenicity
Non-inferiority of JYNNEOS® (MVA-BN) compared to ACAM2000® in terms of vaccinia specific PRNT antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2). Endpoint: PRNT GMT at the Peak Visits.

Efficacy
Showing that vaccination with JYNNEOS® (MVA-BN) prior to administration of ACAM2000® results in an attenuation of take in terms of Maximum Lesion Area (MLA). Endpoint: MLA in mm^2 after scarification with ACAM2000®.

The conclusions from this Phase 3 trial were that the Peak Visit antibody responses (based on PRNT and ELISA GMTs) induced by JYNNEOS® are non-inferior to those elicited by the licensed replicating smallpox vaccine ACAM2000®, which are considered protective. The attenuated "take" and accelerated healing time observed in subjects who received JYNNEOS® prior to scarification with ACAM2000® shows that JYNNEOS® is able to suppress the viral replication induced by ACAM2000®. JYNNEOS® is safe and well-tolerated in vaccinia-naïve healthy subjects. JYNNEOS® shows significantly better tolerability as compared to the standard single-dose ACAM2000® vaccination regimen. JYNNEOS® shows equal induction of neutralizing antibodies compared to ACAM2000® post a single vaccination, at a time when ACAM2000® is considered efficacious based on "take."

To summarize the Phase 2 data in immunocompromised subjects, increasing either the dose or the number of JYNNEOS® vaccinations shown to be safe and well-tolerated when compared to the standard 2-dose regimen. No clinically relevant differences were observed between the different doses/schedules. This study confirmed the established standard dose and regimen in terms of immunogenicity for use in a more severely immunocompromised, vaccinia-naïve population with HIV infection.

Durability data come from the Phase 2 core study and a 2-year follow-up boost study, NCT00316524 and NCT00686582. The core study was a Phase 2, partially randomized, partially double-blind, placebo controlled study with immunogenicity and safety endpoints. This trial enrolled 745 healthy adults into the following 4 groups:

- ❑ Vaccinia-naive subjects: JYNNEOS® 2 doses 4 weeks apart
- ❑ Vaccinia-naive subjects: JYNNEOS® single dose
- ❑ Vaccinia-experienced subjects: JYNNEOS® single dose
- ❑ Vaccinia-naive subjects: Placebo

The boost study was a Phase 2 open-label trial that re-enrolled a subset of participants from the initially vaccinia-naive JYNNEOS® dose groups with immunogenicity and safety endpoints. A single JYNNEOS® boost vaccination was administered to 152 subjects 2 years after the initial regimen. A single boost vaccination with JYNNEOS® in subjects primed with either 1 or 2 doses of JYNNEOS® 2 years earlier elicits an immune response equal or higher than the initial peak following the standard 2-dose schedule. Antibody responses post-boost at the 2 years timepoint are already very high at the one-week readout, indicating a strong memory response.

In summary, JYNNEOS® has a favorable safety profile, with significantly fewer overall AEs as compared to ACAM2000® and no signal of inflammatory cardiac disorders. Immune responses are comparable or higher than those with replicating smallpox vaccines. Boost data at the 2-year timepoint indicate a strong memory response, irrespective of a 1- or 2-dose initial vaccination regimen. JYNNEOS® is easy to administer via subcutaneous injection, is suitable for prevention of smallpox and monkeypox in the general adult population, and does not require exclusion of populations contraindicated for replicating vaccine.

Discussion Points

Dr. Atmar recalled that MVA was originally developed in the 1970s to somewhat attenuate the response to the vaccinia vaccine and to be used in immunocompromised patient populations, which was around the time that smallpox was being eradicated. Looking at these data from a couple of decades ago, it was difficult to tell what kind of efficacy data there were against smallpox when administered alone. He asked whether Dr. Weidenthaler was aware of any efficacy data with an MVA-like construct against smallpox in the historical studies.

Dr. Weidenthaler replied that this brought them back to the historic roots of the company. This product was initially developed in the Bavarian State Vaccination Institute in the 1960s and 1970s and was, indeed, registered in Germany and was administered in 120,000 children in Germany in the early 1970s. It was initially supposed to be a pre-vaccination for the replicating smallpox vaccines. Interestingly, he was born in 1973 and was one of the children in Bavaria who received it. He never received the replicating vaccine after that because they were discontinued roughly at the same time. When the 120,000 doses of MVA were administered in Germany, there was no longer active circulating smallpox in Germany. This is why there is a large body of experience in terms of safety, but safety was not captured at that time in the way that is now according to current standards. In terms of efficacy, it is probably not possible to have a meaningful readout when it was given in a geographic region where smallpox was not circulating at the time.

Regarding the primary safety study for JYNNEOS® vaccine, Ms. Bahta inquired as to how long the 6 cases of cardiac AESIs thought to be causally related to JYNNEOS® vaccination were followed.

Dr. Weidenthaler responded that it depended upon the trial. Most of the trials had a standard 6-months follow-up period. There was an initial period of 4 weeks post-vaccination during which the subjects had frequent site visits and the targeted physical exams. In all of the trials, there has been a least a 6-month long-term follow-up that was conducted via phone conversation. One of the trials had a 1-year follow-up.

Dr. Kimberlin (AAP Red Book) asked whether Dr. Weidenthaler could further describe any possible additional studies or exploration for indication in pediatric patients, given that monkeypox can have pretty devastating effects in children.

Dr. Weidenthaler indicated that for the smallpox development that they initially had in mind, they have a pediatric waiver for that indication because in the absence of smallpox, there was an agreement that it would be unethical to perform this intervention and trial in children. The last cases of monkeypox were imported into the US in 2003. Monkeypox is no longer circulating in the US at this time. Therefore, it is not feasible from an ethical perspective to run pediatric trials in the US. Such trials probably could be run in African Countries. Some data are soon to be published about MVA as a vector platform. The MVA-BN construct is used as the boost component of Janssen's heterologous Ebola vaccination prime boost regimen. They have generated quite a lot of pediatric data that is soon to be published. Bavarian Nordic is trying to combine this with data that they have previously generated in pediatric populations with other recombinant products in pediatric populations, and hope to be able to provide a more comprehensive overview of that in the near future. There are no plans at this time to run a specific pediatric trial for human smallpox or monkeypox with this vaccine.

Variola Virus PRNT Assay for the Assessment of JYNNEOS® Vaccinee Sera

Christina Hutson, PhD
Lead, Virus-Host Molecular Interactions Team
Poxvirus and Rabies Branch
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Hutson gave a presentation on the *Variola Virus* PRNT assay for the assessment of JYNNEOS® vaccinee sera. All of the known remaining variola virus stocks are only in two repositories in the world, one located at the CDC in the US and one in Russia. All studies with live variola virus must be conducted in a Biosafety Level (BSL)-4 laboratory and are all highly regulated and must be approved by the WHO.

In collaboration with Bavarian Nordic, CDC sought and obtained WHO approval to examine serum from a JYNNEOS® non-inferiority clinical study. This was the Phase III clinical trial that Dr. Weidenthaler mentioned with 200 vaccinia-naïve subjects that assessed vaccination with JYNNEOS® versus ACAM2000®. Sera was taken at pre and peak time points post-vaccination, with the peak time points differing for the two vaccine regimens. FDA had a primary endpoint of vaccinia virus Western Reserve (VACV-WR) neutralization; however, they did request that a subset of samples be tested directly against variola viruses that had not been used in the eradication campaigns.

CDC changed the parameters of its assay to make it more similar to Bavarian Nordic's PRNT assay and to increase objectivity and quality control (QC). After these changes, CDC performed reproducibility and sensitivity evaluation of the variola PRNT. These results were written up and submitted to the FDA as a Redevelopment Report. In addition, an Analytical Plan (AP) was submitted that summarized the method, samples, statistical methodology, responsibilities, and timelines for testing clinical trial samples in the variola PRNT.

There are some slight differences in the PRNT protocol depending upon the virus used. VARV and serum can be incubated overnight. Twelve dilutions are done starting with 1:10 and going out to 1:20,480 and those are run in duplicates. After that overnight incubation, the monolayer with that virus/serum combination is inspected for 1 hour before adding overlay. This is allowed to grow for 96 hours in the case of variola. After 96 hours, the crystal violent stains are added to visualize plaque. Any virus that has not been neutralized can be seen as a plaque or clearing of the cells. One of the QCs implemented for the Bavarian Nordic PRNT included the use of a CTL analyzer, which allowed automated counting of the plaques. This also allowed for some additional QC measures such as if greater than 20% of the monolayer is removed, that well is automatically rejected. Alternatively, if there is some monolayer that is missing but it is less than 20%, the CTL will actually normalize the plaque counts to that well to be utilized.

Once the Redevelopment Report and the AP were approved by the FDA, CDC received a total of 200 blinded samples organized into batches of 100 pre-vaccination samples (50 per vaccine) and 100 post-vaccination samples (50 per vaccine). Each batch contained 4 samples of pre- and post-vaccination serum from 1 JYNNEOS® vaccinated individual and 1 ACAM2000® vaccinee. If one sample failed QC testing, the entire batch would be repeated. Once testing was finished, the 50% neutralizing titers of JYNNEOS® vaccinees trended lower than ACAM2000® vaccinees, but this was not statistically significant. Some additional comparisons were done, such as the average fold rise and the proportion of group to reach 4x or 8x rise in titers. None of those comparisons showed a statistically significant difference.

In summary, in the absence of a dermatologic "take" in these next generation vaccines, it is really important to determine neutralization in vitro as a surrogate measure of efficacy. VARV neutralization is particularly informative as a surrogate measure of smallpox vaccine efficacy when the vaccine was not used during the eradication campaign. These data provided increased confidence that this vaccine would be protective against smallpox. JYNNEOS® vaccinees trended lower than ACAM2000® vaccinees, with no statistically significant difference. CDC has received WHO approval to do additional in vitro work with live VARV to examine the long-term titer/neutralization levels from JYNNEOS®. Specifically, CDC hopes to test some of the samples from the DRC study.

Discussion Points

Dr. Atmar observed that there appeared to be about a 4-fold difference in neutralizing antibody titer between ACAM2000® and JYNNEOS®, which is often thought to be important. Although, it is unknown what level of antibody is protective in people. He wondered what level they were expecting to detect based on the analytic plan in terms of what kind of power they had.

Dr. Hutson replied that this is certainly not meant to be a non-inferiority study. This was just a subset of samples from that study. They had enough numbers to do a statistical comparison, but it was not meant to determine if JYNNEOS® was inferior or non-inferior to ACAM2000®. They certainly could say that there is a trend in this group of individuals assessed, but it was not statistically significant and the numbers were not high enough to determine non-inferiority.

Vaccinating Against Monkeypox in the DRC JYNNEOS®

Brett Petersen, MD, MPH
Orthopoxvirus WG Team Lead
United States Public Health Service
Epidemiology Team Lead, Poxvirus and Rabies Branch
NCEZID National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Petersen provided an introduction to an ongoing study on Vaccinating Against Monkeypox in the DRC JYNNEOS®. By way of background monkeypox is caused by the monkeypox virus, which is an orthopox virus. Its clinical presentation is very similar to smallpox. It presents with a disseminated vesicular/pustular rash associated with systemic symptoms of fever, malaise, and lymphadenopathy. It is acquired primarily through zoonotic transmission following contact with infected animals, although there is human-to-human transmission via respiratory droplets and lesion exudates. The animal reservoir is believed to be small rodents (e.g., rope squirrel, Gambian rat, dormouse).

Monkeypox is being increasingly recognized as a re-emerging disease. There have been increases in monkeypox case reports from many countries that have not reported monkeypox in the past or have not reported them for many years. There have been exportation events as well to the US in 2003, the UK 2018, Israel in 2018, Singapore in 2019, and the UK in 2019 [Durski, KN et. al Emergence of Monkeypox – West and Central Africa 1970-2017 *MMWR*. 2018 Mar 16; 67(10):306-310].

All recent exportation events originated in Nigeria. An index case was reported in Nigeria in September 2017, with 183 confirmed cases and 9 deaths reported in 18 states through December 2019. Sporadic cases continued to be reported, with 6 suspected cases reported in December 2019. The majority of confirmed cases (85%) are from 4 states: Lagos, Delta, Rivers, and Bayelsa. The experience in Nigeria has highlighted the nature of re-emerging infections with monkeypox, as well as pointing out how much is not known about how and why monkeypox appears to be re-emerging [Outbreak of human monkeypox in Nigeria in 2017-18: a clinical and epidemiological report. Yinka-Ogunleye A, Aruna O, et el. *Lancet Infect Dis*. 2019 Aug;19(8):872-879. https://ncdc.gov.ng/themes/common/files/sitreps/].

Looking at monkeypox in the DRC, 5060 monkeypox cases were reported with 103 deaths (CFR 2%) from 18 provinces in 2019. The CDC has engaged with the DRC for many years to provide enhanced surveillance in one of the provinces where monkeypox is endemic, the Tshuapa Province. As part of this collaboration and program, approximately 500 samples from suspect monkeypox cases are submitted per year of which approximately 300 are confirmed to be cases. The annual incidence rate in this province is calculated to be 4.4/10,000. Of note, the annual incidence in healthcare workers is almost 4 times the overall incidence rate at 17.4/10,000. That means that 1/100 confirmed cases have been among healthcare workers.

In terms of preventing monkeypox, it can be quite difficult to implement public health measures that would prevent the disease in these austere environments with limited resources. Even simple measures like avoiding contact with animals that could harbor the virus, isolating infected patients, using personal protective equipment (PPE) when caring for patients, and practicing good hand hygiene after contact with infected animals or humans can be difficult to accomplish in these areas. Smallpox vaccination administered 3–19 years previously appeared to provide

over 85% protection against monkeypox disease acquisition in studies of close contacts with cases. These studies were performed during the smallpox eradication era. However, routine smallpox vaccination has not been implemented as a prevention measure for monkeypox largely due to the safety profile of the traditional smallpox vaccine.

With the advent of third generation vaccines, there has been interest evaluating these vaccines for the prevention of monkeypox as this does provide a unique opportunity to evaluate this vaccine in an area where there is actual natural orthopox virus infection. With this in mind, CDC began a collaboration with the DRC Ministry of Health and the Kinshasa School of Public Health in 2015 to develop an Investigational New Drug (IND) Protocol to evaluate JYNNEOS® vaccine in a prospective cohort of adult healthcare workers at risk for monkeypox in the DRC. The objectives of the study were to: 1) evaluate the safety of JYNNEOS® vaccine; 2) evaluate the immunogenicity of JYNNEOS® vaccine; and 3) evaluate the effectiveness of JYNNEOS® vaccine to prevent naturally occurring human monkeypox.

In terms of the study design, the vaccine was administered to study participants on Days 0 and 28. All participants are monitored over a 2-year time period and study visits occur on Days 0, 14 (on a subset of participants), 28, 42, 180 and 1 year, 1.5 years, and 2 years. Blood draws are performed during each study visit for immunogenicity evaluation. On each vaccination day, and AE diary is given to the vaccine recipient for the safety analysis. Exposure diaries are completed throughout the study to document any contact with confirmed or suspect monkeypox patients, as well as any disease occurrence in the study participants.

The study began with the enrollment and vaccination of 1000 participants in Kinshasa and 4 health zones in the Tshuapa Province in 2017. These individuals received the liquid frozen formulation of the vaccine. Over 97% received 2 doses. There have been excellent return rates for follow-up study visits, with over 88% returning through the 2-year timepoint. This first cohort has completed the 2-year monitoring period. No monkeypox disease was identified among participants during that 2-year monitoring period. Although, 1 study participant who was vaccinated with JYNNEOS® in May and June 2017 developed monkeypox in November 2019 and was identified through routine surveillance.

Due to the success of the first cohort, there was interest in expanding the study to evaluate a lyophilized, or freeze dried formulation of the vaccine. In this cohort, 600 participants were enrolled and vaccinated in 2 health zones in the Tshuapa Province in 2019. Over 97% of participants received 2 doses, and return rate again were excellent for follow-up study visits at 88% by Day 180. To date, no vaccine-associated SAEs have been reported and no monkeypox disease has been identified among participants.

From the first cohort of 1000 participants who received the liquid frozen formulation, some preliminary safety analyses have been completed. Local vaccine site reactions and general systemic symptoms were observed in study participants, although the frequency was quite lower than what was observed previously in clinical trials. When comparing previously vaccinated naïve individuals, generally less adverse reactions were observed in those who were previously vaccinated as expected with largely no significant differences.

In terms of SAEs, there have been 12 study participant deaths reported in the first cohort. However, none of these has been determine to be vaccine-associated as other etiologies were identified, including: acute hepatitis and severe anemia; skin infection of the leg (distant from the vaccine site injection); cerebral vascular accident secondary to hypertension; alcohol intoxication (2); cerebral vascular accident secondary to HIV infection and cryptococcal

meningitis; traumatic head injury; acute gastroenteritis associated with severe malaria; opportunistic infections/AIDS; hepatic cirrhosis; suspected complications of tuberculosis; hepatic cancer, and hepatitis B virus infection. For reference, the estimated annual average crude death rate in the DRC is 9.6 deaths/1000 population* compared to what was observed with this cohort of 6 deaths/1000 annually among study participants [*United Nations Department of Economic and Social Affairs. Additionally, 4 female study participants became pregnant within 6 months of receiving the study vaccine despite being advised to avoid becoming pregnant for one month (28 days) after each study vaccine administration. These pregnancies were followed up through delivery, with 3 participants delivering healthy babies and 1 participant experiencing a spontaneous abortion at an estimated 37 weeks gestation based on her last menstrual period. For background, the estimated annual infant death rate in the DRC is 65 infant deaths/1000 live births* (https://population.un.org/wpp/Download/ Standard/Mortality/).

CDC has begun performing immunogenicity testing on the serum samples collected. A total of 6734 samples were available for testing from 999 participants in the first round of testing. An ELISA was adapted for use to specifically test responses to JYNNEOS® vaccine and preliminary IgG and IgM serology analysis have been completed. In terms of the seroconversion rates, 99% of participants seroconverted to IgG and 24% seroconverted to IgM. To go into more detail about the IgG immune response broken out by naïve and prior vaccination, the kinetics of the antibody response is as expected with those with prior vaccination developing seroconversion at earlier timepoints compared to those who are naïve. There was no significant difference on Day 42 of the maximal immune response in terms of seroconversion rates with 99% of those naïve and 97% of those previously vaccinated seroconverting. Even out to Day 730, the 2-year timepoint, seroconversion is being maintained in 77% of all samples and being slightly higher in those with prior vaccination (81%) compared to those who are naïve (71%). Looking briefly at the IgM response, 24% of participants seroconverted among all of the samples. Seroconversion was higher among naïve (50%) versus prior vaccinated (11%) participants. That would be the expected pattern. Providing a gross comparison to seroconversion rates from prior studies from the Bavarian Nordic investigators' brochure of clinical trial data available to date, the CDC seroconversion rates are largely comparable to those previously reported results.

As mentioned, this is an ongoing study and much work remains to be done. In terms of evaluating effectiveness, CDC has collected the surveillance data from areas of enhanced surveillance and plans to evaluate that to determine whether there is a way to evaluate effectiveness. They also will analyze the reported exposures to monkeypox. With regard to safety, the safety data analysis including comparisons with previously collected clinical study data will be finalized. For immunogenicity, there are plans to quantitate the neutralizing antibody response to vaccination and the CDC is currently performing the PRNT analyses on these samples, which they hope to present to ACIP during a future meeting. CDC will continue to monitor the second cohort of study participants who received the freeze-dried formulation of the vaccine, which will include complete safety, effectiveness, and immunogenicity analyses and a comparison of the liquid frozen and freeze-dried vaccine formulations. There also is interest in additional studies with this cohort to provide evidence of persistence of immunity after the 2-year time point. With this cohort, there is a plan to conduct a vaccine booster study in which a single dose of JYNNEOS® will be administered to a cohort of previous study participants 3 years following primary vaccination with JYNNEOS®. For this study, serum will be collected at Days 0, 7, and 14 for immunogenicity and evaluation of memory response.

Discussion Points

Dr. Hayes (ACNM) pointed out that if a woman delivers at 37 weeks after her last menstrual period, it is not considered a spontaneous abortion. It is considered a pre-term birth and would be documented as being born alive or deceased.

Dr. Frey asked whether Dr. Petersen could share any additional information on the participants who developed monkeypox as it related to any underlying conditions, comorbidities, or the antibody response to the vaccine and how severe the disease actually was.

Dr. Petersen indicated that with the individual who was vaccinated but later developed monkeypox, they are still trying to gather more clinical information to determine whether that was a severe case or whether it may have been ameliorated from the vaccination. What they do know is that the individual was 42 years of age at the time of vaccination, 45 years of age at the time of illness, male, reported being previously vaccinated, had a scar suggesting previous vaccination, did not report any significant past medical history, and were taking some medications at the time of vaccination (e.g., paracetamol and artemether-based combination therapy for malaria). The samples from this individual have been identified and this does appear to be someone who did not develop a robust immune response.

Dr. Hunter commented that he cared for one of the cases of monkeypox in 2003 for a few days in a community hospital before the patient was transferred to an academic medical center, and could attest that preventing monkeypox would have significant benefits to the utilization of medical and public health resources in that type of situation. He was thinking theoretically that in a clinical setting, having a vaccine that does not involve an infectious lesion could have significant advantages.

Dr. Petersen agreed that this type of vaccine could play a role in prevention of monkeypox, which was a large part of the rationale behind conducting this study to demonstrate feasibility and effectiveness in the setting of natural monkeypox infection.

Dr. Kimberlin (AAP Red Book) asked Dr. Petersen to comment on antiviral drugs that have activity, such as cidofovir or the relatively newly licensed smallpox drug.

Dr. Petersen indicated that a number of antivirals demonstrate effectiveness against orthopoxvirus infections. Tecovirimat is licensed for the treatment of smallpox disease. It would be effective based on mechanism of action and animal study data to provide benefit in treating other orthopoxvirus infections. Its use clinically has been limited in that there are not a lot orthopoxvirus infections to begin with, although it has been used in at least one infection in a laboratory-involved exposure. It has not been widely used to treat people with poxvirus infections and has not been evaluated directly to treat monkeypox.

Dr. Kimberlin (AAP Red Book) asked whether there would be an opportunity to provide tecovirimat in Africa in patients who acquire monkeypox and are being followed as part of this study.

Dr. Petersen said that there certainly is interest in evaluating antivirals for treatment of monkeypox. The current limitation is resources, but there are talks to pursue effective clinical studies to evaluate the use of tecovirimat and other antivirals for treatment of monkeypox.

Dr. Bell requested more information about the epidemiology of monkeypox at the time of the clinical trials and verification of her presumption that given the expected incidence of monkeypox among healthcare workers in general in this area and the size of the trials, it would be challenging to say a lot about effectiveness.

Dr. Petersen said that even though this is an endemic disease that affects quite a few people, the frequency is still quite low even in these areas of high endemicity. In terms of study design and conducting an ideal RCT, it was not really possible to do that given the rarity of the event. Therefore, they designed the best study that they could under the circumstances and the data available. They have tried to power the study to detect a difference in these healthcare workers over the 2-year time period. That was the calculation that may be able to demonstrate some effectiveness, given the retrospective data available and reach a certain number of monkeypox infections over this 2-year time period. They are still in the process of evaluating that kind of effectiveness analysis and what they actually will be able to say. They do have the exposure data and do know that study participants did have contact with patients with suspect or confirmed monkeypox, so the hope is that the combined effectiveness analysis demonstration of exposures in combination with the immunogenicity will provide a convincing argument for effectiveness for this vaccine to prevent monkeypox.

Dr. Schaffner (NFID) recognized that out of the CDC stockpile, about 200 laboratorians receive ACAM2000® each year. He would think there would be many more recipients of this vaccine in the military each year and wondered if Dr. Petersen could comment on that to put this into perspective for the ACIP members to better understand how much of this vaccine is being used each year.

Dr. Petersen indicated that it is good to distinguish the civilian smallpox vaccine campaigns from the military vaccine campaigns. The numbers he quoted represented smallpox vaccines being used in civilians. Smallpox vaccines are being administered to Active Duty military personnel. Though he did not have the numbers readily available, it is in the thousands annually and he will provide those numbers.

ACIP Orthopoxviruses: Clinical Guidance and Next Steps

Agam Rao, MD
CAPT, US Public Health Service
Co-Lead, ACIP Rabies WG
NCEZID National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Rao pointed out that JYNNEOS® is a new vaccine for orthopoxviruses and for that reason the WG determined that a policy question, systematic review, GRADE, and EtR have to be presented to the ACIP before the committee can vote on a recommendation. The WG drafted this policy question, “Should JYNNEOS® be recommended for persons who are at risk for occupational exposure to orthopoxviruses?” This policy question is not intended to be a preferential recommendation for JYNNEOS® over another vaccine. It is just whether JYNNEOS® should be recommended by ACIP at all.

For the PICO question, the “population” is persons who may be at risk for occupational exposure to orthopoxviruses. In the most recent update of the ACIP recommendations, persons who are at risk for occupational exposure include healthcare workers who administer vaccine, change bandages, are involved in clinical trials, research laboratorians, et cetera. The

"Intervention" is vaccination with JYNNEOS®. The "Comparison" is vaccination with ACAM2000®. The last component of the PICO is "Outcome." The WG brainstormed about all the potential outcomes that could impact the committee's decision to vote for or against recommending JYNNEOS®. Those outcomes that would help the committee understand the effectiveness of JYNNEOS® compared to ACAM2000® are prevention or reduction of orthopoxviral disease and immunogenicity against all orthopoxviruses. Those outcomes that would help explain safety are SAEs, myocarditis and pericarditis, and minor AEs. By prevention or reduction of disease of orthopoxvirus, the WG is accounting for the fact that some orthopoxviruses may be prevented by the vaccines but others may only be reduced in severity. Prevention, reduction, immunogenicity, SAEs, and myocarditis/pericarditis were deemed "critical" or "important" outcomes for deciding the policy question. Minor AEs were deemed "not important" for deciding the policy question. This table summarizes the completed PICO question drafted by the WG with the four "critical" or "important" outcomes listed in the outcome section:

	Policy question: Should JYNNEOS® be recommended for persons who are at risk for occupational exposure to orthopoxviruses?
Population	Persons who may be at risk for occupational exposure to orthopoxviruses
Intervention	Vaccination with JYNNEOS®
Comparison	Vaccination with ACAM2000®
Outcome	1) Prevention or reduction of disease by orthopoxviruses 2) Immunogenicity against all orthopoxviruses 3) Severe adverse events 4) Myo-/ peri-carditis

Once the WG drafted the policy question, they began working on the systematic review of the published literature. With the help of the CDC librarian who has expertise in systematic review searches, they developed the search terms "JYNNEOS," "Imvamune," Imvanex," and "Modified Vaccinia Ankara." The search was limited to human data only, no animal data, and they searched these databases: Medline, Embase, Cochrane Library, CINAHL, NTIS, Scopus, Clinicaltrials.gov, and Global Index Medicus. The WG is in the process of doing title and abstract sorting for the 740 articles identified by this search. Once the WG completes the systematic review, they will conduct the GRADEing for all four "critical" or "important" outcomes. The WG will then complete the ACIP EtR Framework for each outcome. The WG anticipates being able to present all of this to the ACIP during the February 2021 meeting and possibly could have a vote on this policy question as soon as the June 2021 ACIP meeting.

Dengue Vaccines

Robert Atmar, MD
ACIP Member
Chair, Dengue Vaccine Work Group

Dr. Atmar reported that between March 2020-October 2020, the Dengue Vaccines WG has engaged in a number of discussions. The WG initially reviewed the February 2020 ACIP Dengue Vaccines session and discussion of possible phased implementation of CYD-TDV vaccine in Puerto Rico; heard data from Sanofi Pasteur on a CYD-TDV cost-effectiveness study; examined the acceptability of a CYD-TDV vaccination program for 9-16 year old children in Puerto Rico based on input from pediatricians, school officials, and key informant interviews; heard an overview of two economic analyses by a CDC ACIP health economist; reviewed preliminary results of a CDC Phase 1 evaluation of dengue IgG tests and their performance in identifying people previously infected with dengue; and reviewed initial drafts of the Evidence to Recommendation (EtR) results for CYD-TDV.

The WG engaged in considerable discussions about a phased approach to work out the logistics and feasibility of pre-vaccination screening in Puerto Rico. The discussions included observations that keeping an ACIP recommendation simple is desirable, although possibly challenging. There were suggestion that an *MMWR* background document could comment that CYD-TDV vaccine poses novel challenges that would make a phased implementation potentially helpful. Ultimately, territorial health departments will be responsible for determining how to roll out the vaccine.

In terms of the WG's discussion regarding acceptability, CYD-TDV appears acceptable to Puerto Rico stakeholders. However, further education is needed for physicians and parents regarding the benefits and risks. No information has been available to the WG during the past 6 months on vaccine acceptability and feasibility in other US territories. While efforts are under way to obtain that information, it may not be available by February 2021.

In the Notre Dame cost-effectiveness study for which a pre-print is available, the base case scenario was that a diagnostic assay would have a specificity of 95% and sensitivity of 80%, there would be 50% dengue seroprevalence in the target population, 9 year olds would be vaccinated and followed over a 10-year period, with 80% of the 9 year olds screened. Based on that cost-effectiveness analysis, 3415 hospitalizations would be averted. There is a ratio of 18.6 hospitalizations averted for each additional hospitalization that might occur due to vaccinating a child who on initial screening was determined to be seropositive who was in fact seronegative and had not been previously infected with dengue. The Notre Dame study found incremental cost-effectiveness ratios (ICERs) for hospitalizations averted of $16,000 ($9,400 - $29,000) and quality-adjusted life-years (QALYs) of $122,000 ($74,000 - $182,000). The estimated range based the uncertainty of model parameters to fit the vaccine trial data that had been obtained previously [Espana et al. MedRxiv doi: https://doi.org/10.1101/2020.10.07.20208512].

One of the critical pieces of information that the WG is still awaiting are the pre-vaccination laboratory screening tests and the characteristics of those tests. The EtR judgments are dependent upon the performance of pre-vaccination screening tests for prior dengue infection to sensitively, and more importantly specifically, detect prior dengue infection. There is a second phase CDC evaluation of dengue IgG candidate assays showing good specificity and sensitivity in the primary analyses to examine early convalescent serum samples that is pending. The second phase testing will be assessing samples from later convalescent periods and from people who have been infected previously with Zika virus and a variety of other control samples. With the assumption that one or more of these commercially available dengue IgG assays will meet the international target product profile for acceptable specificity of 95% and sensitivity of 85%, the expected judgment on benefits/harms in the WG's initial discussion would be that it "favors intervention." The WG has not had discussions about what such a recommendation would be if an assay did not achieve the target profile.

Anticipated WG discussions over the next several months will include efforts to try to finalize the EtR incorporating the results of the dengue IgG lab test evaluation. These discussions are likely to focus on health equity in terms of access to the diagnostic test and the vaccine; feasibility in Puerto Rico and other US territories, including the cost and availability of laboratory testing; whether a recommendation should be shared decision-making versus unqualified if a recommendation is made; and new data in an August 2020 *Science* paper suggesting that prior Zika infection enhances risk of severe dengue [Katzelnick et al, *Science* 369:1123-1128 (2020)].

In terms of the Dengue Vaccine WG's 2021 schedule, the presentation topics for the February 2021 ACIP meeting are anticipated to be CDC assessment of laboratory tests for pre-vaccination screening, and the EtR Framework with draft CYD-TDV recommendations. An ACIP vote on the CYD-TDV recommendations is anticipated for the June 2021 ACIP meeting.

In closing, Dr. Atmar posed the following questions for the ACIP members:

- ❑ Are there specific data ACIP would like presented?
- ❑ Are there other considerations the WG should address?

Discussion Points

Dr. Maldonado (AAP) asked other than hospitalization what other morbidity was taken into account in the Notre Dame ICER assessment and if mortality also was assessed.

Dr. Waterman indicated that the ICER assessment in the Notre Dame study looked at hospitalizations, severe illness, and QALYs. There were no deaths in the clinical trial, so mortality was not assessed in this study. Deaths with dengue are fairly rare at less than 0.1% with good clinical management.

Pneumococcal Vaccines

Introduction

Katherine Poehling, MD, MPH
Chair, Pneumococcal Vaccines Work Group

Dr. Poehling introduced the Pneumococcal Work Group (WG). The Pneumococcal WG's terms of reference are to: 1) review current data including efficacy, effectiveness, immunogenicity, epidemiology, and cost-effectiveness of pneumococcal conjugate and polysaccharide vaccines and assess the strength of the evidence; 2) review current recommendations considering up-to-date evidence; and 3) revise or update recommendations for pneumococcal vaccine use as needed.

Overview

Miwako Kobayashi, MD, MPH
Respiratory Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Kobayashi briefly summarized the rationale for the last ACIP vote on pneumococcal vaccines in June 2019 and the reasons for reactivating the WG. In terms of the history of ACIP recommendations on pneumococcal conjugate vaccines (PCV), the 13-valent PCV vaccine (PCV13) was first recommended for use in adults with immunocompromising conditions, cerebrospinal fluid (CSF) leaks, or cochlear implants in 2012. In 2014, ACIP recommended routine use of PCV13 in series with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for all adults ≥65 years old. ACIP recognized that there would be a need to re-evaluate this recommendation because it was anticipated that PCV13 use in children would continue to reduce the disease burden among adults through reduced carriage and transmission of vaccine serotypes from vaccinated children, or indirect effects. This table summarizes the EtR Framework presented during the June 2019 ACIP:

Conclusions from the EtR leading to ACIP vote in 2019

Element	Favoring Continued PCV13 Use	Favoring No Longer using PCV13
Burden of Disease	• PCV13-type disease reduced, but not eliminated through indirect effects from pediatric PCV use	• Indirect effects from pediatric PCV use have reduced the burden of PCV13-type disease to historic lows
Benefits	• PCV13 effective in preventing PCV13-type pneumococcal disease	• **Impact from PCV13 use in older adults observed to date is minimal; no impact on IPD and inconsistent findings across studies for impact on pneumonia** • **Benefits from continued PCV13 use are expected to be minimal**
Acceptability	• **Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations**	• Credibility comes from evidence-based recommendations
Resources Used	• A recommendation change would incur a cost to update electronic medical records, decision support tools, etc.	• Economic analyses results do not favor continued PCV13 use
Feasibility	• **Universal prevention strategies are easier to implement effectively than risk-based ones** • **Frequent changes in recommendations present implementation challenges**	• Simplifies the recommendations—current recommendations have been confusing and difficult to implement

The WG agreed that PCV's greatest impact on adults has been through indirect effects from pediatric vaccination. Since 2014, consistent population-level impact from PCV13 use among older adults had not been observed and continued use of PCV13 in older adults was not considered to be cost-effective by usual standards. On the other hand, frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations and present implementation challenges. Some WG members favored the scientific rationale for changing the recommendations, while others considered that the acceptability and feasibility issues were more important and preferred keeping the 2014 recommendations. In 2019, ACIP voted to remove the 2014 recommendation for routine PCV13 use among adults ≥65 years old and to recommend administration of PCV13 based on shared clinical decision-making for adults ≥65 years old who do not have any immunocompromising conditions, CSF leaks, or cochlear implants and who have not previously received PCV13. The recommendation for adults with these conditions was unchanged.

Currently, there are two new adult PCV products that are expected to be considered for licensure in 2021. One is the 15-valent vaccine (PCV15) by Merck. In addition to PCV13 serotypes, this vaccine contains serotypes 22F and 33F. The other is the 20-valent vaccine (PCV20) by Pfizer. In addition to the PCV13 serotypes, this vaccine contains serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F. All of these additional serotypes are currently included in the 23-valent PPSV23 vaccine, which is currently recommended for all adults ≥65 years old.

Because two adult PCVs are expected to be licensed in 2021, the Pneumococcal WG was reactivated to review considerations for and evidence supporting the use of higher valent pneumococcal conjugate vaccines in the general population of US adults and adults with certain underlying conditions. In addition, the WG will present policy options for an ACIP vote following licensure.

Dr. Kobayashi briefly summarized the current epidemiology of invasive pneumococcal disease (IPD) in the US from the Active Bacterial Core (ABC) surveillance data and presented the WG proposed work plan. Since PCV13 replaced PCV7 in 2010, the incidence of PCV13-type IPD declined markedly in children under 5 years of age who are targeted for vaccination. Reduction of PCV13-type IPD incidence also was seen in adults. The observed reduction is likely due to indirect effects from PCV13 use in children. In 2014, PCV13 was recommended for all adults ≥65 years of age. However, no population level impacts were observed on PCV13-type IPD incidence in this age group. The trends of IPD associated with non-PCV13 types remain relatively stable in adults.

In 2017-2018, PCV13-type IPD accounted for approximately 23% of all IPD in children less than 5 years of age, 30% in adults 19-64 years of age, and 27% in adults ≥65 years of age. PCV-13 serotypes were more common than others. Serotypes 3, 19F, and 19A were the most common remaining PCV13 types in all age groups. Serotype 3 by itself was identified in 10% or more of all IPD in all age groups. The 2 additional serotypes contained in PCV15 accounted for approximately 13% to 16% of IPD. The additional serotypes contained in PCV20 but not in PCV15 accounted for 14% of IPD in adults ≥65 years of age to 21% of IPD in children less than 5 years of age.

As mentioned earlier, PCV20 for adults is expected to be approved for licensure in mid-2021 if priority review is granted by the FDA. PCV15 for adults is expected to be approved in mid- to late-2021 depending upon the type of review that would be granted by the FDA. Licensure of PCV15 in children is anticipated in Q2 or Q3 of 2022 and licensure of PCV20 in children is projected for mid-2023.

In the months leading to the ACIP vote, the Pneumococcal WG plans to review the following pieces of evidence:

- ❑ Immunogenicity and safety from Phase III studies for PCV15 and PCV20

- ❑ Epidemiology of pneumococcal disease and vaccine-preventable disease burden for:
  - ➢ Invasive pneumococcal disease
  - ➢ Non-invasive pneumococcal pneumonia
  - ➢ Mortality

- ❑ Expected public health impact and cost-effectiveness of PCV15/PCV20, including the following:
  - ➢ Estimated direct effects in adults
  - ➢ Estimated indirect effects from vaccine use in children
  - ➢ Impact on health equity

- ❑ New evidence on the effectiveness of PPSV23

- ❑ GRADE and EtR to summarize the evidence

During the February 2021 ACIP meeting, the WG plans to present further details on the current epidemiology of pneumococcal disease, including both invasive and non-invasive disease; data from the Phase III clinical trials for the new vaccine products; and the policy question(s) proposed by the WG. The WG's current goal is to review all of the relevant evidence to have votes on the vaccine recommendations soon after licensure.

Discussion Points

Dr. Hunter commented that it is very unfortunate that the adult vaccines will come out before the childhood vaccines, given that it is going to make the ACIP's decision about making recommendations extremely difficult because there will not be indirect/direct effects that would be very easy to figure out.

Cholera Vaccines

Pablo Sanchez, MD
Chair, Cholera Vaccine Work Group

Dr. Sanchez introduced and described the Cholera Vaccine Work Group (WG). In 2017, ACIP recommended the cholera vaccine CVD 103-HgR (Vaxchora™) for adult travelers 18–64 years of age from the United States (US) to an area of active cholera transmission. This WG will now review more recent pediatric data to inform whether ACIP should recommend cholera vaccine for travelers 2–17 years of age.

The policy topic under consideration by the WG is, "Should ACIP cholera vaccine recommendations be expanded to include children and adolescents aged 2–17 years?" The WG activities to address this question will be to review available safety and immunogenicity data for CVD 103-HgR among children and adolescents; develop evidence-based recommendations

using the GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach; and eventually publish an update in the *MMWR*.

It is important to note that the company that makes the cholera vaccine, Emergent, has made the decision to temporarily discontinue product distribution as of December 17, 2020 due to significant reductions in demand. Vaxchora™ is the only licensed and approved cholera vaccine.

Discussion Points

Dr. Mark Schneider (Emergent) indicated that he was joined by his colleague, Dr. Stephanie Campbell, and thanked ACIP for the invitation to join the meeting and provide remarks. Emergent has made a very difficult decision to temporarily discontinue distribution of Vaxchora™ (Cholera Vaccine, Live, Oral) and Vivotif® (Typhoid Vaccine Live Oral Ty21a) due to market reduction in demand. Emergent continuously assesses travel data from a wide range of sources to include, but not limited to, government institutions, research firms, and industry experts that all point to a protracted recovery period for international travel due to the COVID-19 pandemic. Pending further notification, the last shipment date for Vaxchora™ will be December 17, 2020. Customers can continue to order the product through that date. All products being distributed through December 17th will have an expiration of January 2021 for Vivotif® and June 2021 for Vaxchora™. That said, Emergent remains fully committed to addressing the needs of public health and travel medicine and seeks to properly position themselves to return these products to market in anticipation of the return of global travel in the near future.

Dr. Cohn indicated that CDC/ACIP did not realize that Emergent was planning to speak and that this would not be the appropriate time to speak, given that they must follow the agenda as posted and not have outside companies speak unless they were previously approved. She requested that Emergent hold their comments at this time and that an effort would be made to find time on the agenda at a later time.

Public Comment

Mark Gibbons
President and Chief Executive Officer
RetireSafe Organization

Dr. Romero and members of the committee, good afternoon. My name is Mark Gibbons. I'm President and CEO of the RetireSafe Organization. RetireSafe is an organization whose mission is to educate and advocate on behalf of older Americans on issues including Social Security, Medicare, health, safe retirement, and financial well-being. We believe that older Americans must have a voice in public healthcare policies that affect them. Older Americans are an important population. Currently, there are nearly 70 million Americans over the age of 60. Due to immune system decline as part of aging, as well as the prevalence of chronic disease comorbidities, many of them are particularly vulnerable to infectious diseases such as influenza, pneumococcal pneumonia, and of course COVID-19. Vaccines for these and other conditions can truly be a matter of life or death for so many. We must keep this population, their increased risk, and their access needs at the forefront of vaccine development and ACIP consideration. One of our major concerns is a need for more expertise and representation for older Americans

among ACIP members. As ACIP deliberates on important vaccine issues, we need to hear from experts who understand health factors and needs of older adults, as well as how their behaviors and lifestyles impact being able to fully benefit from these immunizations. The make-up of ACIP members should better reflect clinical expertise in these areas such as gerontology and the ability of vaccinations to work well for patients with chronic diseases and conditions often associated with advancing age. Even before the pandemic, older Americans face challenges in accessing care. The pandemic has obviously made that worse. There is a clear need to not only develop new vaccines, but also to consider the technology and innovation of new methods of making them available, accessible, and usable to those who need them, including the potential for oral options. We believe that we need to incorporate that reality into ACIP thinking. We urge ACIP to be open to expansion of working groups and panel membership to include both clinical and cultural expertise. We need to keep looking at innovative platforms and solutions to providing immunizations to our vulnerable population. Please let our voices be heard. Thank you.

Joanna Colbourne
Deputy Executive Director
National Foundation for Infectious Diseases

Good afternoon. Hello, my name is Joanna Colbourne. I am the Deputy Executive Director of the National Foundation for Infectious Diseases, or NFID. The 2020-2021 influenza season is expected to be characterized by an unprecedented dual threat, co-circulation of influenza and the novel coronavirus SARS-CoV-2 that causes COVID-19. In addition, amidst the pandemic, immunization rates have decreased for recommended vaccines across all age groups, with demand plummeting as much as 95% for some vaccines. We must reverse this trend now to avoid seeing outbreaks of flu and other vaccine-preventable diseases across the country. Influenza, or flu, and COVID-19 can be dangerous for anyone, but for more than 6 in 10 US adults living with a chronic health condition, including heart disease, lung disease, and diabetes flu and COVID-19 may be especially dangerous. Adults with chronic health conditions experience an inflammatory reaction caused by influenza infection that can worsen their underlying disease and lead to a number of serious outcomes including hospitalization, heart attack, or stroke, catastrophic disability, and death. To make matters worse, many of the underlying health conditions that make adults vulnerable to flu are also linked to increased vulnerability to COVID-19. Although there is currently no approved COVID-19 vaccine in the US, there are safe and effective vaccines they can help protect against flu and many other vaccine-preventable diseases. To address this urgent public health threat, NFID has launched the “Keep Up The Rates” flu awareness campaign in recent months. “Keep Up the Rates” is a national campaign to encourage all individuals to receive recommended vaccines that may have been delayed during the COVID-19 pandemic. To date, more than 100 leading organizations have joined and are sharing information and resources in support of this critical public health initiative. Earlier this month, NFID released a new “Call to Action: The Dangers of Influenza and COVID-19 in Adults with Chronic Health Conditions,” which was the result of a multidisciplinary roundtable to explore the potential impact of influenza and COVID-19 on adults with chronic health conditions. The campaign includes more than 35 leading medical organizations that are sharing best practices for administering flu vaccines amidst COVID-19 mitigation efforts. NFID and its partners are urging all healthcare professionals, particularly specialists treating adults with chronic health conditions, to implement strategies from the “Call to Action” and utilize tools or resources from the “Keep Up the Rates” campaign, all of which are available at www.nfid.org. It is the responsibility of all healthcare professionals to educate, motivate, and insist that patients prioritize annual flu vaccination this season and stay up-to-date on all recommended

vaccines. Thank you for your time and attention today and special thanks to the members of ACIP for the work you continue to do.

Michael Arnold
Parent and Activist

Yes, hello. My name is Michael Arnold and I'm here to talk about vaccine problems and solutions. Vaccines are not tested against placebo, saline, and manufacturers have no liability for serious injury or death. Vaccine ingredients, as explained by Dr. Sherri Tenpenny, have many toxins in them such as aluminum, formaldehyde, mercury, polysorbate 80, and aborted fetal tissue deoxyribonucleic acid (DNA). There is a chart from the journal of the *American Academy of Pediatrics* (*AAP*), December 2000, which shows how vaccines did not play a major role in the decline of disease. It was clean running water. The book, "How to End the Autism Epidemic" by J.B. Handley explains in Chapter 5 how aluminum plays a major role in the autism epidemic by causing encephalitis. In the book, "Vaccines: Are They Really Safe and Effective?" by Neil Z. Miller, there is a graph. Doctors, pediatricians, were surveyed and they were asked about the Hepatitis B vaccine, and 87% said they did not believe that that vaccine was necessary for their patients. Okay, well there's Justice for Evee. Evee died 36 hours after her vaccinations. The Medical Examiner (ME) said it was because of sudden infant death syndrome (SIDS), but Evee's mother is fighting for a tissue sample so that she can prove that it was actually VIDS, vaccine-induced death syndrome, not SIDS. Christopher died shortly after the GARDASIL® vaccine for human papillomavirus (HPV). You can learn about him from learntherisks.org and #neverforgetChris. Adam got autism after his wellness visit like thousands of other babies, and you can learn about that from the documentary about him. Solutions. Take Hepatitis B off the schedule as soon as possible. Ask Congress to terminate the National Childhood Vaccine Injury Act (NCVIA)of 1986. Ask Congress to change vaccines from a biologic to a drug. Ask the CDC and WHO to get clean water and proper sanitation for the world's poorest 1 billion people and work with the Behavior Analyst Certification Board (BACB), bacb.com.

Michaela Jackson
Prevention Policy Manager
Hepatitis B Foundation

My name is Michaela Jackson. I am the Prevention Policy Manager for the Hepatitis B Foundation. The current health emergency has shown that prevention truly is essential for the health of the public. As one of the primary causes of liver cancer and an underlying condition that can increase severe outcomes from COVID-19, preventing Hepatitis B infection should be an immunization priority. Today, we are advocating for a universal Hepatitis B vaccination recommendation to help protect the 75% of adults who are susceptible to Hepatitis B virus. Adult HepB vaccination rates are low amongst healthcare workers despite recommendations. They comprise 6% of the US population and face significant exposure to blood-borne diseases daily. Yet only 61% of health care workers have completed a full vaccine series. The disproportionate emphasis on the flu vaccine and the lack of targeted immunization messaging for healthcare workers have been identified as major barriers to increasing this percentage. In addition, the average age of a nurse in America is 50 years old. The majority of the nurse population are between 45 and 59 years old. This highlights issue that current guidelines fail to capture. Susceptible individuals were born before the universal infant HepB vaccine recommendation. These individuals are relying upon their providers to recommend the HepB vaccine, which becomes problematic if the providers are unaware of a person's job or other risk factors. Other essential workers are at risk as well. In the past decade, there have been 18

documented outbreaks of HepB in non-hospital settings. Our foundation has heard stories from essential workers who have developed HepB after being stuck by a needle on the job. Studies show that 95% of needles are still discarded in municipal waste streams, despite national and state protocols for disposal. The average risk of contracting HepB from a needlestick exposure ranges from 6% to 30%, placing all unvaccinated workers who may come in contact with a needle, such as food service employees or sanitation workers, at significant risk for infection. Protection should not be contingent upon which job you have. Accessing the vaccine is another barrier to increasing immunization rates. Some state and federal programs recover the cost of HepB vaccines for adults if they're in one of the high-risk categories named by ACIP. However, some of those risk factors, such as diabetes or fatty liver, can go undetected for years. This means that a person who is at risk may not be able to access the vaccine due to costs simply because the risk factor has yet to be identified. Despite ACIP recommendations that anybody who wants to be vaccinated for HepB can get immunized, many Insurance programs, including Medicare, will not cover this group. Current HepB vaccination guidelines are simply not enough. The complexities of the current recommendations act as a barrier to achieving satisfactory adult HepB immunization rates, but ACIP has the power to change that. With a recommendation for universal adult HepB vaccination, we could be one step closer to eliminating viral hepatitis in the United States. Thank you for your time today.

Kimberly Hall
Florida Freedom Keepers

Good afternoon. My name is Kimberly Hall. When I was 25, I lost twin girls at 23 weeks gestation. The doctors told me it was unexplainable. My twins would be 5 years old this year. I am 5 years still recuperating from the memory of the profound pain, confusion, trauma, and complete upheaval of my entire life. It was at 22 weeks with the nurse taking my basic vitals requested me to take a shot for pertussis. When I stated that I didn't know what pertussis even was, the nurse shortly explained to me that it would protect me from obtaining this disease and alongside that, I would be passing on protection to my twins. I was not given any further information about this medical intervention. What information is there really that shows it provides any protection that she claimed? What is available states that a Proceedings of the National Academy of Sciences (PNAS) study, and I quote, "While all groups possessed robust antibody responses, key differences in T-cell memory suggest that aP vaccination induces a suboptimal immune response that is unable to prevent infection." There is also available a 2017 review of 15 published articles that determined that while vaccination boosted maternal antibodies, evidence was lacking on whether or not this had any impact on reducing the incidence of pertussis, serious complications, or death in infants. It seems the Tdap vaccine does not prevent the spread of disease or even prevent you from catching the disease. If today I pull up the CDC website, I very clearly see that the CDC recommends pregnant women to get the whooping cough vaccine between 27 and 36 weeks of each pregnancy. Why was I offered this at 22 weeks? That nurse represents this country's entire lack of any informed consent with these injected biologics. The Food and Drug Administration (FDA) has classified Tdap as a Category C drug because of this complete insufficient evidence regarding any administration in pregnant women. The argument is used that it could be seen as unethical to test such a vaccine, but it is being pushed and coerced on woman every day as a complete off-label use. Furthermore, the FDA has never even approved a vaccine specifically for use in pregnancy to prevent disease in the infant. I was not given any information of the injected ingredients: formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80, phenoxyethanol, ammonium sulfate. In what doctor's insane mind does this ingredient list seem like an injectable concoction for a pregnant woman carrying an undeveloped fetus? Why is it the GARDASIL® package insert reference to page 10, where it shows the use in populations of pregnancies

within clinical trials? The GARDASIL® vaccine contains 225 micrograms of aluminum hydroxide and 7 of 55 women lost their babies (12.7%). GARDASIL® vaccine was made with more than a 50% increase of aluminum, 500 micrograms and 17 of those 62 women lost their babies. That percentage spiked up 27.4%. It is shown through the studies and science that aluminum hydroxide alone plays a major role, causing fetal demise and spontaneous abortions with the Tdap containing more than 300 micrograms. The CDC and vaccine manufacturers are both completely exempt from liability, exempt from providing randomized control trials (RCTs), and exempt to provide any evidence to do what you claim it will do and only to show it could create antibodies. That doesn't equal immunity. It is awfully disappointing that in 2020, we have such a widespread knowledge deficit within the scientific community. Thank you.

Albert Faro, MD
Vice President of Clinical Affairs
Cystic Fibrosis Foundation

Good afternoon. My name is Dr. Albert Faro and I'm the Vice President of Clinical Affairs at the Cystic Fibrosis Foundation (CF Foundation). On behalf of the foundation, thank you for this opportunity to provide comments to the Advisory Committee on Immunization Practices regarding developments in allocation of COVID-19 vaccines. The CF Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis (CF), a rare life-threatening genetic disease that affects over 30,000 people in the United States. The build-up of thick, sticky mucus in the lungs characteristic of the disease makes people with CF particularly prone to chronic airway infections, punctuated by pulmonary exacerbations, events associated with morbidity and mortality in people with CF. A significant proportion of pulmonary exacerbations are triggered by respiratory viral infections. With continued progression of the disease, individuals with CF and advanced lung disease may pursue lung transplantation. Due to the known risks posed by respiratory viral infections, the unique dangers of the SARS-CoV-2 virus and the multi-system manifestations of CF, some people with CF, such as those with advanced disease or who are post-transplant and therefore immunocompromised, should be considered at high-risk for poor outcomes from COVID-19 infection. The strongest evidence to date on the dangers of COVID-19 for people with CF comes from a forthcoming global analysis of 181 COVID-19 cases among people with CF. From that analysis, it appears CF patients with advanced lung disease and those that are post-lung transplantation, are at risk of severe outcomes, including death. We therefore urge the advisory committee to consider information beyond the CDC's list of comorbid conditions to inform prioritization determinations. That list may mischaracterize the true risk for some rare disease populations like CF. We further urge the advisory committee to give equal priority to anyone with a condition that puts them in a high risk for severe disease from COVID-19 instead of adopting the National Academy of Medicine's (NAM) recommendation to first prioritize people with multiple comorbid conditions for access to a vaccine—a focus that relies on multiple conditions and neglects other indications of disease severity and vulnerability. We believe that scenario inappropriately disadvantages someone whose underlying disease condition is advanced or severe. This segment of the population should be prioritized for early access to a vaccine and includes patients with CF with advanced disease or who are post-transplant. Thank you again for your attention and consideration of people with CF as you tackle these critical issues.

Del Bigtree
Founder
Informed Consent Action Network

I want to thank the committee for giving me this opportunity to speak. I want to say that, you know, given that almost everything we talk about these days involves discussion of COVID-19, I want to say I found it shocking that in the discussion about the flu shot this morning, there was no discussion about the risk of COVID-19 being increased by flu shots, given the fact that there's so many studies that are showing this type of connection. Specifically, we have the Cleveland Clinic study that's entitled "Safety of Influenza Vaccine During COVID-19." It found a highly statistically significant increased rate of mortality, ICU admission, and hospitalization for COVID-19 among those that received a flu shot in 2019 as compared to those that did not. In fact, it reflected that those receiving the flu shot in 2019 had a 175% increased rate of mortality and a 195% increased rate of ICU admissions. Additionally. There was a gigantic study that just came out looking at 39 countries called "Positive Association Between COVID-19 Deaths and Influenza Vaccine Rates in Elderly People Worldwide." Given that there are those studies and studies out of Japan that have shown 400% increased risk in other upper respiratory infections amongst those that got flu shots compared to those that didn't. All of this science around the world is pointing to there may be a real danger to giving flu shots during COVID-19, yet the CDC seems to plow forward with this idea of a twindemic and using it as a way to force the largest flu vaccine campaign in US history. We're also watching the 59 deaths from flu shots and growing in South Korea where they are involved in this mission, yet none of this seems to matter to you at the Advisory Committee of Immunization Practices, which is really shocking. Given the lack and waning confidence that the American public now has in the CDC, it seems by many articles to be at the lowest point in history, how do you expect to be relevant or even be considered necessary in a process of protecting our population when you're not even having the most obvious conversations you should be having when it comes to vaccinations. This is your world. This is what you're supposed to be looking at. We are supposed to have confidence that when there are studies all around the world showing a risk of delivering a flu shot vaccine and the increased risk of death from COVID-19 that certainly it's a conversation and you'll be able to bring up studies to discount or, you know, somehow refute this issue. Instead, you avoid it altogether, which is continuing to drive the confidence in the work that you do down to the floor. I would like to see you be a little more responsible with these conversations, given that they are so important and may include and involve the risk of death for hundreds of thousands if not millions of people in this country and around the world. Thank you.

Erin Olszewski, RN
US Citizen

Yes. Hello. Good afternoon and thank you for having me today. My name is Erin Olszewski and I'm a Registered Nurse (RN). This year, I also became a COVID whistleblower who uncovered the fraud, negligence, greed, and unnecessary deaths being covered up in New York City's (NYC's) Elmhurst Hospital and the CDC at the height of that pandemic, with actual video and audio indisputable proof. So, we both know the numbers you're basing your new COVID vaccine recommendations off of are inflated and fraudulent. You cooked the books on vaccines just like you've been cooking the books on COVID. You've rigged the studies, you've covered up the data, you've buried the injuries and deaths, you've removed yourselves and the vaccine manufacturers from all liability, and you've lied to the American people long enough. I needed to alert the American public to something they may not know. There is a CDC scientist whistleblower named Dr. William Thompson who the CDC is attempting to cover up. Dr.

Thompson discovered that the measles, mumps and rubella (MMR) vaccine was causing a dramatic rise in autism in African American boys. However, his CDC bosses have ordered him to silence. I believe that this is the year of the whistleblower and accountability, especially as it relates to our minority populations. Most recently, yesterday in fact, whistleblower Tony Bobulinski came forward exposing even more fraudulent activity happening within our government. If there is any hope in recovering the trust of Americans, the executive government needs to step up, do what's right, and immediately subpoena Dr. William Thompson and all his CDC co-authors to testify before Congress. Congressman Bill Posey here in Florida has thousands of damning CDC documents Dr. Thompson handed to him. If forced to testify, Dr. Thompson stated he's not going to lie. The public deserves the truth before this panel continues their unethical practices of adding even more vaccines to the already overly crowded, toxic, liability-free schedule. Each one of you on that panel know that the science has been corrupted. Yet, you continue to dish out fraudulent data because money, power, and greed is much more lucrative than protecting public health. The CDC and mainstream media continue to bury this information. They know that vaccines are causing detrimental harm and death to children and adults. Yet here we are today watching you discuss a fast-tracked, liability-free COVID vaccine for a virus with a 99% survival rate. A quote from your very own silenced CDC scientist, Dr. William Thompson, in 2004 to Dr. Brian Hooker, "That's the deal. That's what I keep seeing again and again and again where the senior people at CDC just do completely unethical vile things and no one holds them accountable. Your time is running out, because the American people are waking up and accountability is coming for you mark my words. First, do no harm. I hope all of you do some soul-searching and remember why you're here. Thank you.

Susie Olson Corgan
Representing Self

Hello. My name is Susie Olson Corgan. Thank you so much for the opportunity to speak today. I have been attending the ACIP meetings, as well as Board of Health (BOH), Department of Justice (DOJ), and National Vaccine Advisory Committee (NVAC) meetings. The thread among these meetings has been vaccine hesitancy. The one thing I have heard many of you say is that vaccine hesitancy is due in large part to anti-vaccination campaign. As you know, most of these campaigns are carried out on social media. However, social media censorship is at an all-time high. Major platforms such as YouTube, Facebook, Instagram, Pinterest, Linked-In, Vimeo, and even search engines like Google are frequently removing contents and banning accounts without warning or explanation that even has the slightest appearance of questioning the current vaccination program. Despite the fact that this information is being censored, vaccine hesitancy is still on the rise. Some of the reasons that people are questioning vaccine are the following: the withholding of the COVID-19 vaccine trial data, lack of transparency regarding adverse events (AEs) in the trials, using another vaccine as the placebo—a placebo to be an inert substance, concurrent studies phases, lack of liability if something goes wrong—and this applies not only to the COVID-19 vaccine candidates, but also to those currently on the recommended childhood vaccination schedule, partnerships with organizations such as the Gates Foundation to create marketing campaigns, and questioning whether there has been corporate capture of our regulatory agencies. I know that some of these issues are out of your scope, but you have enormous influence among the medical and scientific communities worldwide. They will consider any recommendations that you make. I urge you to consider increased transparency throughout this process. Vaccine hesitancy will continue to rise and if and when a COVID-19 vaccine candidate is approved for distribution, supply will not be your primary issue—demand will be. Thank you.

Charles Lee, MD
President Elect
American College of Correctional Medicine

Thank you very much. I am Charles Lee. I am the President Elect of the American College of Correctional Physicians (ACCP). I'd like to thank the academy for allowing me to give this presentation on behalf of the inmates and correctional workers throughout the country. Just yesterday, there was a news release that 75% of inmates at the Marquette Michigan Prison were positive for coronavirus. In addition to that, 42% of the employees were positive. Also, about a month ago, there was an article about in Virginia, 70% of the inmates were positive. Inmates' rate of infection of coronavirus is 5 times that of the general population and the death rate is 1.5 times that of the general population. Correctional workers and inmates go home. They contract the illness, disease, coronavirus, within the institution and conceivably can spread it to their family, friends, neighbors, stores, and wherever they may be. Ninety percent of inmates are released at some point in time. They, too, are our friends, family, and neighbors. In a correctional facility, it is extremely challenging to follow the CDC guidelines of masking, sanitizing, and distancing. Consequently, it is a big challenge to keep them safe. In October, the National Academy of Science, Engineering, and Medicine (NASEM) developed a framework of prioritization for coronavirus. It was Phase 1b in rural facilities where there are older patients with comorbidities in congregate settings, and Phase 2 for employees and inmates in correctional facilities. I will be submitting a resolution to the American Medical Association (AMA) along these same lines that hopefully in November will be approved. We asked the ACIP to adopt the National Academy's framework of prioritization for the vaccine of a safe, and effective, and FDA-approved vaccination. I thank you very much.

Kermit Kubitz
Individual

Thank you. I am 73 years old and was a polio pioneer in 1954. My wife and I have just gotten our flu shots in the last two weeks—in my case, the high-dose flu shot. I support Emergency Use Authorization (EUA) of COVID-19 vaccines showing preliminary efficacy and safety with the 3 following recommendations. First, there should be a substantial review of effectiveness for a group of 5,000 to 10,0000. Second, use new serology methods to study immune response. Third, give similar EUA approval for follow-on vaccines, including those with adjuvants for better protection. On the first point, the effectiveness of COVID-19 vaccine may be uncertain. Uncertainty results from the novel technologies used, the possibility of differential effectiveness for different groups, and the number of degrees of freedom (i.e., behavior variability among trial program participants, including NPIs; that is, non-pharmaceutical interventions such as masks and social distancing). Therefore, I recommend follow-up studies of effectiveness, not just safety, in approximately 5,000 to 10,000 vaccinated patients, including stratified groups of older patients and those with other health conditions. Second, follow-up on effectiveness for vaccinated patients should include serology studies to permit evaluation of the types of immune responses resulting from vaccination. Just as we are using novel vaccines such as mRNA, we should use innovative serology techniques such as the Multiplexed Identification of T-cell Receptor Antigen (MIRA) available now. Third, the FDA and CDC must be prepared through EUA follow-on vaccines which show greater effectiveness or duration of immunity. This should include single dose vaccines or vaccines using newer adjuvants like AS03 or CPG1018 which can stimulate a stronger immune response. But in order to do this, that is included follow-on vaccines, the FDA and CDC also need to understand and evaluate the effects of multiple vaccination iterations (i.e., what if you get an mRNA vaccine and then a subunit or inactivated

virus vaccine?). We need to understand what happens if you have antibody response to a subsequent vaccine. Thank you for your work. Keep it up. Keep it up.

Antony Hsu, MD, FACEP
Clinical Emergency Physician
American Colleges of Emergency Physicians

Good afternoon, ACIP. Thank you for what you do. I'm an actively practicing Clinical Emergency Physician with a concern for my family, children, community, city, state, nation, and humanity in that order. I'm not an epidemiologist or health care economist, but I do know a few and as a frontline emergency physician balancing community practice and academic pursuits with national advocacy, I base my advice on the more than 60,000 patient encounters and diverse work and life background I have had. The topics I'd like to address first are SARS-CoV-2 vaccine safety concerns that I've heard and thought about while working on an Indian Reservation in Montana in September: 1) Regarding generating trust on sufficient testing and safety, open up the books about side effect profiles of each vaccine. Transparency is needed in times of rationing to promote trust in government; 2) Consider community nomination committees to reach out to social influencers, faith-based, elected government representatives, and medical and scientific representatives for trust-building teams; 3) Consider anonymous polling by a panel of renowned experts about whether they would immunize themselves and their families, but their votes must remain anonymous to engender trust; and 4) Consider ranking the efficiency of each vaccine for each population profile. On the second larger topic of vaccine distribution, my thoughts are: 1) Ensure complete informed consent based on continuously updated benefit and risk profiles; 2) Consider buy-in for healthcare workers and gradually broadening the enrollment as safety and efficacy numbers are sustained and continuously reevaluated; 3) Consider calculating a relative risk reward or r^3 ratio for each person. This r^3 ratio addresses the risk of vaccination versus the risk of delayed vaccination. Gradually slide scale the availability based on the r3 ratio. This can defer depending on local, regional, and national priorities. The r^3 ratio method might avoid the concern of favoritism with an A, B, C, D or a 1, 2, 3, 4 approach and replaces it with a straightforward sliding scale. Each manufacturer can then provide what their sliding scale criteria are, especially since the safety profile for each vaccine may differ; 4) As availability improves, consider peer navigators and influencers discussed previously to step up messaging; 5) The nation must buttress its system for the distribution of preventive healthcare. Specifically, emergency departments (EDs), which operate 24/7/365 already vaccinate for tetanus, diphtheria, and pertussis. They have not been included in outreach, but they are at the frontline for pandemic responses. There are pilot projects in the States of Michigan and Washington that vaccinate for influenza and hepatitis A. Hospitals have the facilities to store vaccines that require extremely low temperatures and have security 24/7; and 6) EDs are uniquely positioned to work with public agencies for the work of mass immunization to ensure all people can be reached, including those facing homelessness and the underinsured for whom Eds may be the most likely source of care. Thank you so much for taking the time to listen to my suggestions and thank you for what you do.

Kim Freitas
Mother

Hello, and thank you for the opportunity to speak. I would like to discuss some critical areas of concern regarding the COVID vaccine. It is unethical to vaccinate a person using a high-risk, untried, liability-free vaccine when you have a safe and proven medicine available. Per the CDC, over 98% of the population recovers from COVID-19. We cannot risk injury to an otherwise healthy person using a vaccine we know very little about. One of the biggest areas of

concern is enhanced illness, when the vaccine triggers a reaction which causes a person to acquire the exact virus you are trying to protect them against. We have seen this happen in previous coronavirus animal trials, which are currently being skipped during COVID trials. These trials are also being conducted on healthy people, yet the vaccine is due to be administered to our most vulnerable populations first, who typically have the health issues with at least 1 if not 3 underlying conditions that makes them high-risk. How can we use an untested vaccine on them when we have no idea what the outcomes will be? Also, how can we disperse a product that is free from liability, especially a warp speed vaccine using mRNA technology that has never been used before? No contraindications have ever been studied regarding administering the COVID vaccine with other vaccines. This means it should not be administered in the same day, week, or even month with other vaccines. Who is going to monitor and control that? Which leads to my next concern, viral priming. This occurs from the heavily pushed flu vaccine. Studies have shown that the flu vaccine makes us 36% more likely to get an upper respiratory illness (URI), which includes COVID-19. We should be warning against use of the COVID vaccine for those who have already received the flu vaccine. Let's also be very clear that the recipient of the vaccine should be given the vaccine insert—not a short list of information. True informed consent involves knowing all of the risks, not just watered-down points. Lastly, we must have transparency from the Data and Safety and Monitoring Boards (DSMBs) who oversee these trials. J&J, AstraZeneca, and Oxford trials only provided fragmented information that we are not clear about adverse reactions during the ongoing trials. At one point, transverse myelitis was mentioned by the media, but then the wording was changed to a much vaguer language on the trial patient information sheets. In closing, we demand tested, tried, and proven vaccines that offer benefits greater than the already 98% recovery time with little to no interventions. These vaccines might be liability-free by the makers, but that does not make you, the advisory committee, morally free from the harm that can be caused by the decisions that you make. Please remember, where there is risk there must be choice. Thank you.

Friday: October 29, 2021

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier shared a few updates about the breadth of CDC's work on the response to the COVID-19 pandemic. CDC has been actively responding to the COVID-19 pandemic for nearly 300 days. This meeting marked Day 298 since NCIRD activated in January. To date, 7400 CDC staff have participated in the response, representing 3.5 million hours logged in responding to this event. Given that CDC staff is comprised of about 10,000 people total, this reflects that the vast majority of CDC staff have been engaged directly in the response and she expects the rest have been engaged in filling behind those who have been deployed. While they would hear about CDC's epidemiology and vaccine-related activities during the emergency meeting on October 30th, CDC staff remain committed to responding more broadly, including activities to support data and analytics; laboratory diagnostics and testing; global migration, including travelers' health; contact tracing; student travel support; health systems; and mitigation for schools, worksites, and food systems.

In terms of routine vaccine coverage, CDC recently published results from the 2009 National Immunization Survey (NIS)-Teen and NIS-Child surveys. Both reports identified strong immunization coverage, but also areas where more could be done to reduce disparities. The results of the 2019 NIS-Child found that only 1.2% of children had received no vaccinations by 24 months of age, but there continued to be disparities in coverage by race, ethnicity, poverty, and Metropolitan Statistical Area (MSA). NIS-Child was released in August and vaccination generally was showing improvement. However, the impact of the COVID-19 pandemic on childhood immunization has been extreme. Despite many efforts, child and adolescent vaccination coverage are lagging. The gap in measles vaccine is telling at approximately 1.5 million doses of measles vaccine behind where it should be this year. That means that a large number of children are unprotected against routine childhood diseases. This is a call to action to everyone at this meeting that children must be caught up on their vaccinations. If they fall behind, they continue to fall behind. That puts the US at risk for vaccine-preventable disease epidemics, as well as for HPV and the cancers related to it. She expressed her hope that everyone would emphasize the importance of getting people caught up on these visits.

CDC is also working to improve influenza vaccine coverage this season and to address disparities in influenza vaccination and influenza outcomes. The estimates from last season show that vaccine coverage increased slightly among adults from the previous season. However, racial and ethnic disparities in influenza vaccination persist. In an average year, more than half of US adults remain unprotected against influenza. A recent analysis of influenza hospitalization rates by race and ethnicity during 10 influenza seasons showed that non-Hispanic Black persons had the highest influenza hospitalization rates, followed by non-Hispanic American Indian or Alaska Natives (AI/AN) and then Hispanic or Latino persons compared to non-Hispanic Whites. Among other activities to address these ongoing disparities, CDC, the American Medical Association (AMA), and the Ad Council launched a collaborative campaign called “No Time for Flu” to increase awareness about the importance of influenza vaccination, especially among African American and Hispanic audiences. This year, there has been a large upsurge in demand for influenza vaccine compared to other years. That is great news, but CDC needs help sustaining that increase throughout the last quarter of 2020. While they would like everyone vaccinated in October, they still need to keep passing the message along that if folks did not get their vaccine in October, it is still not too late to get vaccinated in November and December.

While Acute Flaccid Myelitis (AFM) is not vaccine-preventable, it is a topic of concern and it is uncertain how the pandemic and recommended social distancing will affect enterovirus (EV) circulation in the US. While the CDC was prepared for a surge in cases considering that 2020 was anticipated to follow the pattern of national increases in AFM every 2 years, that is not being seen. The agency is still on high alert for AFM, but will need to continue to determine the effect social distancing has on that as well as on other respiratory viral diseases.

In a time when there is so much bad news, Dr. Messonnier said she wanted to end on a happy note. World Polio Day was celebrated on October 24, 2020 as an opportunity to highlight global efforts toward a polio-free world and honor the tireless contributions of those on the frontlines in the fight to eradicate polio from every corner of the globe. This year there is additional reason to celebrate in that on October 25, 2020, the Africa Region was officially certified as wild poliovirus (WPV)-free. With the African Region certification, 5 of the 6 WHO regions representing over 90% of the world’s population are now free of WPV.

Centers for Medicare and Medicaid Services (CMS)

Ms. Hance reported that CMS issued the fourth COVID-19 Interim Final Rule on October 28, 2020 with a comment period that addresses coverage of COVID-19 vaccines in Medicare, Medicaid, and private health plans. In addition, CMS issued 3 COVID-19 toolkits aimed at state Medicaid agencies, providers who will administer COVID vaccine, and health insurance plans. All of these materials are available on https://www.cms.gov/. Regarding influenza, CMS has coordinated with CDC on the release of their influenzas campaign materials. Influenza materials include videos, flyers, and drop-in articles all of which are available in both Spanish and English and are all available on https://www.medicare.gov/. In addition, consumers who subscribe for email updates from Medicare have received a specific email about the importance of influenza vaccine. Post-cards also have been sent to those who are dually eligible for Medicare and Medicaid. The CMS Office of Minority Health (OMH) has also included influenza vaccine information on their website. Specific to pediatric vaccines, CMS has repeatedly emphasized the importance of routine immunizations to states and other partners. In June and July, CDC Immunization Services Division (ISD) staff joined CMS calls with state Medicaid and children's health insurance program staff and emphasized the need for catch-up vaccines. CMS has a Connecting Kids to Coverage National Campaign. Materials specific to vaccines are available on that website: https://www.insurekidsnow.gov/campaign-information/index.html

Food and Drug Administration (FDA)

Dr. Fink reported that earlier in October, the FDA published guidance on data to support Emergency Use Authorization (EUA). The Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC) convened an open meeting for a general discussion for considerations for the development, licensure, and/or EUA of COVID-19 preventive vaccines. He indicated that he would be discussing the VRBPAC meeting in more detail during the COVID-19 session of the emergency ACIP meeting on October 30, 2020.

Health Resources and Services Administration (HRSA)

In terms of Ebola vaccine coverage by the Countermeasures Injury Compensation Program (CICP), Dr. Rubin reported that the National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In Fiscal Year (FY) 2020, petitioners filed 1191 claims through the program. $186.8 million was awarded to petitioners and $31 million was awarded to pay attorney fees and costs. In addition, at the end of the FY 2020, HRSA had a backlog of 966 vaccine injury claims awaiting review. As of October 1, 2020, the CICP determined that 39 claims were eligible for compensation totaling $6 million. The CICP also published a Notice of Proposed Rulemaking (NPRM) for the Smallpox Countermeasures Injury Compensation Table on October 15, 2020. The comment period ends on December 14, 2020.

Indian Health Service (IHS)

Dr. Weiser reported that IHS has established a COVID Vaccine Task Force that is developing a system-wide plan for vaccine allocation and distribution for IHS Tribal & Urban Indian Health Centers that choose to receive their vaccine from IHS. The COVID Vaccine Task Force has a focus on distribution, prioritization, administration, communication, data management, and safety. Vaccine adverse event monitoring through the Vaccine Adverse Event Reporting System (VAERS) and active internal reporting systems based on current for COVID-19 treatments have been developed. The IHS appreciates the development of the new element in VAERS this year for the first time for reporting specifically to the IHS. The IHS Pharmacy and Therapeutics

Committee will be providing outreach to IHS Tribal & Urban Indian Health Centers to ensure that they are familiar with reporting systems and understand the importance of close safety monitoring. While data published in the *MMWR* in August described at least a 3-fold higher incidence of COVID-19 for AI/AN compared to non-Hispanic Whites, data on underlying conditions, hospitalizations, and mortality are insufficient at this time to fully assess the severity of the COVID-19 pandemic in AI/AN communities. Despite this, IHS greatly appreciates the continued assistance provided by the CDC Tribal Support Unit. The IHS is monitoring ILI for the 2020-2021 influenza season and also has created a COVID-like illness (CLI) surveillance report. Influenza vaccination activities demonstrate higher uptake of influenza vaccine earlier in the season compared to previous years. As of October 10, 2020, 11.6% have received at least one dose of seasonal influenza vaccine in patients 6 months of age and older compared to 8.5% at the same time last year. During COVID-19, routine and catch-up AI/AN childhood immunization coverage has decreased. IHS has engaged in various initiatives to promote routine and catch-up immunizations during COVID-19. This has included hosting webinars and sharing CDC and HHS communication and education materials, provider resources, and toolkits. IHS appreciates CDC's ongoing support in these efforts as well.

National Institutes of Health (NIH)

Dr. Beigel provided a few NIH updates of interest to ACIP. There was a report in the *New England Journal of Medicine* (*NEJM*) about a month ago for the National Institute of Allergy and Infectious Diseases (NIAID) Phase I study of the Moderna COVID-19 vaccine, mRNA-1273. As a follow-on to a prior report, this report details the experience in older adults defined in this study as ≥56 years of age and shows that the vaccine is well-tolerated and generated a very robust immune response. That set the stage for including that population in the larger pivotal studies. NIAID continues to support the large pivotal Phase III studies through its COVID-19 Prevention Network (CoVPN). Moderna has completed full enrollment of the mRNA-1273 Phase III study. A fourth vaccine study has been started as well for the Janssen (J&J) product. This provides 4 large, currently ongoing pivotal studies to try to provide an effective vaccine for COVID-19. NIAID awarded a contract to begin development of a vaccine for enterovirus-D68 (EV-D68) that causes Acute Flaccid Myelitis (AFM).

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

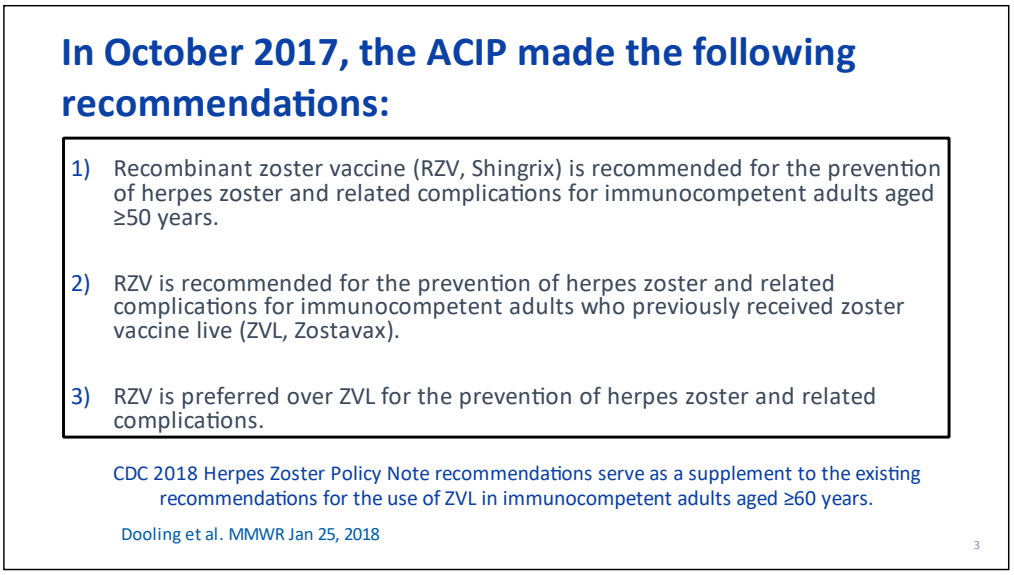
To help support the influenza vaccination efforts by CDC, OIPD developed an online toolkit that provides materials designed to encourage people to get their influenza vaccine by Halloween known as "Boo to the Flu." These materials are available at https://www.vaccines.gov/flu-toolkit. OIPD continues to work on updating the National Vaccine Plan (NVP) with support from the Interagency Vaccine Work Group whose members include the federal agencies represented on ACIP plus others. The NVP is scheduled to undergo an abbreviated public comment period in November, with a plan to release the revised plan by the end of 2020 or in early 2021. The National Vaccine Advisory Committee (NVAC) met on October 16, 2020 and reviewed a draft report containing responses to questions on COVID-19 vaccination hosted by Admiral Brett Giroir, the Assistant Secretary for Health (ASH). The committee will meet again in December to continue work on this. The NVAC website will be update once this report is finalized.

Zoster Vaccines

Introduction

Grace Lee, MD, MPH
ACIP Chair, Herpes Zoster Work Group
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine

Dr. Lee introduced the zoster vaccine session, reminding everyone that ACIP made the following recommendations in October 2017:



Since October 2017, there have been a few notable updates. Effectively July 1, 2020, ZOSTAVAX® no longer will be sold in the US. The remaining product will expire by November 18, 2020. In terms of RZV, 33 million doses of SHINGRIX have been distributed from launch through the second quarter of 2020. SHINGRIX inventory is currently available to meet the demand across all distribution channels. The European Medicines Agency (EMA) approved an expanded indication on August 25, 2020. SHINGRIX is now approved in the European Union (EU) for prevention of herpes zoster (HZ) and postherpetic neuralgia (PHN) in adults 50 years of age or older and adults 18 years of age or older at increased risk of HZ[1]. An sBLA was submitted to the FDA on September 24, 2020 to expand the indication of SHINGRIX to include the prevention of HZ in adults 18 years of age who are at increased risk of HZ due to immunodeficiency or immunosuppression caused by either disease or therapy following the EMA's approval [[1]https://www.ema.europa.eu/en/medicines/human/EPAR/shingrix#assessment-history-section].

Another important update to highlight in the context of the COVID-19 pandemic is that in adults 65 years of age and older in the US, the WG has been reviewing weekly uptake data for RZV between January 6, 2019 – July 20, 2019 that was steadily increasing over time. However, during the same time period between January 5, 2020 – July 18, 2020, there was steep decline in the number of doses administered after the national emergency was declared on March 13, 2020. This is concerning because there is a cohort of older adults who may not be protected against HZ and its complications. These numbers are now rising and the Herpes Zoster Work Group (HZWG) anticipates continuing to track how the pandemic is affecting healthcare utilization and vaccination rates in the US. She emphasized the hope that their immunization partners would continue to support vaccination efforts for all age groups during the pandemic. This is affecting children, adolescents, and adults throughout healthcare systems [CDC, Unpublished Data].

In June 2019, the ACIP HZWG presented a summary of RZV post-licensure safety monitoring activities to date in three systems, including the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and Medicare data. The HZWG's interpretation of the findings also were presented. The HZWG has met 14 times since that meeting to review the data on RZV post-licensure safety and uptake monitoring, review the RZV efficacy and immunogenicity data in both immunocompetent and immunocompromised adults, and to develop the PICO for use of RZV in immunocompromised adults in order to develop the Evidence to Recommendations (EtR) Framework needed to guide a recommendation.

The presentations during this session focused on an update of post-licensure safety monitoring of RZV in VAERS, a VSD update on post-licensure safety monitoring of RZV, data on the risk of Guillain-Barré syndrome (GBS) following HZ infection, and a summary and planned risk-benefit analysis regarding use of RZV in immunocompetent adults.

Update on Post-Licensure Safety Monitoring of RZV (SHINGRIX)

John R. Su, MD, PhD, MPH
Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

[*Note: Dr. Shimabukuro presented on behalf of Dr. Su, who was experiencing a power outage and connectivity issues due to severe storms overnight that left many areas of Georgia without power*].

Dr. Shimabukuro provided an update on post-licensure safety monitoring of RZV in the VAERS. As a reminder, VAERS is a passive surveillance system that is co-managed by the CDC and FDA. Anyone wishing to file a report with VAERS can go to the website to complete an electronic form online. VAERS accepts all reports from all reporters and does not judge causality or clinical severity of the event. Instead, VAERS is an early-warning system that identifies potential vaccine safety concerns for study in more robust data systems. The strengths of the system are that it can rapidly detect safety signals and rare AEs. However, the primary limitations is that causality cannot be assessed from VAERS data alone. It is a signal detection or hypothesis-generation system that requires additional follow-up with more robust systems when signals are detected.

CDC performed a descriptive analysis of RZV reports from October 2017 through June 2018 that was published in the *MMWR* in 2019. Most reports (97%) were non-serious, which is consistent with what is observed with other vaccines administered in this age group. The most common AEs were systemic like fever, chills, and headache and also injection site reactions. That analysis has been updated with data through October 2020. Although there are more reports, there are no appreciable changes proportion-wise in the safety profile. The breakdown of non-serious events remained at about 97%, which is consistent with the initial data. Over 90% of RZV doses are given alone without other concomitant vaccines. This table provides a more specific breakdown of the AEs as coded by the Medical Dictionary for Regulatory Activities (MedDRA), demonstrating that they look very similar to the initial data:

Signs and symptoms (MedDRA Preferred Terms)*	**38,902 total reports n (%)**
Pyrexia (fever)	9,294 (23.9)
Chills	7,965 (20.5)
Pain	7,820 (20.1)
Headache	7,444 (19.1)
Injection site pain	7,359 (18.9)
Fatigue	6,362 (16.4)
Pain in extremity	6,165 (15.8)
Injection site erythema	5,609 (14.4)
Myalgia	4,424 (11.4)
Nausea	4,223 (10.9)

*Not mutually exclusive; a report may contain more than one MedDRA Preferred Term

There was a signal in the VSD Rapid Cycle Analysis (RCA) fairly early on for GBS, as well as a finding of an association in the CMS data. During the period from October 2017–April 2019, there were 46 reports of GBS. Of these, 31 met the Brighton Level 1–3 diagnostic certainty (N=24) or were physician-diagnosed (N=7). Among them, 29 (94%) developed symptoms within 42 days of vaccination. During the analysis period from May 2019–October 2020, there were 44 reports of GBS of which 27 met Brighton Level 1–3 diagnostic certainty (N=16) or were physician diagnosed (N=11). Among these, 25 (93%) developed symptoms within 42 days of vaccination—the risk window used for monitoring. Proportionality reporting ratios (PRR) and Empirical Bayesian (EB) data mining identified no disproportional reporting of AEs after SHINGRIX compared to other vaccines. There was one data mining finding, which was, “Product administered to patient of inappropriate age.” This is a medication error, not an AE health event following immunization.

In summary, the RZV post-licensure safety monitoring findings in VAERS as of October 2020 are generally consistent with the safety profile observed in pre-licensure clinical trials. Most reported AEs were systemic or at the injection site. SAEs were rare at 2.6% of reports, which is similar to other vaccines administered to same age groups. The number and composition of reported GBS events are comparable to the last update. There have been no disproportional reporting findings of any AEs by PRR or EB data mining other than the medication error of product being administered in inappropriate age.

VSD Update on Post-Licensure Safety Monitoring of RZV (SHINGRIX)

Jennifer Clark Nelson, PhD
Director of Biostatistics & Senior Investigator
Kaiser Permanente Washington Health Research Institute

Dr. Nelson indicated that this work was led by their KPW team in collaboration with CDC colleagues at other VSD sites. As a reminder, the VSD is a public health and research collaboration that was established in 1990 between CDC and 8 participating integrated healthcare organizations in the US. It captures and curates medical care and demographic data currently on over 12.1 million persons per year or about 3.7% of the US population. The VSD captures and links electronically available data elements and conducts manual review of medical charts since these data are not collected for research purposes. The key domains include immunizations, potential AEs primarily using ICD-9 or ICD-10 codes that occur in outpatient emergency department (ED) or inpatient settings.

The results Dr. Nelson shared during this session were obtained using VSD's RCA targeted surveillance methodology that uses data like these from across the VSD. RCA was established in 2006 for near real-time vaccine safety monitoring. Like a traditional epidemiologic study, primary vaccine exposure and comparator populations, about 5 to 10 AE outcome targets of interest, and potential factors that may confound the relationship between exposure and outcome are pre-specified. Unlike a traditional epidemiologic study, RCA involves routine and cumulative updating of study data (e.g., monthly) and repeated interim analyses over time to compare risks. Statistically significant findings are deemed to be preliminary "signals" that are fully investigated with numerous follow-up activities, including chart validation to confirm true incident cases.

In terms of the design details for the RZV surveillance activity, the aim was to sequentially monitor RZV safety among adults ≥50 years during the initial uptake surveillance period from January 2018 – December 2019. The primary analysis involved comparing the RZV recipients with historical ZOSTAVAX® in the prior 2 o 5 years. The secondary analysis involved age-comparable concurrent comparators of those who had either a well visit or received another vaccine like pneumonia or Tdap during the RZV uptake period. A number of baseline covariates were measured (e.g., dose, concomitant vaccines, prior receipt of ZVL, health care utilization measures, and chronic medical conditions). In terms of the sequential testing plan, the interim analysis involved conducting the first analysis after 6 months of uptake in June 2018 and then conducting 18 more monthly analyses subsequently.

Two sets of pre-specific health outcomes of interest (HOIs) were designated. For formal sequential analyses, the following 10 high priority outcomes were identified that occurred incidentally at 1 to 42 days post-vaccination:

- ❑ Acute myocardial infarction (MI), stroke
- ❑ Convulsion, polymyalgia rheumatica, supraventricular tachycardia, Bell's palsy
- ❑ Anaphylaxis (days 0-1), giant cell arteritis, optic ischemic neuropathy, GBS

Exploratory analyses were performed for other post-vaccination outcomes, including the following:

- ❑ 1-42 days: gout, pneumonia, non-specific adverse effects, stroke subtypes, pericarditis, myocarditis, and eye-related outcomes (e.g., keratitis)
- ❑ 1-7 days: systemic reactions, local reactions, urgent care or ED visit

At the time of the final monthly analysis, almost 650,000 doses had been observed. There was steady uptake during the approximately 2-year surveillance period. Here are the primary sequential results for the 10 primary outcomes:

Sequential analysis results for RZV

N = 647,833	Observed Events	Expected Events	Observed rate/100K	RR	Preliminary signal[1]?
Stroke	287	376.2	44.3	0.76	No
Acute MI	320	379.8	49.4	0.84	No
Polymyalgia rheumatica	134	152.7	20.7	0.88	No
Supraventricular tachycardia	151	125.5	23.3	1.20	No
Convulsion Assoc. terms	112	123.6	17.3	0.91	No
Bell's Palsy	86	95.72	13.3	0.90	Yes[2]
Anaphylaxis	20	15.15	3.1	1.32	No
Giant Cell Arteritis	35	49.20	5.4	0.71	No
Optic Ischemic Neuropathy	37	52.61	5.7	0.70	No
GBS	6	4.83	0.9	1.24	Yes[3]

1. Statistical significance is based on an adjusted sequential likelihood ratio test of H_0: RR=1 vs H_A: RR>1
2. Signaled preliminarily at Analysis #5 (36 events vs 24 expected; RR=1.51, adj p=0.03) but effect attenuate
3. Signaled preliminarily at Analysis #2 (3 vs 0.6 expected; RR=5.25, adj p=0.02)

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For most outcomes, no preliminary signal was observed and the estimated relative risk was <1. Two preliminary signals were detected, one of which was for Bell's Palsy at the 5th analysis when there were 36 observed events as compared to 24 that were expected for an estimated relative risk of 1.5. This effect has attenuated over time with twice as much data and the relative risk is 0.90. A preliminary signal also was observed early on for GBS. This was at the second look during which 3 events were observed in the SHINGRIX group compared to <1 event expected based on historical data, with a relative risk at that time of >5. That effect also has attenuated considerably to the current estimated relative risk of 1.24. This is based on only about 6 presumptive AEs, so there is considerable uncertainty in this estimate.

Considerable further follow-up was done on the preliminary GBS signal found when using the ICD-10 coded definition, including a chart review to determine the true GBS status for these 6 presumptive ZVL cases. Among those, 3 were ruled out as they had symptoms prior to vaccination and 3 were confirmed—2 as Brighton Level 2 and 1 as Brighton Level 3. Chart review also was conducted among 5 presumptive historical cases. Of these, 2 cases were ruled out, 1 case was unable to be validated as chart data were missing, and 2 confirmed as Brighton Level 2. Based on chart validated outcomes, the best estimates in VSD are that relative risk is 1.55 (95% CI: 0.17, 18.60) assuming that 2 ZVL cases are confirmed or 1.03 (95% CI: 0.14, 7.73) if all 3 cases are assumed to be confirmed.

In summary, after receipt of about 650,000 doses of RZV were received in the VSD between January 2018 – December 2019, a preliminary signal was observed for Bell's Palsy (RR=1.51), but this effect did not persist as more doses accrued (RR = 0.90). A preliminary signal also was observed for GBS (RR=5.25) based on ICD-9/10 codes, and this effect also waned over time (RR=1.24). Chart review was conducted to confirm true GBS case status. In the final chart-confirmed analysis, VSD does not have sufficient evidence to determine whether there is an increased risk of GBS. The relative risk that can be estimated based on these data is 1.55 (95% CI: 0.17, 18.60), but the confidence intervals are very wide and crossed 1. Overall, there is not sustained evidence of increased risk among RZV recipients for any of the pre-specified outcomes being followed. Considerable subgroup and secondary analyses have been performed that provide further reassurance of these primary results.

Discussion Points

Dr. Atmar requested a reminder about how the expected number is determined for the comparator, and if the GBS might be accounted for by some other infection that was circulating in the community during the period of surveillance. That is, is the control group a contemporaneous group that would take into account environmental and other issues in the communities at the time?

Dr. Nelson indicated that these are historical comparators who received ZVL in the 5 years prior to the uptake period for SHINGRIX, so the primary analyses are based on numbers of events observed in that population that are then adjusted for age, gender, site, and cardiovascular outcomes to equalize between groups. These results do not fully adjust for all of the confounders. Those analyses are currently in progress using end-of-study cumulative data. Additional analyses that use a group other than the historical group. This is a historical comparative group, so any other changes over time during the prior to SHINGRIX uptake compared to during SHINGRIX uptake cannot be untangled. Differences between the vaccine groups could be due to other things that changed during those two periods of time, which is why contemporaneous control groups are being used in the end-of-study analysis, such as people who received well visits during the SHINGRIX period and also had an influenza vaccine in the prior year or received other vaccinations during the SHINGRIX period. Several analyses have been performed to manage different biases that exist depending upon the type of observational study designs used.

Risk of Guillain-Barré Syndrome Following Herpes Zoster

LCDR Tara Anderson, DVM, MPH, PhD
CDC Lead, Herpes Zoster Work Group
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Anderson presented a CDC-led analysis of the work on GBS following HZ. GBS is a rare immune-mediated disease of the peripheral nerves. In the US, the estimated annual incidence across all ages 1 to 2 cases per 100,000 persons. Risk factors for GBS include increasing age, male gender, immunocompromised status, previous viral and bacterial infections, and recent vaccinations (e.g., some influenza and rabies vaccines). Regarding previous infections, the strongest evidence in the literature is for the viral infections cytomegalovirus (CMV), Epstein–Barr Virus (EBV), hepatitis E, and Zika virus. The strongest evidence in the literature for bacterial infections is *Campylobacter jejuni* and *Mycoplasma pneumoniae*. As the HZWG discussed RZV post-licensure safety monitoring results, it was noted that in some instances

both disease and vaccination have been associated with GBS as with influenza virus infection and some influenza vaccinations. Therefore, the WG agreed that it would be important to further explore the risk of GBS following HZ.

A possible temporal association between HZ and GBS has been noted in a small number of case reports in the literature. One previous epidemiologic study by Kang, Sheu, and Lin in 2010 reported an increased risk of GBS following recent HZ. In this population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD), the investigators found that 0.03% of patients developed GBS within 2 months following HZ and that the adjusted hazard of GBS during follow-up period was 18.37 (95% CI, 10.22–33.01) times greater for patients with HZ than those without HZ. To the WG's knowledge, there are no published epidemiologic studies in other settings or using other methods.

Therefore, the WG conducted a case series study that was designed to strengthen the epidemiologic understanding of the risk of GBS following HZ and to help clarify the benefits versus the potential risks of vaccination. The primary objective of the study was to evaluate the risk of GBS following HZ using a self-controlled case series (SCCS) analysis of healthcare claims data from 2 large national data sources. The secondary objective was to describe the characteristics of these GBS cases in terms of demographics and outcome severity (e.g., duration of GBS hospitalization, ICU admission).

To provide some brief background, the SCCS methodology was developed in 1995 for use in vaccine safety studies and has since been broadly applied in epidemiology. This approach is used to examine the temporal association between a transient exposure (e.g., HZ) and a subsequent event (e.g., GBS). The precise timing of the exposure and event is important. Only individuals with both the exposure and the event of interest are included in the analysis. Each case serves as its own control; therefore, confounding by time-invariant factors is eliminated. The SCCS method estimates the relative risk of rates in the risk window compared to rates in the control window.

Two data sources were used for this study. The first is the IBM MarketScan® Commercial database that includes individual-level, de-identified healthcare claims for persons covered by employer-sponsored insurance. The MarketScan® Commercial data are a convenience sample drawn from IBM Watson Health's clients, which include approximately 30 to 50 million persons enrolled annually since 2006. The second data source was the CMS Medicare database that include individual-level, de-identified healthcare claims information for Medicare beneficiaries. The CMS Medicare data include a 100% sample of all fee-for-service (FFS) clinical claims data from Medicare for approximately 50 to 60 million Medicare enrollees annually. Approximately one-third of Medicare beneficiaries are covered under Medicare Parts A, B, and D FFS.

The study populations for the analysis included: 1) MarketScan® Commercial Claims and Encounters (CCAE) data from 2010–2018 for persons 18–64 years of age with private health insurance with drug data supplied for those who enrolled in MarketScan® 180 days before through 365 days after the HZ index date; and 2) CMS Medicare data from 2014–2018 for persons ≥65 years of age with Medicare insurance with Parts A, B, and D enrolled in Medicare 180 days before through 365 days after the HZ index date. Of note, no drug data were available prior to 2014. In addition, beneficiaries enrolled in Medicare Part C or Medicare Advantage managed care plans since drug claims data were not available for these populations.

In terms of study exposure definitions, HZ cases were defined as persons with an ICD-9 or ICD-10 outpatient claim with a primary or secondary diagnostic code for HZ. In order to capture incident HZ cases, persons were excluded for whom the first HZ code was a code for PHN. Persons with subsequent PHN codes were retained. Persons also were excluded with claim for administration of any zoster vaccine of either ZOSTAVAX or SHINGRIX within one day of the HZ claim, given that the HZ diagnostic code may more likely represent instances of miscoding. The HZ index date was defined as date of first HZ claim during the study period.

For GBS, cases were defined as persons with an ICD-9 or ICD-10 inpatient claim for GBS as the principle diagnostic code. To increase the specificity of the GBS diagnostic code, this was required to be paired with a procedural code for lumbar puncture, electromyography, or nerve conduction study for patients. These procedures are typically part of the diagnostic procedures for patients with GBS. Persons with GBS in the 180 day window prior to HZ were excluded. Persons also were excluded persons who had select previous infections and SHINGRIX during the 42-day period prior to GBS. These infections included the previously noted viral infections (e.g., CMV, EBV, influenza, hepatitis E, Zika) and bacterial infections (e.g., *Campylobacter jejuni, Mycoplasma pneumoniae*) that currently have the strongest association with GBS.

Several negative controls also were evaluated to validate the methods. Conditions were selected that were similar to GBS (i.e., acute, frequently result in hospitalization, low rate of reoccurrence) that were not expected to increase after HZ. These negative controls included appendicitis, nephrolithiasis, cholecystitis, and fractures of the upper limb. These were defined based on ICD-9 and ICD-10 codes. Persons were excluded with claims for these conditions in the 180 day window prior to HZ.

As previously noted, SCCS design was selected in which only cases are included in the analysis and each case serves as its own control. In this analysis, the rate of GBS or negative controls were compared in the risk window as compared to the rate in the control window. The risk window for this study was the 1 to 42 day window after the HZ index data, which is comparable to the period typically used in vaccine safety studies. Two control windows were selected. The primary control window was the 100 to 365 days from the HZ index date. The secondary control window was the 43 to 99 days after the HZ index date. Conditional Poisson regression was used to compare rates in the risk window versus the 2 control windows.

In terms of the study results, a total of 489,516 persons with HZ were identified who were ages 18 to 64 years from the 2010-2018 MarketScan® Commercial among whom 11 developed GBS during the 1 to 365 days following HZ. A total of 650,229 persons with HZ were identified who were 65 years of age and older from the 2014-2018 CMS Medicare data among whom 41 developed GBS during the 1 to 365 days following HZ. For those 18 to 64 years of age, there was a slightly higher percentage of cases aged 50 to 64 years. For those 65 years and older, the highest percentage of cases was in the 70 to 79 year age range. Among those 18 to 64 years of age, 82% of GBS cases were female. For those 65 years of age and older, 54% of GBS cases were female. Regarding the interval between HZ and GBS, a higher proportion of GBS cases among those 18 to 64 years of age occurred within the first 42 days after HZ compared to the primary control window. For those 65 years of age and older, a higher proportion of GBS cases was observed in the risk window and secondary window compared to the later primary control window. Regarding duration of GBS hospitalizations and ICU admissions, evidence was identified of more severe GBS among those 65 years of age and older with a median duration of hospitalization of 9 days and 51% admitted to the ICU.

For the SCCS analysis, the rate ratio of GBS was increased during the 42 day risk window following HZ as compared to the primary control window for both age groups, with a rate ratio of 6.3 (1.8–21.9) for those 18 to 64 years of age and a rate ratio of 4.1 (1.9–8.7) for those 65 years of age and older. For both age groups, the rate ratios during the 42 day risk window following HZ compared to the secondary control windows were not statistically significant based on the confidence intervals. For those 18 to 64 years of age, the rate ratios of the negative controls were not increased during the 42 day risk window as compared to either control window. These values ranged from 0.9 (0.7–1.3) to 1.2 (0.8–1.7) in the primary control window and 1 (0.9–1.1) to 1.3 (0.8–2.0) in the secondary window. Given the confidence intervals, these values were not statistically significant. For those 65 years of age and older, the rate ratios of the negative controls during the 42 day risk window as compared to the control windows ranged from 1 (0.7–1.5) to 1.4 (1.0–2.0) in the primary control window and 0.9 (0.6–1.4) to 1.5 (1.0–2.2) in the secondary control window. Although some confidence intervals indicated statistical significance, all negative control values were much lower than the rate ration of 4.1 observed for GBS in this age group during the 42 day risk window as compared to the primary control window.

There are several strengths and limitations for this study. Regarding strengths, large national datasets were used that include medical and pharmacy claims. The SCCS design inherently controls for potential confounders (e.g., gender, underlying medical conditions) and each case serves as its own control. The study inclusion criteria strengthened HZ and GBS case identification, while the exclusion criteria account for potential confounders (e.g., antecedent infections). Regarding limitations, a small numbers of GBS cases were identified in both data sources. MarketScan® is a convenience sample and is not nationally representative. There is a potential for miscoding or misclassification bias in claims data. Finally, it was not possible to validate GBS, HZ, or other diagnoses using medical record review.

In conclusion, this SCCS analysis identified an increased risk of GBS in the 42-day window following HZ compared to the primary control window of 100 to 365 days. This increased risk was identified across adult age groups and in two different large administrative data sources. The negative control results strengthened the findings. The negative control rate ratios clustered around the null effect of 1, with a range of 0.9–1.4 for the primary control window. These values were lower than rate ratios for GBS identified in both data sources. Finally, evidence was identified of more severe GBS in terms of longer duration of hospitalizations and a higher percentage admitted to the ICU among those ≥65 years.

Summary & Planned Risk-Benefit Analysis For Use of RZV in Immunocompetent Adults

LCDR Tara Anderson, DVM, MPH, PhD
CDC Lead, Herpes Zoster Work Group
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Anderson provided a summary of the session, ACIP HZWG discussions, and next steps that include a planned risk-benefit analysis for the use of RZV in immunocompetent adults. On behalf of the HZWG, she expressed gratitude to the Immunization Safety Office (ISO), the VAD, and the FDA for their contributions toward monitoring RZV safety. The WG also thanked the many CDC staff and other contributors who provided valuable information and insight.

Two critical safety monitoring updates from VAERS and VSD were shared during this session. As discussed by Drs. Su and Shimabukuro regarding VAERS, SAEs have rarely been reported. RZV post-licensure safety monitoring findings in VAERS are generally consistent with the safety profile observed in pre-licensure clinical trials. As discussed by Dr. Nelson regarding the VSD RCA conducted based on data from January 2018 – December 2019, results from the final chart-confirmed analysis indicate that VSD has insufficient evidence to determine whether there is an increased risk of GBS.

As presented during the June 2019 ACIP meeting, FDA has conducted assessments of the risk of GBS following RZV in Medicare data in collaboration with CDC and CMS. The preliminary results of the cohort analysis presented during that meeting compared the post-vaccination GBS rate between persons ≥65 years of age who received RZV between October 2018 and December 2019 and historical controls who received ZVL between October 2012 and September 2017 indicated an elevated adjusted rate ratio of 2.34 (95% CI 1.01, 5.41). On the advice of the HZWG, FDA conducted additional analyses using SCCS methods. The FDA has additional results available from the claims-based SCCS analysis and the medical record review SCCS analysis. These results are currently under review t FDA, and will be shared during a future ACIP meeting.

As discussed during Dr. Anderson's previous presentation, a possible temporal association between HZ and GBS has been noted in a small number of case reports and one previous epidemiologic study (Kang, Sheu, and Lin, 2010) reported an increased risk of GBS following recent HZ. In a CDC-led self-controlled case series analysis, an increased risk of GBS was identified 1–42 days following HZ compared to the primary control window of 100-365 days across adult age groups and in two different administrative data sources.

To summarize the HZWG discussions since the June 2019 ACIP meeting, the HZWG is currently reviewing evidence regarding use of RZV in immunocompromised adults. The HZWG is concurrently reviewing and discussing findings regarding the possible risk of GBS following both disease and vaccination, and agrees that continued safety monitoring of RZV in VAERS and VSD is warranted. In addition, a dynamic risk-benefit assessment that incorporates new data on the risk of GBS associated with disease and vaccination will inform recommendations on the use of RZV in immunocompetent and immunocompromised adults. This planned risk-benefit analysis will evaluate the benefits of averted HZ cases and complications versus the risk of AEs. SMEs and the HZWG will collaborate on model parameters and scenarios and the outcomes per 1,000,000 vaccinated individuals to be estimated would include episodes of HZ, episodes of postherpetic neuralgia and other HZ complications (e.g., GBS), injection site reactions, systemic reactions, and rare adverse events (e.g., GBS).

Regarding next steps, the HZWG is committed to providing updates to the ACIP at the earliest opportunity. Future ACIP meeting presentations will address the FDA's assessments of the risk of GBS following RZV in Medicare data, the results of the risk-benefit analysis results regarding use of RZV in immunocompetent adults, and RZV use in immunocompromised adults. Dr. Anderson posted the following questions for ACIP discussion and input:

- ❑ Does ACIP have any other suggested follow-up regarding RZV safety monitoring?
- ❑ Does ACIP have any feedback on planned risk-benefit analysis for use of RZV in immunocompetent adults, particularly any other outcomes of interest?

Discussion Points

Dr. Romero observed that the presentation and extensiveness of these data serves to exemplify the degree and type of collections systems available to monitor vaccine safety in this country. This bodes well for the future with regard to monitoring newer vaccines that will be coming out.

Dr. Talbot emphasized the amazing amount of work that had been shown during this session. She requested clarification about whether they were saying that there is a signal following vaccination, but they are not yet clear if it is a random occurrence or a true event.

Dr. Anderson indicated that based on the results to date, the safety profile is reassuring. However, follow-up is continuing given the previous results from the FDA analysis showing an elevated adjusted risk in the Medicare data and given the study results she just presented regarding the risk of GBS that also has been noted for an association with GBS.

Regardless of GBS associated with HZ, Dr. Talbot noted that the numbers Dr. Anderson showed did not show risk after vaccination. They talk about GBS risk as being 1 in 1 million for influenza and she wondered whether Dr. Anderson could provide an idea of that number for the current shingles vaccine. She also asked what future studies are planned and what future evidence will be provided to ACIP, and said that she is slightly hesitant that this vaccine has a very powerful adjuvant.

Dr. Anderson said that she could not provide a number for the risk of GBS at this time. The results shared to data are related to the information she presented during this session based on the RZV versus the ZVL comparator groups, with an elevated adjusted ratio of 2.34. During a future meeting, the FDA intends to present the results of their SCCS analyses, which are under review at this time with FDA and they will share them as soon as possible.

Dr. Messonnier add that there are two studies that show a positive signal. However, the risk-benefit evaluation that would get to the additional risk of GBS compared to the risk of prevention of HZ has not been completed. The FDA is conducting a third study that is expected before February 2021.

Dr. Anderson confirmed that as Dr. Nelson shared earlier, the results of a VSD analysis initially indicated a signal for GBS. Over time, that signal has attenuated so now the results of that study do not have sufficient evidence to say that there is a signal in VSD. There has not been a signal in VAERS. In the results presented to date by the FDA from the original cohort analysis, there was an elevated risk in the RZV versus the ZVL comparator group. The results of the FDA SCCS analyses using Medicare data will be presented at another time, given that they are currently under review at the FDA. While awaiting the results of those analyses, the HZWG is discussing moving forward with the planned risk-benefit analysis in which new information related to the possible risk of GBS after vaccination and the risk of GBS after infection will be taken into consideration.

Dr. Messonnier said she thought Dr. Talbot was asking about the upper bound of potential increased risk. That is, GBS is 1 in 1 million for influenza. What is the absolute maximum risk and is there enough concern to act now as opposed to waiting for additional analyses?

Dr. Anderson said that at this point, there has not been sufficient evidence or information presented in order to be able to determine that.

Dr. Lee emphasized what Dr. Romero said, which is that they absolutely rely on the surveillance systems to detect signals. This signal in VSD and the surveillance from VAERS were presented previously. Based on follow-up, those signals have attenuated in those databases over time. The HZWG is waiting for the FDA's CMS analysis. That database has the greatest power to provide the information needed, in addition to making sure that these cases are validated. The way she would frame this is that in thinking about signals, a statistically signal was detected. After a statistical signal is identified, signal refinement and signal evaluation activities are undertaken. Those activities are underway in several systems. During this session, they heard that those signals are not identified in VAERS and have attenuated in VSD. The HZWG is looking forward to seeing the FDA's CMS data because they have a large proportion of older adults who are receiving these vaccines, which she thinks will be very helpful to ensuring that ACIP is making decisions based on the best possible data. Also very important was the analysis of GBS following disease. Dr. Lee said she has not intuitively understood the high rate of GBS following HZ infection. She appreciated it following campylobacter or other types of infections, but had not had GBS on her radar. The reason she thinks this is important is because it is different from the way they are used to thinking about vaccine safety, which is against the background of the general population. It is very important to remember that the benefit-risk analysis is around people who get the disease and people who are vaccinated. Having the rates of GBS following HZ infection is incredibly helpful in terms of understanding the benefit-risk balance in the population, particularly for this vaccine. The HZWG absolutely thinks that vaccine safety needs to undergo continued monitoring. They presented the results during this session of the vaccine safety evaluation and evaluations on disease because they think it is so important from a transparency perspective to present all of these data to ACIP. They anticipate that more data will be forthcoming, but wanted to propose the benefit-risk analysis because of the statistical signal that is continuing to undergo evaluation as well as the new information regarding the risk of GBS following HZ infection.

Dr. Bell echoed the importance of these safety monitoring systems for all new vaccines. In that context, it is important to remember that the evaluation of this signal is ongoing. This type of issue must be assessed and worked out over time, so they must keep looking at it as more people are vaccinated in order to address signals as they arise. Perhaps the signal for GBS will change over time, which is what they are looking for. Another potential benefit of doing a risk-benefit analysis is the sensitivity analysis that could be part of the process that might help with some of the questions regarding the upper bound, where the risk-benefit balance would shift with respect to an association between vaccination and GBS, and so forth. There is benefit to using this risk-benefit analysis partially as another way of exploring the meaning and the potential impact of these signals as they arise.

Dr. Hunter said he was very reassured by the data being presented, and reminded everyone that he is the person who voted against the preferred recommendation. He said that while he needed more data, he was almost to the point of being able to tell his patients that they would be at lower risk by getting the vaccine because it would protect against getting an HZ outbreak.

Ms. McNally asked when the HZWG estimates an update on the risk-benefit analysis and the FDA assessment.

Dr. Anderson indicated that they would be presenting these as soon as possible during an upcoming ACIP meeting, ideally in February 2021.

Dr. Cohn reassured everyone that when the FDA analyses are available for review by the HZWG, any concerning data that would necessitate the need to meet earlier in order for the ACIP to review the data before February 2021, that absolutely could be done.

Tick-Borne Encephalitis Vaccine

Introduction

Katherine Poehling, MD, MPH
Chair, Pneumococcal Vaccines Work Group

Dr. Poehling introduced the Tick-Borne Encephalitis (TBE) Vaccine Work Group (WG) and session. The TBE Vaccine WG formed in September 2020 following notification that Pfizer plans to submit a Biologics License Application (BLA) to the Food and Drug Administration (FDA) for their TBE vaccine by the end of 2020. Several TBE vaccines are manufactured and licensed internationally, but none are produced or licensed in the United States (US) and there are no existing ACIP TBE vaccine recommendations. If Pfizer's TBE vaccine receives priority review designation, FDA's goal is to take action on an application within 6 months[1]. Licensure is possible by the third quarter of 2021 [https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review].

The purpose of the ACIP TBE Vaccine WG is to discuss use of TBE vaccine in US adults and children visiting or living in TBE-endemic areas and laboratory workers. The Terms of Reference for the TBE Vaccine WG are to: 1) review information on TBE, including its epidemiology, clinical presentation, diagnosis, treatment, and outcome; 2) review data on infection risk and burden for US civilian and military travelers and laboratory workers; 3) review data on vaccine safety, immunogenicity, and effectiveness; 4) provide evidence-based recommendation options for ACIP; 5) identify areas in need of further research for informing potential future vaccine recommendations; and 6) publish ACIP recommendations in the *Morbidity and Mortality Weekly Report* (*MMWR*).

Topic discussed during this session included the following:

- ❑ Background on TBE disease and vaccines
- ❑ Immunogenicity and safety of Pfizer's TBE vaccine
- ❑ Next steps for the TBE Vaccine WG

Background on TBE Disease and Vaccines

Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention
Fort Collins, Colorado

Dr. Hills presented background information on TBE disease and vaccines as an introduction for ACIP members. TBE virus is a flavivirus with three main subtypes: European, Siberian, and Far Eastern subtypes. TBE virus is primarily transmitted to humans through the bite of an infected

Ixodes species tick, mainly *Ixodes ricinus* or *Ixodes persulcatus*. Infections are usually acquired in wooded or surrounding areas during recreational (e.g., camping, hiking, fishing, cycling or foraging for mushrooms/berries/flowers) or by persons involved in outdoor occupations such as in the forestry service or in military training. TBE virus transmission also can occur occasionally through other means such as ingestion of unpasteurized dairy products from infected cattle, sheep, or goats; slaughtering of viremic animals; laboratory exposure; and rarely through blood transfusion, transplantation, or breastfeeding.

TBE virus is focally endemic in a geographical region spreading from Western and Northern Europe through to Eastern and Northern Asia, reflecting the distribution of the vector of ticks. In endemic areas, there are approximately 5,000 to 13,000 cases reported annually and the number of reported cases varies from year-to-year. Most cases occur from April through November, with a peak number of cases reported during early and late summer when ticks are most active. Most cases result from exposures occurring in areas under 2,500 feet. However, the geographic range of TBE virus appears to have expanded to new areas during the last 30 years, including altitudes up to and including 5,000 [Dobler et al, Wien Med Wochenschr 2012].

In terms of the clinical features of TBE, the incubation period is typically between 7 to 14 days but can range from 4 to 28 days. About 25% of persons with TBE virus infection develop clinical symptoms. The clinical presentations of disease can range from a non-specific febrile illness through to neurologic illness presentations (e.g., meningitis, encephalitis, or meningoencephalomyelitis). A monophasic or biphasic illness can occur. A monophasic illness is more typical for patients infected with the Far Eastern and Siberian subtypes of the virus. The biphasic illness is more typical with the European subtype and has a clinical course that consists of a first phase of non-specific febrile illness, followed by remission of symptoms, and then a second more severe phase with neurologic illness. There is no specific antiviral treatment for TBE and clinical management consists of supportive care.

The frequency of neurologic sequelae depends upon the viral subtype. Sequelae occur in up to 30% of patients with the European subtype and up to 80% of patients with the Far Eastern subtype. For the Siberian subtype, sequelae rates fall in the middle of these other rates. Case fatality rates similarly depend upon the viral subtype. The case fatality rate is about 1% to 2% with the European subtype, about 20% with the Far Eastern subtype, and somewhere in the middle of those rates with the Siberian subtype. The incidence and severity of disease are highest in older persons.

Overall, TBE cases in US persons are rare. Cases are reported occasionally among US civilian and military travelers. There are 2 recent cases series publications, including 5 cases reported among civilian travelers that were diagnosed at CDC in the 10 years from 2000-2009[1] and 8 cases reported among military service members or their family members stationed in Europe during the period 2006-2018, including 7 cases in 2017 and 2018[2] [[1]CDC. MMWR Morb Mortal Wkly Rep 2010; [2]Mancuso J et al. MSMR 2019].

TBE vaccine is of substantial interest to the Department of Defense (DoD) in relation to these cases among military persons stationed in parts of Europe. Dr. Hills indicated that she would not be discussing these cases in any more detail as the WG would be presenting a more thorough review and a discussion of traveler, military, and laboratory cases for ACIP members during the February 2021 meeting.

Four TBE vaccines are currently available internationally, including the 2 in Europe and 2 in Russia shown in the table, in addition to 1 vaccine that is available in China for which limited information is available in the public domain:

Trade Name	Manufacturer (Location)	Age Group
FSME-IMMUN, TicoVac	Pfizer (Austria)	≥1 year
Encepur	Bavarian Nordic (Denmark)	≥1 year
EnceVir	Microgen (Russia)	≥3 years
TBE-Moscow	Chumakov Institute (Russia)	≥3 years

The Pfizer TBE vaccine is marketed in Europe as FSME-IMMUN® or TicoVac, which the ACIP TBE WG is considering at this time. Bavarian Nordic is considering licensure of their TBE vaccine, Encepur, in the US. However, there is not a fixed timeline for submission of a BLA at this point. The European vaccines are licensed in children from 1 year of age and the Russian vaccines from 3 years of age. Pfizer's TBE vaccine is an inactivated vaccine that is available in pediatric and adult formulations. The original formulation of this vaccine was first used in Europe in the late 1970s. The current vaccine formulation has been used since 2001 or approximately 20 years. This vaccine is currently licensed in more than 30 countries in Europe.

In summary, TBE is a focally endemic disease with the geographic risk area extending from Western and Northern Europe through to Northern and Eastern Asia. The virus is transmitted to persons primarily through tick bites when visiting or working in wooded areas in endemic regions, although other modes of transmission can occur. TBE virus can cause clinical disease that can be severe and there can be high case fatality and sequelae rates with some of the TBE virus subtypes. Cases among travelers are rare. At this stage, one TBE vaccine among several available internationally will be submitted for licensure in the US, which is the Pfizer vaccine. The vaccine is an inactivated vaccine that has both adult and pediatric formulations, which has been used in its current formulation for roughly 20 years in Europe. A TBE vaccine has never previously been licensed in the US. As a result, there are no existing TBE vaccine ACIP recommendations.

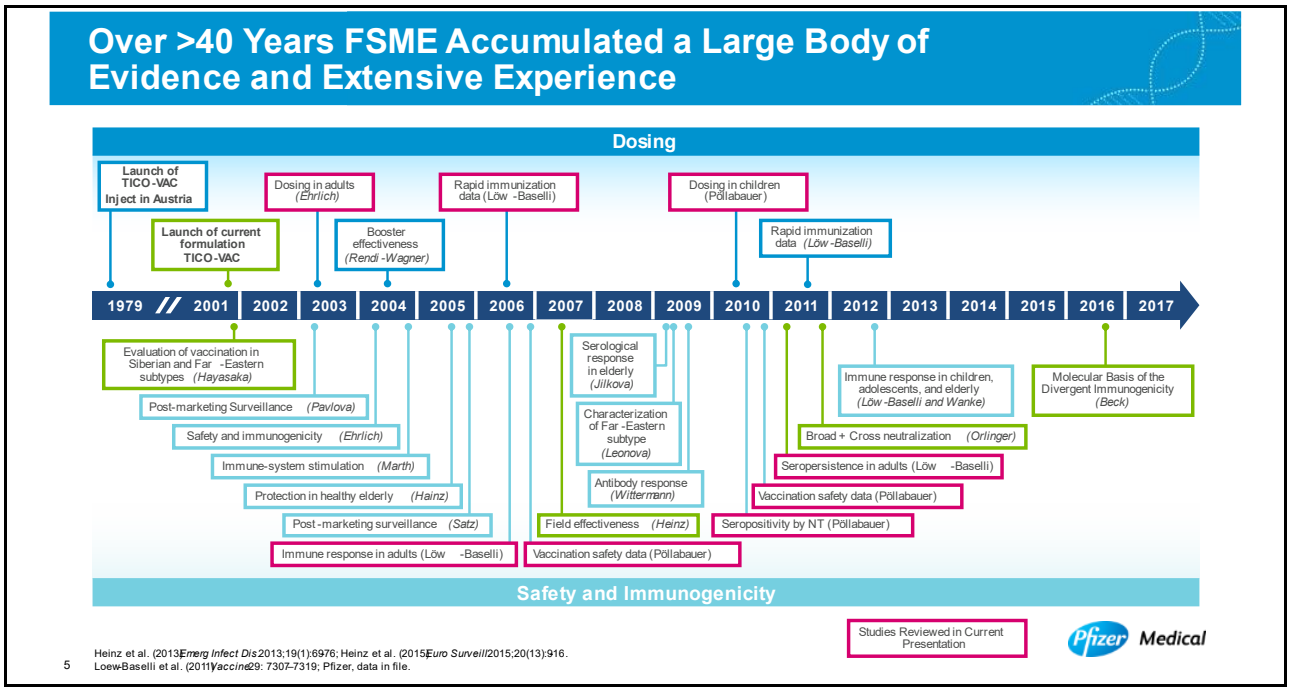
Immunogenicity and Safety of Pfizer's TBE Vaccine

Heinz-Josef Schmitt, MD, PhD
Global Viral Vaccines Medical and Scientific Affairs Lead, Pfizer

Dr. Schmitt presented data on the immunogenicity and safety of Pfizer's TBE vaccine. FSME-IMMUN® is an inactivated whole-virus vaccine that was developed and then first licensed in Austria in 1976. This is a vaccine that does not seek a new license to begin with and has a long history. Lifecycle management addressing local needs and new situations is not as clear-cut from the literature with a new license application, but it is somewhat complicated in some respects. The vaccine is basically a suspension of purified TBEV-EU subtype strain that was isolated in Austria in the small town of Neudörfl. It is propagated in chicken embryo fibroblast cells derived from pathogen-free eggs. It is highly purified by the use of continuous-flow zonal ultracentrifugation, free of thiomersal, and uses human serum albumin (HSA) as a stabilizer. Approved tradenames outside of the US are:

- ❑ FSME-IMMUN® / Tico Vac with adult and pediatric formulations with 2.4µg or 0.5mL of TBEV-EU for use as of 16years of age
- ❑ FSME-IMMUN® Junior / Tico Vac Junior with 0.25mL with 1.2µg of TBEV-EU for use in children and adolescents 1–15 years of age
- ❑ US tradename to be determined

In terms of historical development, the vaccine was first approved in Austria as a vaccination for high-risk groups. In 1981, TBE mass vaccination was introduced in Austria. In 1999, thiomersal and its stabilizer was removed in fulfilment of European Pharmacopoeia (Ph. Eur.) requirements. In 2000, HSA was removed and use began of a production virus seed free of potential contaminating mouse brain protein, achieved by subjecting the master virus seed to 2 sequential passages in primary chick embryo cells. These changes to the manufacturing process and final formulation required a new marketing authorization to be obtained. The newly approved vaccine was called FSME-IMMUN®. HSA removal was associated with a substantial increase in the rate of high fever in infants and young children. In 2001, HSA was again added to the TBE vaccine, which was again named FSME-IMMUN® and licensed based on a new clinical development program. The incidence of adverse reactions (AEs) decreased to expected levels. FSME-IMMUN® Junior was launched in 2003. This graphic depicts the large body of evidence and extensive experience that has accumulated for over 40 years with FSME, which Dr. Schmitt further described for the boxes shown in pink:



The FSME-IMMUN® TBE vaccination schedule is highly complicated, which relates to the fact that there has never been an efficacy study. The only marker for protection is neutralizing titers or serology based on ELISA. Whenever the titer grouped to below a certain threshold, people were advised to give a booster dose. There are 2 doses for adults and children given 1 to 3 months apart. There also is a rapid schedule in which the vaccine doses are given 2 weeks apart, which is of particular of interest for travelers. The third dose is given 5 to 12 months later. Usually, the third dose would be called a “booster” dose. While there is good reason to think that this is a booster dose, the 3 doses have been called the “primary series” throughout the history and on the label. Following serology, the first booster (e.g., Dose 4) was given 3 years later.

Later boosters (doses >5) are given every 5 years. The titers dropped in those >60 years of age, so the booster is supposed to be given every 3 years after 60 years of age.

There is no known serological correlate of protection for TBE, even after 40 years. There are more than a dozen ELISAs and they use different test strains. Usually in all Pfizer studies, this was the seed strain. It is very important to keep in mind that use of different strains may produce different results. One other strain is used in the ELISA that is the seed strain of the competitor vaccine, which is a mutated K23 antigen. For the purpose of the Pfizer vaccine and Immunozym FSME-IgG ELISA, about 126 VIE U/ml are considered positive, 63−126 VIE U/ml are considered borderline, and <63 VIE U/ml are considered negative. For the neutralization assay (NT), Pfizer used the Adner method described in 2001 for which a neutralization value of ≥ 1:10 is considered positive [Adner N et al (2001) Pharmacokinetics of human tick-borne encephalitis virus antibody levels after injection with human tick-borne encephalitis immunoglobulin, solvent/detergent treated, FSME-BULIN S/D in healthy volunteers. [*Scand J Infect Dis* 33(11):843-7].

The studies Dr. Schmitt described used the vaccination schedule described earlier of the primary series of 3 doses, with the first booster dose 3 years after the third dose and the second booster at 5 years, except in those who are over 60 years of age for whom it is 3 years. For the adult schedule, there is a blood draw at baseline, 21-35 days after Dose 2, and 21-28 days after Dose 3. In the dose finding study, 0.6µg, 1.2µg, and 2.4µg of the Neudörfl strain were used. Very nice seroresponse rates were achieved with 1.2µg and 2.4µg. These were further assessed with regard to titers and reactogenicity. Titers differed for the 0.6µg antigen dose with lower titers and higher titers for the 1.2µg antigen dose. While the seropositivity rates between 1.2µg and 2.4µg are quite similar, the titers are much higher with the higher antigen dose. At the time, an efficacy study was never done and never planned, so the goal is to go for the higher titers if reactogenicity allows. There was not much of a difference in terms of the reactogenicity studies. Systemic reactions were mainly mild and their frequency decreased with later doses. The occurrence of local reactions was not dose-dependent and their frequency was lowest after Dose 2. Fever >38°C was observed at a very low rate. Only 1 case of fever was reported in the 2.4µg dose group. No unexpected AEs or vaccine-related SAEs were observed during the study. This is why the 2.4µg dose was chosen in the end for the adult preparation.

In terms of the primary series (Doses 1, 2, 3) it was important to know when to give Dose 3. A study was conducted in which blood was drawn after Dose 3, after 2 years, after 3 years, and then the first booster dose is given. Blood is drawn before and after Dose 4. One month after primary immunization, seropositivity rates were close to 100% using ELISA and 100% using NT. By 2 and 3 years after primary immunization, seropositivity rates had decreased from 99.1% to 87%. After the first booster, seropositivity rates increased to 100% regardless of the test method. Between 1 month and 2 years after primary immunization, GMCs/GMTs decreased about 4-fold. After the booster vaccination, GMCs/GMTs increased above 1-month levels. The geometric mean of the fold increase between pre-booster and the post-booster antibody levels were 11.2 using ELISA and 7.5 using NT. No SAEs were reported during this study.

Turning to the study of the rapid schedule that is of particular interest to Americans wishing to visit Europe or Asia, there is a pre-vaccination baseline blood draw and a second dose at Day 10-13. There are then repeated blood draws post-Dose 2 at Days 3, 7, 14, 21, and 42. Similar developments were seen in terms of GMCs and GMTs, with peaks reached 21 days after Dose 2. Seropositivity was 21% at 3 days, 28% at 7 days, 92% at 14 days, 96% at 21 days, and 98% at 42 days by ELISA. Seropositivity was 89% at 3 days, 96% at 7 days, 98% at 14 days, 100% at 21 days, and 100% at 42 days by NT. In terms of reactogenicity, most systemic and all local

reactions were mild. The most frequently reported systemic reactions were myalgia, headache, and fatigue. Injections-site pain and tenderness were by far the most frequent local reactions. No SAE experiences were reported.

The schedule and dose finding were the same for the pediatric studies. This is somewhat complicated based on the publication. The basic principle is that there are 2 dose-finding studies (N = 1278) and 1 open label safety study (N = 2417) with the pediatric formulation in children and adolescents 1–15 years of age. The conclusions were that the FSME-IMMUN® pediatric vaccine formulation is safe and highly immunogenic for children <12 years of age and also for adolescents <16 years of age. Both the 0.6µg and 1.2µg doses were highly immunogenic in both age groups. The 0.3µg dose induced slightly lower seroconversion rates, with the lower level of the 95% CI after dose 2 in the older age group below 85%, the pre-defined lower limit for the optimal vaccine dose. Based on the results of these dose-finding studies, 1.2µg was considered the preferred dose for children 1–15 years of age. In both age groups, a clear dose-dependent immunogenic response was seen for GMCs after Doses 2 and 3.

FSME-IMMUN® was found to be safe in children 1–15 years of age at all 3 doses. Fever and other adverse reactions were not dose-dependent. Fever was more frequent in the younger age group, with most cases of fever mild in severity. Total systemic reactions, excluding fever, occurred at a relatively low frequency of <13% after Dose 1 and were comparable between the three dose groups. Local and systemic adverse reactions occurred at a much lower frequency after Doses 2 and 3. No serious adverse reactions were reported in either age group. In the open label safety study, fever rates after Dose 1 were low (9.7%) and decreased after doses 2 and 3 (2.4% and 2.4%, respectively). Fever was more frequent in the youngest age class, with most cases of fever being mild in severity. The most common systemic reaction, excluding fever, was headache.

From the open label study in more than 2000 children, the most common local reactions were injection-site pain and tenderness. The important message then and now is that no vaccine-related SAEs were observed during the studies. In terms of seropersistence in children and adolescents after the 3-dose primary immunization series, seropositivity rates were quite high and decreased over time from 99% to 86%. Titers by NT were 375 at 1 month and decreased to 47 at 58 months.

Based on almost 20 years of experience and over 47 million doses distributed of the new formulation since 2000, it is concluded that TICO-VAC is well-tolerated and there are no safety concerns at this point. The following table summarizes safety data from the most important studies for children and adults:

Safety: Vaccination Safety Data from Pivotal Clinical Studies

TICO-VAC 0.5ml		
Symptom	**n/N**	**(%)**
Local pain	392/2977	13.2%
Tenderness	890/2977	29.9%
Headache	171/2977	5.7%
Fever	23/2947	0.8%
Muscle pain	144/2977	4.8%
Nausea	59/2977	2.0%
Joint pain	38/2977	1.3%
Fatigue	186/2977	6.2%
Malaise	133/2977	4.5%
Lymphadenopathy	17/2977	0.6%

TICO-VAC 0.25ml Junior		
Symptom	**n/N**	**(%)**
Local pain	272/2417	11.3%
Tenderness	438/2417	18.1%
Headache	261/2417	10.8%
Fever	230/2374	9.7%
Muscle pain	85/2417	3.5%
Nausea	76/2417	3.1%
Loss of appetite	71/2417	2.9%
Changes in sleeping behaviour	66/2417	2.7%
Restlessness (only age 1–5 years)	53/584	9.1%
Fatigue (only age 6–15 years)	102/1833	5.6%
Malaise (only age 6–15 years)	76/1833	4.2%

Pfizer Medical

30 Source: Pöllabauer et al. *Vaccine* 28, 2010; Löwenbaselli et al. *Vaccine* 24, 2006.

There are 2 publications regarding long-term serology, 1 in adults and 1 in children. Blood was drawn in the Spring of every year. If the titer dropped below a pre-defined threshold, the respective trial subject received a booster dose to make sure that he/she was protected for the upcoming season. The seropersistence-rate through 10 years after the first booster (Dose 4) across all age groups measured by ELISA were consistent with the results as measured by NT.

A TBE antibody response by ELISA before and after the catch-up vaccination in a study by Schosser in 2014 showed that subjects who missed the second, third, or fourth dose who receive one more booster dose achieves the same amount of titers regardless of whether they had 3 or 4 doses previously. This is important for Americans traveling to Europe. This table illustrates that while booster doses in this study had not been given for up to more than 20 years, there were very high response rates in all age groups:

Catch-up Study: ELISA Responses

(Schosser, 2014 – In adults ≥16 years (N=1115) and children 6–15 years (N=135))

Adult Subjects with Putative Seroprotection (≥25 U/ml) After Study Vaccination by Each Irregular Interval Category (Sensitivity Analysis Irregular Interval Requirement)

Age Group	Time Interval from Last Vaccine to Catch-up Dose	n/N	%
≥16–<60 years	**5–9 years (1827-3651 days)**	**797/802**	**99.4**
	≥10 years (≥2652 days)	**405/409**	**99.0**
	10–12 years (3652-4747 days)	257/259	99.2
	13–15 years (4748-5843 days)	81/83	97.6
	16–18 years (5844-6939 days)	51/51	100.0
	19–20 years (6940-7670)	10/10	100.0
	≥21 years (≥7671 days)	6/6	100.0
≥60 years	**5–9 years (1827-3651 days)**	**245/252**	**97.2**
	≥10 years (≥2652 days)	**74/76**	**97.4**
	10–12 years (3652-4747 days)	43/44	97.7
	13–15 years (4748-5843 days)	15/15	100.0
	16–18 years (5844-6939 days)	10/11	90.9
	19–20 years (6940-7670)	4/4	100.0
	≥21 years (≥7671 days)	2/2	100.0

Pfizer Medical

36 Pfizer– data on file Schosser et al. (2014) *Vaccine* 32:237581.

In terms of the breadth of subtype coverage, a hybrid neutralization test is used to standardize the growth rates of the different viruses. In the end, what is in the label is that all 3 subtypes are covered by FSME-IMMUN®. There now are additional data to show that this is still true today.

In terms of vaccine effectiveness, vaccine uptake was very high in Austria from 1979-2019 at up to 88%, which resulted in a decrease in the number of TBE cases. There was no such effect in neighboring countries. From that followed vaccine effectiveness calculations. Irrespective of whether a regular schedule is given, effectiveness is about 90%. Based on data from a TBE outbreak due to dairy products in Germany in 2017, vaccine effectiveness was demonstrated to be 80% to 100% among those who ingested TBE virus.

To highlight some additional topics, two studies show that there is no association with multiple sclerosis (MS). In one study, 28 subjects with MS were vaccinated and there was no sign of clinical recurrence of the disease. While vaccine is not licensed to be given in pregnancy, there are 138 cases of pregnancy in the databases from the full 40 years. At this time, there is no signal that would raise any concerns. There are no data on simultaneous administration with other vaccines.

In summary, this is a 40-year old product and there is no efficacy study. The complexity of the study results from the fact that serology is followed, and the vaccine is well-tolerated.

Next Steps for the TBE Vaccine WG

Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention
Fort Collins, Colorado

Dr. Hills presented the current planned timeline for the TBE Vaccine WG's activities and presentations to ACIP. As mentioned earlier, they are working on the basis of possible licensure of the vaccine in the third quarter of 2021. This session was utilized to present background information on TBE and vaccine immunogenicity and safety data. During the February 2021 ACIP meeting, the WG intends to present data on traveler and laboratory worker risk data and additional data and considerations relevant to vaccine recommendations. In June 2021, the plan is to present GRADE and EtR data to ACIP. An ACIP vote on vaccine recommendations and finalization of the *MMWR* are anticipated in October 2021.

Discussion Points

Dr. Bell inquired as to whether there are any data about breakthrough infections, understanding that there is not a correlate of protection and that this is a rare disease.

Dr. Schmitt indicated that there is information on breakthrough disease. Basically, there are two types. The first is those subjects who are non-responders who have IgM and IgG later on that looks like a primary infection. The second are breakthrough cases where there is little IgG to begin with and high IgG right from the beginning, which is the real breakthrough case. Overall, breakthrough cases are quite rare. There is a recent published series from Germany, which is an endemic country. Among a population of 85 million, there were 6000 TBE cases and approximately 200 vaccinated subjects with all types of doses, irregular schedules, and so forth.

Dr. Hunter asked whether there is any change this pathogen could be in other *Ixodes* tick vectors and therefore become established in any of the ticks in North America.

Dr. Schmitt said that he did not know, but guessed the spectrum is broader than *Ixodes*. There are other tick species in Russia and Japan, but he will follow up to find out.

Dr. Hills added that there is another tick-borne flavivirus in the US, Powassan virus, which she will follow up on.

Dr. Sanchez requested additional information about the sequelae of this infection in terms of morbidity and mortality and whether there is any cross-reactivity or cross-protection for Powassan virus.

Regarding sequelae, Dr. Schmitt reported that the death rate is 0.6% in a population-based study in Latvia over an 18-year observation period. In other countries in Russia it is much higher at up to 30%. Dr. Hills has presented those data previously. Overall, it is very difficult to compare mortality rates based on different hospitalization systems, who pays for what, and all of that. There are several studies on sequelae in adults such as paresis, mental changes, psychiatric changes, et cetera of up to 40% to 50%. In children, it is believed to be a mild disease. Children who have symptomatic TBE usually present with meningitis and less with encephalitis. However, there are now data to show that these children may have mental sequelae as well that may affect academic performance, concentration, and so forth. He is happy to follow up on this further. For Powassan virus, there are no serology data to look for cross-protection or any cross-reaction.

Dr. Erin Staples, the SME, indicated that the genetic relatedness for Powassan virus is such with TBE that they do not think there will be cross-protection provided by the TBE vaccine. Limited studies have been done on Powassan virus, and they were mostly in animal models that also suggest that the vaccine may not provide protection.

Dr. Romero asked whether there is any evidence of transplacental transmission from mothers to babies if the mother is infected during pregnancy and Dr. Sanchez asked about transmission through breastmilk.

Dr. Schmitt indicated that there are 6 such reports in the literature of transmission from mother to baby and to date, there is no indication for transmission. With very limited data, he would tentatively say that there is likely not transmission from mother to baby. There are some older reports with missing data, but from all that is known, this is unlikely. While it could be in breast milk, he did not know of publications to support this. He would assume that in the viremic phase, if the mother has a TBE virus, a high fever, and is breastfeeding at that time, it may be in the milk. He will follow up on that as well.

Dr. Staples added that this will be covered in the February ACIP meeting in presentations about all of the risk groups and known modes of transmission to clearly document potential risk.

Rabies Vaccine

Introduction

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

Dr. Frey introduced the Rabies WG session. As a reminder, the Rabies WG was introduced in October 2018. During October 2019 and February 2020, the WG:

- Presented a review of vaccine safety and WG considerations for changes to the pre-exposure prophylaxis (PrEP) series

- Presented a systematic review of published literature about primary immunogenicity and duration of immunogenicity of intramuscular (IM) [0, 7 days] PrEP series involving human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV) vaccines

- Gathered feedback from ACIP about the data needed in order to consider shortening the PrEP series from IM [0, 7, 21/28 days] to IM [0, 7 days]

The WG's focus continues to be that rabies is nearly always fatal and that no proposed changes should be considered that could be inferior to current IM [0, 7, 21/28 days] series. The WG considered improvements to the current PrEP recommendations that are supported by robust data, enable an anamnestic response for the duration of a recipient's life, and are based on what is known about compliance, acceptability, and reasons for current guidance.

The WG's activities related to PrEP since the last ACIP meeting have included the following:

- Comprehensive re-review of PrEP in the context of ACIP's feedback:
  - Reviewed the purpose of PrEP and expectations for data if changes proposed are accepted
  - Deliberated over policy questions that can be confidently proposed that are an improvement from current recommendations and grounded in data
  - Leveraged WG members' rabies subject matter expertise in immunology, historical basis of current recommendations, travel medicine, clinical practice, public health, veterinary medicine, and considerations made by WHO in the 2018 update of PrEP recommendations
  - Completed GRADE and EtR framework for 2 policy questions

- Completed discussions about newly licensed rabies immune globulin (RIG) products and data to support any changes to anatomic site(s) of RIG administration

The WG faced a number of challenges during its deliberations. For instance, some of the previous recommendations were based on expert opinion and some of the current recommendations are legacy from an extremely conservative approach to less optimal rabies vaccines. Limited data exist to modify recommendations that are known to be excessive. The diverse recipients of PrEP including research laboratorians, bat biologists, veterinarians, animal control experts, spelunkers, and travelers to canine-rabies endemic countries make it difficult to create "one-size fits all" recommendations given differing types and levels of risk. In addition, compliance to current ACIP recommendations has been of concern in that veterinarians are known to be non-compliant with titer checks and PrEP is not covered by the employer or insurance for many professions.

The WG's agenda for this session were to present the results of the WG's deliberations, obtain feedback and discussion from the ACIP, answer tough questions, and determine whether the proposed policy questions could be voted on during the February 2021 ACIP meeting. To achieve these goals, the agenda for this session included the following presentations:

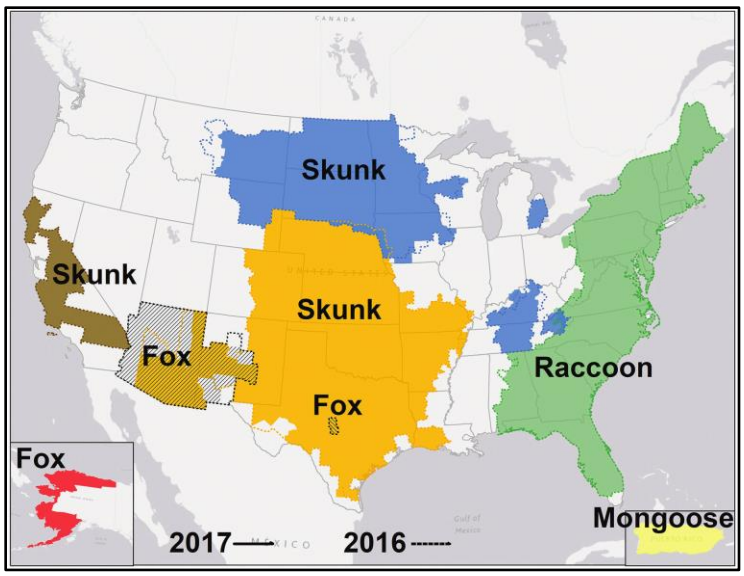
- ❑ Background and Summary of WG Considerations
- ❑ Minimum Antibody Titer and Implications on ACIP Recommendations
- ❑ More Fundamentals of Rabies Immunology
- ❑ Review of Policy Questions and Systematic Review about the PrEP Schedule and Presentation of GRADE
- ❑ Evidence to Recommendations Framework
- ❑ Summary and Next Steps

Rabies PrEP in the US and WG Considerations

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

Dr. Rao explained that human rabies is an acute, progressive encephalomyelitis that is nearly always fatal. It is transmitted from infected mammals. Worldwide, dogs are the most common cause. There are approximately 59,000 human cases of rabies worldwide each year. In the US, bats are the most common cause. Canine rabies virus variant (RVV) has been eliminated since 2007 in the US, with only 0-4 human cases each year. One of the reasons there are few cases in the US is that over time, rabid domestic animals (e.g., livestock, cows, and dogs) has decreased because of various implemented measures. During the same time and for multiple reasons, rabies among wild animals has increased.

However, there is still a lot of potential for human rabies in the US. Approximately 5000 animals test positive for rabies each year. Mammal reservoirs vary by geography. Terrestrial or wildlife rabies is the RVV for which wildlife are the reservoir. Non-terrestrial rabies is the RVV for which bats are the only reservoir. Terrestrial rabies are restricted to specific US regions, while non-terrestrial rabies can be found in all US states except Hawaii as depicted in this map:



There are multiple prevention strategies for human rabies and that is why there are so few cases like behaviors such as avoiding trying to pet wild animals, animal vaccinations of pets and of wildlife through oral baits, education and training (e.g., awareness of the need to seek medical care for exposure; training for proper use of personal protective equipment (PPE) if handling bats or working in a laboratory), PEP, and PrEP.

For the general US population, if a rabies exposure is going to occur, it occurs during occupational or recreational activities inside the US. It is a “recognized” exposure which is a very important concept meaning that it is a bite or scratch from a racoon, mongoose, or fox that has rabies for instance. It is an exposure that any person with intact mental status would realize that they had and would seek medical attention and PEP. It is not an exposure that would go unnoticed. PrEP is not advantageous for the general US population and has never been recommended by ACIP for the general population. As a side note, it is expensive and is typically not covered by insurance.

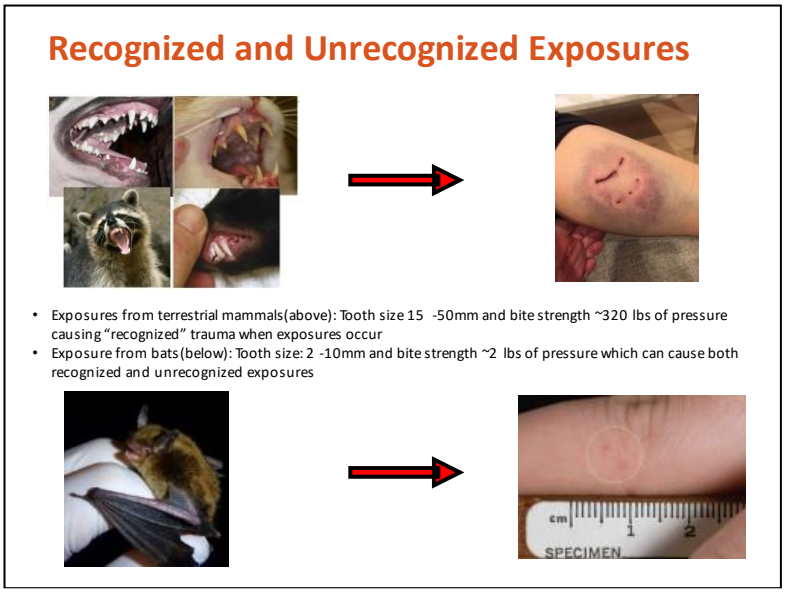
It is important to keep in mind that rabies PrEP is not a substitute for PEP. Anyone who gets PrEP should still get PEP if he or she has an exposure. The current vaccine series for healthy persons who have an exposure is: A) for someone who received PrEP, 5 total vaccines and no RIG; or B) for someone who did not receive PrEP, 4 vaccine doses and RIG are given as PEP after an exposure occurs. PrEP is not a substitute for PEP. Someone who gets PrEP actually ends up getting more total vaccines if the number of vaccines given as part of PrEP are counted. The benefits of PrEP are that it eliminates the need for RIG, which is expensive and may not be easily available during some international travel. It shortens the PEP series for persons who may have multiple rabies exposures in their lifetime. In addition, it provides some protective coverage if a delay in PEP administration could occur or if the exposure type is the sort that only laboratorians have such as a high concentration of rabies virus.

Rabies risks that warrant PrEP are higher than those of the general population. Persons should receive PrEP if they have any of the following:

- ❑ An unrecognized exposure, meaning an exposure that a person with intact mental status may not notice and so PEP is not sought
- ❑ A potential for exposure to high potency virus or unusual exposures (e.g., high concentration or research grade rabies virus, aerosolized rabies virus, or non-rabies lyssaviruses) all of which are only potential exposures for laboratorians
- ❑ Opportunities for frequent contact with potentially rabid mammals because of one's job or recreational activities (e.g., bat biologist, veterinarian, or spelunker)
- ❑ Travel to a canine rabies endemic country where one may not have easy access to PEP, such as a rural region within that country

The WG organized this information into the 3 risk groups, including: 1) laboratorians who have high potency or unusual exposures, unrecognized exposures, and/or frequent contact with potentially rabid mammals; 2) persons who frequently handle bats or enter environments with high concentrations of bats (e.g., bat biologists and some pest control workers) who may have unrecognized exposures and/or frequent contact with potentially rabid animals; and 3) persons who work with animals (e.g., wildlife workers and veterinarians) or who may come in contact with dogs in a canine-rabies endemic country (e.g., travelers) who have frequent opportunities for recognized exposures. The highest risk is for the laboratorians.

These photographs illustrate recognized and unrecognized exposures:



On the top of this above set of photos are exposures from terrestrial mammals with a tooth size of 15-50mm and bite strength of as much as 320 pounds of pressure, which would make it difficult not to know if one was bitten by one of these animals. On the bottom is exposure from bats. The tooth size is 2-10mm and the bite strength is only about 2 pounds of pressure. For the vast majority of people, that is still going to be a recognized exposure. However, someone who

is swarmed by a cave full of bats may not know whether they had an exposure. This is the population of people who are referred to as those who frequently handle or enter environments with a high density of bats, and who are placed in their own category to separate them from the general population.

This is a table from the current ACIP rabies recommendations. Pre-exposure recommendations including schedules and frequency of titer checks are listed in the last column, but those are different depending upon risk level in the first column. For example, at the bottom of the first column is the risk category for the general population which has very little risk for rabies. No PrEP is needed for the general population. Moving up the table, risk increases. The risk categories (Infrequent, Frequent, and Continuous) in the first column correspond nearly completely to the 3 risk groups described earlier. Those in the highest risk group are laboratorians who can have recognized and unrecognized exposures and may be exposed to aerosol generating procedures and high concentrations of virus, those in the second risk group have recognized and sometimes unrecognized risks, and those in the third risk group have only recognized risks:

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 titer is below acceptable level.*
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, cavers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below 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.

* 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.

What is different is the Typical Populations column here. This section has been very confusing to clinicians and public health authorities. One type of laboratorian is in the second risk category instead of up in the highest risk category with the other laboratorians. Travelers remain in the third risk group, but some occupations are listed in both the second and third risk categories. For example, veterinarians and animal care workers are listed in both risk groups but the distinction pertains to whether they work in terrestrial or non-terrestrial regions.

The WG thought a lot about whether working in terrestrial or non-terrestrial region should have any impact on PrEP recommendations and concluded is that it is important for PEP recommendations but not for PrEP. That is, one's occupation is the most important factor for the purposes of PrEP. Someone who works in a terrestrial rabies region as a wildlife worker may have more opportunities for exposure to a rabid animal than wildlife workers in a region without terrestrial rabies. The WG concluded that the number of potential risks does not matter for PrEP.

There are more opportunities for exposure in terrestrial versus non-terrestrial regions, but the exposure type remains a recognized exposure. Going back to the WG's categories, the WG believes that there is no reason for whether the work occurs in a terrestrial region versus a non-terrestrial region to figure into the risk categories for PrEP. This revised table shows the changes the WG made to the current table after all of this deliberation:

Proposed Revisions

Risk category	Nature of Risk	Typical Population	Disease Biogeography[1]	Primary Immunogenicity PrEP	Long-term Immunogenicity
#1: Elevated risk for unrecognized and recognized exposures and	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized. Direct and indirect exposures.*	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)	Laboratory	Goal: Same primary series for 3 risk groups	Goal: Titers maintained high in case of unrecognized exposures
#2: Elevated risk of both unrecognized and recognized exposures	Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized and is greater than for those in the #3 risk group. Direct exposures and rarely indirect exposures	Persons who frequently handle bats or at frequent risk for coming into contact with bats because of entrance to high density bat environments (e.g., bat biologist)	All geographic regions where bats are a reservoir for rabies**		
#3: Elevated risk of recognized exposures	Risk of virus exposure greater than population at large. Exposure is a recognized one. Direct exposures.	Persons who work with animals • Animal care professionals (e.g., veterinarians, technicians, animal control officers) • Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) • Spelunkers • Veterinary students • Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods*	All geographic regions where terrestrial and non-terrestrial mammals are reservoirs for rabies		Goal: Anamnestic response elicitation to recognized exposure
		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 area). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler's Health destination pages)*	• Geographic regions internationally with canine rabies		
#4: Low risk of exposure / (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	U.S. population at large	• Nationwide	• No pre-exposure prophylaxis • No serologic monitoring	n/a

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

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

*Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock). **Bats are reservoirs for rabies in all US states except Hawaii

For the purposes of removing any confusion about the previously titled "Continuous, Frequent, and Infrequent" risk groups, the WG used #1, #2, and #3 based on the type of risk they have. The differences in the typical populations and the fact that terrestrial and non-terrestrial regions does not figure into the decisions is clear from these 2 columns. What are left to fill out are the last 2 columns of the table. The WG's goal for primary immunogenicity was to identify the same series for all 3 risk groups, given that this will result in the least amount of confusion. The goal for long-term immunogenicity is more complicated. Since those in the #1 and #2 risk groups have risk for unrecognized exposures, the goal for long-term immunogenicity is different from those in the #3 risk group. Those with unrecognized exposures should have titers persistently found to be over the minimum acceptable antibody cut-off in the event that they have an unrecognized exposure and do not seek PEP. The goal for those in the #3 risk group for long-term immunogenicity is different. It is to ensure that if an exposure occurs 20 years after PrEP was completed, the person will still have an anamnestic response to an exposure. If they cannot be guaranteed to be "previously immunized" 20 years after completion of PrEP, they cannot be given the shortened PEP series that is typically given to someone who received PrEP. The last 3 presentations during this session provide information that fills in the WG's preferences for these two columns "Primary Immunogenicity" and "Long-Term Immunogenicity."

The next two presentations provide more background information to fill in the last two columns. The first is a presentation about minimum acceptable rabies antibody titer and implications on ACIP recommendations. The purpose of this talk is to share problems with the current ACIP cut-off titer, propose a solution, and outline the potential implications of the proposed change. The other presentation regards pertinent fundamentals of rabies immunology. The purpose is to show how efficacious the current vaccines used for rabies are. ACIP recommends only IM use of rabies vaccines for several reasons and is not proposing a change to that. However, intradermal (ID) is used more worldwide because of the cost-savings associated with ID administration. Because there is so much international data for ID, a second purpose of this presentation is to show why the WG feels that ID data can be used to inform decisions about IM administration.

During the February ACIP meeting, the committee pointed out various factors that will weigh into their decision to vote for or against any changes to the current ACIP recommendations, which include the following:

- ❑ 2008 ACIP recommendations have been effective
- ❑ Rabies is nearly 100% fatal
- ❑ Proposed changes must:
  - ➢ Be supported by robust data
  - ➢ Address the evolving rabies landscape
  - ➢ Reflect new data and increased confidence in modern cell culture vaccines (CCVs)
  - ➢ Not have suboptimal immunogenicity to current PrEP
- ❑ WHO and ACIP recommendations do not have to align
  - ➢ Dose and cost-sparing options are top priority for WHO, but not necessarily for the US population

Minimum Acceptable Rabies Antibody Level

Susan Moore, PhD, MS HCLD (ABB)/adjunct professor
Diagnostic medicine/pathobiology/College of Veterinary Medicine
Kansas State University, Manhattan, Kansas

Dr. Moore expressed gratitude for the invitation to speak to ACIP about minimum acceptable rabies antibody level. As part of the presentation, she explained the rationale and history of the minimal antibody level and technical issues related to the testing and reporting of this level to explain the proposal for changing the minimal rabies antibody level to 0.5 IU/mL.

To start, as Dr. Rao presented, PrEP is not indicated for the general US population. It is indicated for persons who are at risk for unrecognized exposures to rabies virus, work with high potency rabies virus and may have unusual exposures to rabies (e.g., aerosolized), frequently are in contact with potentially rabid mammals (e.g., wildlife biologists), or travel to canine rabies endemic regions where they may be at risk of delayed PEP if a rabies exposure occurs. The minimum acceptable antibody level is the target level for primary immunogenicity 2 to 4 weeks after completion of a primary pre-exposure vaccination schedule and the target level at the intervals for which antibody level checks are recommended.

Referring to the table Dr. Rao presented with the proposed revisions, the primary vaccination series will be in the column labeled “Primary Immunogenicity PrEP” and the frequency of antibody level checks will be indicated for each risk group in the last column titled “Long-Term Immunogenicity.” The minimum acceptable antibody level is the level that a healthy person would be expected to mount after completion of any ACIP-recommended primary series. The minimum acceptable antibody level is also the level used as the goal when levels are checked at various time points. For the future presentations during this session, when the WG’s proposed recommendations are presented, ACIP members may wonder what impact those recommendations may have if the minimum acceptable antibody level is set at one value versus another.

As an introduction, Dr. Moore first established why/how the minimal level is important. This level is used as an indication of a successful primary pre-exposure vaccination series and is used to monitor for evidence of immunity. The current antibody level as stated in the ACIP recommendations are confusing and difficult to interpret. To emphasize this point, she showed what is posted on the Kansas State University (KSU) Rabies Laboratory website to aid clients in interpretation of rabies serology results, which she wrote years ago in response to the many questions the KSU Rabies Laboratory received on the reported results in relation to what the ACIP says. KSU is one of 3 places that perform rabies serology testing on human samples for the public and much time and effort is spent in explaining how the reported results relate to the ACIP minimal acceptance level for antibody. In her years of directing the KSU Laboratory, this has been a major issue for reporting results. For a fatal disease such as rabies, the recommendations need to be crystal clear.

To understand the cut-off levels, Dr. Moore first talked about what is known about the immune response to rabies infection and the role of vaccination in protection, particularly the significance of neutralizing antibodies. Rabies is well-known to be 100% fatal, primarily due to the poor immunological response to infection. It also is known that rabies is nearly 100% preventable through pre- and post-exposure vaccination. High circulating antibody targeting the glycoprotein of the virus has been proven to be the most important component for immunity to rabies. For obvious reasons, no efficacy studies have been performed in human subjects for determination of the antibody level required for rabies protection. Instead, animal rabies vaccine challenge studies are utilized for surrogate data. In animal vaccine studies, some animals with low levels of antibody succumb to challenge. Conversely, some with no detectable antibody pre-challenge survive. No definitive titer is known to be universally protective.

One of the first studies looked at the level of antibody associated with survival in animals was published in 1984 by Bunn and Ridpath. They used statistical methods to calculate probability of survival from pre-challenge titers, concluding that at a level of 0.2 IU/mL, the probability of survival was 95% and at 0.5 IU/mL, it was 99%. Note that the test results are given in 2 ways, titer and IU/mL, which Dr. Moore addressed later. Other subsequent publications of summary studies in dogs, cats, ferrets, and wildlife gave similar results regarding practical significance of rabies antibodies. These papers also commented strongly on the variability of the test method and need for standardization in testing. In animals, the level of 0.5 IU/mL is robustly associated with survival and is the level used to verify adequate rabies immunity in pets traveling to rabies-free areas of the world. In addition, though there is no absolute antibody level indicator, the level 0.5 IU/mL is the consensual criterion for immunogenicity in rabies vaccine evaluation.

The minimum level of rabies virus neutralizing antibody (RVNA) determined for humans was based on results of early vaccine clinical trials, where the rabies serology data came from either the mouse neutralization test (MNT) or the rapid fluorescent focus inhibition test (RFFIT). RFFIT results are reported in terms of the 50% endpoint titer and/or in IU/mL. Both the WHO and ACIP used the same rationale in setting this cut-off level, which was by evaluating the data to determine the minimal titer or IU/mL robustly associated with detection of specific RVNA. The WHO and ACIP cut-off levels are different AND are expressed in different ways. The WHO cut-off, which is 0.5 IU/mL, is approximately 5 times higher than the ACIP cut-off. ACIP states the cut-off level as a description. This a quote from the current recommendations, “Complete neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT).” This loosely converts to anywhere from 0.1 to 0.3 in IU/mL. No cases of rabies have occurred in the US using this cut-off, this fact is misleading because many factors contribute to survival. The ACIP recommendations also state that rabies serology results should be reported in IU/mL, but does not provide the relationship of the recommended level to reported values. The ACIP cut-off is neither a titer value or an IU/mL value.

This chart displays the history of published recommendations from WHO and ACIP regarding the level of RVNA representing an adequate antibody response and the laboratory methods recommended to measure the antibodies:

Agency/Year	Booster vaccination recommended if level is below:	Method of Testing:
WHO		
1992	0.5 IU/mL	MNT or RFFIT; ELISA only with caution
2005	0.5 IU/mL	RFFIT or FAVN; ELISA if RFFIT not availa
2013	0.5 IU/mL	RFFIT or FAVN; ELISA
2018	0.5 IU/mL	RFFIT or FAVN; ELISA
ACIP		
1976	None, boosters recommended every 2 years	None stated
1980	1:16 titer or booster every 2 years	RFFIT
1984	1:5 titer per CDC; 0.5 IU/mL per WHO	RFFIT
1991	1:5 titer *	RFFIT
1999	Complete neutralization at a 1:5 serum diluti	RFFIT
2008	Complete neutralization at a 1:5 serum diluti	RFFIT

*Recommended response 2 -4 weeks after either pre- or post -exposure vaccination is complete neutralization at a 1:25 serum diluti on which is equivalent to the WHO level of 0.5 IU/mL

†Recommended response 1 -2 weeks after post -exposure vaccination is complete neutralization at a 1:5 serum dilution

‡RVNA titer most properly reported according to a standard as IU/mL

The ACIP cut off value is confusing and hard to interpret against the RFFIT value reported for determination of booster vaccination.

Mouse Neutralization Test=MNT; Rapid Fluorescent Foci Inhibition Test=RFFIT; Fluorescent Antibody Virus Neu
FAVN; Enzyme Linked ImmunoSorbant Assay=ELISA

The WHO has consistently recommended 0.5 IU/mL. ACIP has recommend using the RFFIT method consistently, but has expressed the cutoff level variously and at times in unclear terms. In 1984 and 1991, two different levels were recommended for differing situations. In 1999, the level was expressed in a description of the reaction microscopically read on the RFFIT slide, “complete neutralization at a 1:5 serum dilution.” Unless one has performed the assay, there would be no reason to know that the calculation of a result of complete neutralization at a 1:5 serum dilution is a titer of 1:11. The ACIP cut-off is confusing and hard to interpret for determination of a need to boost.

As mentioned, the test used for rabies serology is the RFFIT and can be reported in titers, IU/mL, or both. Dr. Moore briefly explained what actually is a complex series of steps for testing and reporting rabies serology results. A titer is the serum sample dilution that neutralizes a standard dose of live rabies virus. Titer values are variable due to the inherent variability in cell based serum neutralization methods. Anyone who has worked in a serology or virology laboratory knows that not all factors that affect a biological interaction, such as antibody neutralizing a virus or virus infecting a cell, can be exactly controlled over the course of the interaction. Ranges are given in laboratory methods for pH, temperature, incubation times, virus dose, cell count, et cetera to attempt to control the conditions, but there are many factors beyond these that can influence variability. This variability occurs within the same laboratory between each time the test is run and between laboratories. Titer values will vary between testing events, which is a given. However, the reference serum will vary in the testing event similarly as any other sample tested at the same time. This fact is used to standardize the titer value into International Units.

In terms of how this is accomplished, Dr. Moore explained the steps to calculate first the titer and then to convert the titer to IU/mL. The RFFIT readout using a microscope is a count of the virus positive fields on a slide out of 20 total fields. This count is entered into the Reed and Muench formula which gives the 50% endpoint titer value. The formula for the conversion of titer to IU/mL is simpler by taking the sample titer, dividing it by the reference serum titer, and then multiplying by the potency of the reference serum in IU/mL. Per the WHO “Laboratory Techniques in Rabies” manual, in the RFFIT, the reference serum is tested at a potency of 2 IU/mL. For example, a sample serum titer of 50 divided by reference serum titer of 200, multiplied by the potency of the reference serum 2.0 IU/mL, gives a value of 0.5 IU/mL. There is no direct correlation between titer and IU/mL because of the RFFIT variability previously mentioned. However, in most laboratories using internationally recognized RFFIT protocols, the ACIP cut-off (a titer of 1:11) is in the range of 0.1 – 0.3 IU/mL. In summary, rabies serology testing and reporting is all very complicated. The main point is that the ACIP cut-off level is hard to correlate directly to the associated titer value, and that there is a range of IU/mL values that can be associated with it.

In terms of how this works in real life, the following table helps to explain the complexity of the testing:

			RVNA result		Rabies Vaccine Boost Recommendation	
			Titer	IU/mL	ACIP 1:11	WHO 0.5IU/mL
Lab A	Low Challenge Virus Dose 10 $TCID_{50}$	Mary	1:24	0.2	NO	YES
		John	1:90	0.6	NO	NO
		Reference Serum	1:300	2.0		
		Negative Serum	1:2	0.0		
Lab B	Medium Challenge Virus Dose 50 $TCID_{50}$	Mary	1:10	0.2	YES	YES
		John	1:37	0.6	NO	NO
		Reference Serum	1:125	2.0		
		Negative Serum	1:2	0.0		
Lab C	High Challenge Virus Dose 100 $TCID_{50}$	Mary	1:4	0.2	YES	YES
		John	1:10	0.6	YES	NO
		Reference Serum	1:35	2.0		
		Negative Serum	1:2	0.1		

One of the variability factors in the RFFIT is the virus dose. Per the WHO “Laboratory Techniques in Rabies” manual, the virus acceptance range is 30 to 100 $TCID_{50}$ with a target of 50 $TCID_{50}$. There are 3 laboratories: A, B, and C. Laboratory A uses a virus dose below the range, Laboratory B uses a virus dose near the target, and Laboratory C uses a high virus dose. Each of the laboratories test the same samples, from Mary and John, as well as the same control sera—the reference serum which serves at the positive control and the calibrator for conversion of titer to IU/mL and the Negative control. The titer values vary between the 3 laboratories. The titer values (all, samples and control sera) decrease as the virus dose increases, yet the calculated IU/mL values remain the same. This shows that IU/mL values are less variable than the titer values. Conversion to IU/mL controls for the variability in the test. Looking at these results from these 3 laboratories, it is possible to see how the titer results from Laboratories B and C recommend booster vaccination for Mary per the ACIP cut-off. However, all 3 laboratories’ IU/mL results using the WHO level indicate a booster vaccination is needed for her. The same is true for John in that Laboratory C’s titer result indicates a booster vaccination is needed per ACIP, but all other results say no booster needed. It can then be concluded that normal variability in laboratory testing of the RFFIT can lead to incorrect interpretations of antibody levels if the titer is not standardized into IUs.

For serum neutralization assays, anything that inhibits virus infection or growth will cause non-specific neutralization reactions. These can be related to cell health, interfering factors in the serum or virus strength, et cetera. The ACIP cut-off is very near the lower limit of quantitation of the assay. This table shows the percentage of samples from unvaccinated subjects who produced a positive RVNA result in the RFFIT:

	False Positive Titer Results			
IU/mL	Study 1	Study 2	Study 3	**Average**
>/=0.1	2.4%	4.3%	1.3%	**2.7%**
>/=0.2	1.2%	2.9%	0.8%	**1.6%**
>/=0.3	1.2%	2.9%	0.4%	**1.5%**
>/=0.4	0.0%	0.0%	0.4%	**0.1%**

The percentage of non-specific neutralization results (false positives) increases the lower the cut-off level is set, introducing some uncertainty in accuracy at this level. For a disease that is 100% fatal, the cut-off level should ensure minimal false positives.

The summary results displayed in the following table are from a number of rabies antibody monitoring events at veterinary conferences and veterinary schools. In purple shading are the percent of people with results above a 0.5 IU/mL cut-off and the percent of people with results above the ACIP cut-off. Using these percentages, the percent of people who need boosters based on the 2 different cut-offs were calculated and are in the Yellow shaded columns. The Pink column shows how the effect of changing the cut-off to 0.5 IU/mL, given in fold increase, has on the number of people recommended to receive a booster vaccination. Overall there is a 2.5 fold increase in people recommended to receive a booster if the acceptable level changes to 0.5 IU/mL:

Implications for a change in antibody cutoff level for adequate response to vaccination

Rabies Titer checks at Veterinary Conferences and Schools

	% of people with RVNA ≥0.5 IU/mL	% of people with RVNA ≥ ACIP cut-off	% people needing a booster at ACIP cutoff	% of people needing a booster at 0.5 IU/mL cutoff	Fold increase of people needing a booster if cut-off changes
Las Vegas 2000	62	78	22	38	1.7
Boston 2001	76	89	11	24	2.2
Nashville 2002	77	89	11	23	2.1
Denver 2003	86	95	5	14	2.8
Philadelphia 2004	88	97	3	12	4.0
Minneapolis 2005	82	94	6	18	3.0
Dallas 2008	95	99	1	5	5.0
Dallas 20152018	93	98	2	7	3.5
6 Vet Schools 2005-2014	80	97	3	20	6.7

On average 2.5-fold increase (range 1.7 – 6.7) in people recommended a booster between current ACIP cutoff and 0.5 IU/mL

In summary, an antibody level of 0.5 IU/mL is a better alternative to the current ACIP cut-off for defining the minimal antibody response to vaccination for several reasons. Repeatedly in published animal studies, 0.5 IU/mL is robustly associated with survival from challenge, and data show that the 0.5 IU/mL is the RVNA level that assures minimal false positives in the RFFIT. In addition, using a standardized unit of measure, IU/mL provides results that are more accurate and precise than titer values. IU/mL is globally used to report rabies serology and is also the primary unit of measurement reported in the US. There are clear advantages for the proposal to change the cut-off from "complete neutralization at a 1:5 serum dilution" to 0.5 IU/mL, including reducing confusion in interpretation for those at risk of this high stakes infection, increasing the precision and accuracy of the results, decreasing the risk of reporting false positive results, and using a unit that controls for the inherent variability of the RFFIT. The disadvantage is that there is real potential that more people would be recommended to receive a booster vaccination.

Discussion Points

Dr. Romero observed that this outstanding presentation provided ACIP with a good basis for making a decision regarding the proposed change.

Dr. Hunter inquired as to whether there were any numbers to show what percentage of people would need boosters that could be provided to the clinicians this would affect to increase their acceptance of the change. He suggested conducting a survey with veterinary, medical schools, and occupational health departments that could help with the "Acceptability" component of the EtR Framework.

Dr. Moore indicated that because the ACIP says that rabies serology results should be reported in IU/mL, that was a quandary for laboratories reporting this because they were struggling with how to report per mL when the cutoff is not given in that unit. The rabies laboratory at KSU does global work and wound up putting both cutoffs on the reporting, which the website explains. In talking to veterinary schools and at conferences, they were very conservative in saying that the WHO says 0.5 IU/mL and ACIP says 0.1-0.3 IU/mL. However, the 0.5 IU/mL is a more conservative cutoff. It seems like a lot of schools and occupational groups use 0.5 IU/mL. The actual increase in the number of people who would be getting a booster if the ACIP said 0.5 IU/mL is not likely to be a large number. However, it is difficult to calculated.

Pertinent Fundamentals of Rabies Immunology

Deborah J. Briggs, PhD
Adjunct Full Professor
Kansas State University

Dr. Briggs expressed gratitude for the opportunity to speak about cell culture rabies vaccines and the fundamentals of rabies immunology. She provided a brief history about the production of rabies vaccines, explained why there are two routes of administration, and presented clinical data to show that the ID and IM routes of administration for cell culture rabies vaccines for both pre-exposure vaccination and PEP are equitable.

The first human rabies vaccines was developed from infected nerve tissue by Louis Pasteur and his colleagues in the late 1800s. Various versions of nerve tissue vaccines (NTVs) were used globally through the 1900s and even into the 2000s. These vaccines required multiple doses to be administered into the abdominal region of the patient over a lengthy period of time, and they

caused serious adverse reactions. One of the first improved rabies vaccines was the duck embryo vaccine developed in the 1960s, but it required 14 doses and produced low titers.

In 1976, the first field trial of HDCV was endorsed by the WHO. It was conducted in Iran due to the number of rabies cases in the country and the fact that there was a reliable WHO reference laboratory in Tehran. In that first clinical trial, 45 patients severely bitten by rapid wolves received HDCV and 44 of those patients also received antirabies serum and 1 patient who had been exposed to aerosol rabies only was not given the antirabies serum. Each patient was given 6 subcutaneous doses and all of those patients survived. This was actual proof that HDCV, the first generation cell culture rabies vaccine, was efficacious.

In 1980, two important events occurred. HDCV was licensed for IM use in the US and the WHO experts met in Essen, Germany and recommended a 6-dose IM PEP and a 3-dose IM regimen for PrEP. During this meeting, the WHO urged research into finding alternate routes of vaccine administration, including the ID route. That was because the cost of PEP was so high using HDCV that they wanted a lower cost vaccine or route of administration so that they could encourage low-income countries to replace NTVs with cell culture vaccines. In 1982, the US approved the ID administration of HDCV pre-packaged as a 0.1 mL dose. However, it was taken off of the market in 2001 due to the high cost of packaging that particular dose. From the late 1980s through the 2010s, clinical trials were conducted investigating the immunogenicity and efficacy of the ID route of the administration of HDCV and newly developed cell culture rabies vaccines, including Purified Chick Embryo Cell Vaccine (PCECV) and Purified Vero Rabies Vaccine (PVRV). Data from those trials proved that these vaccines were as effective as HDCV when administered either IM or ID in both PrEP and PEP regimens.

Taking a closer look at the published data the WG examined comparing ID to IM in various clinical trials, the WG reviewed these data to determine whether data from ID administration studies could be used to inform recommendations for IM administration of cell culture rabies vaccines. The WG also reviewed efficacy data for cell culture rabies vaccines. There were 3 basic factors the WG needed to verify in evaluating the equivalence of the IM and ID routes of administration: 1) equal efficacy, meaning that both routes will protect patients exposed to proven rabid animals; 2) equal primary immunogenicity, meaning that both routes will produce adequate levels of neutralizing antibodies in vaccinated individuals (in this case 0.5 IU/mL); and 3) equal long-term immunogenicity (i.e., anamnestic response) in previously vaccinated individuals when they receive a booster vaccination series.

The very first study investigating the efficacy of PEP administered ID was conducted in Thailand by Dr. Phanuphak and his colleagues at the Thai Red Cross Society. Their goal was to find a safe, effective, and inexpensive strategy to replace the crude NTVs that were being produced and used in Thailand and to reduce the high cost of rabies deaths occurring in their country. The patients enrolled in this trial had experienced minor exposures to rabid animals. The CCV used was PVRV because its cost was lower than HDCV and the exposed patients were given one of 4 regimens. Group 1 received the full IM vial (Day 0,3,7,14,28); Group 2 received 0.1 mL of vaccine administered ID at 4 sites (Day 0,3,7)l Group 3 received 0.1 mL of vaccine administered ID at 2 site (Day 0,3,7); and Group 4 received 0.1 mL of vaccine administered at 1 site (Day 0,3,7). All of the ID vaccination regimens were given on Day 0, 3, 7 and on Day 28 the same ID groups received 1 more dose of 0.1 mL in the upper deltoid region. In this study, all patients survived. Regardless of whether patients received post-exposure PVRV via the ID or IM route, all patients developed neutralizing antibodies above 0.5 IU/mL by Day 14. Their antibody levels remained above 0.5 IU/mL through Day 35, which was the last day a blood sample was taken [Phanuphak et al. 1987. Asian Pacific J Allergy & Immunol. 5:33-37].

The Thai Red Cross Society wanted to conduct a confirmation efficacy study to confirm that the earlier study investigating the efficacy of the ID route for PEP, which was done in collaboration with CDC in Atlanta. This study enrolled 100 patients who were severely bitten by confirmed rabid animals. All of the patients were followed for 1 year after vaccination. All of the patients received two ID doses of PVRV vaccine administered on each of Days 0, 3, 7 and 1 dose was administered on Day 30 and Day 90. This became known as the "Thai Red Cross ID Post-Exposure Regimen." All of these patients survived. Table 1 shows the type of bites the patients received and the expected mortality rate, reflecting that there most certainly would have been deaths due to rabies infection without the administration of ID PEP in these patients:

TABLE I—LOCATION OF ANIMAL BITES AND EXPECTED NUMBER OF DEATHS BASED ON HISTORICAL STUDIES*

No of patients	Location of bite	Expected mortality rate (%)
2	Face	45
2	Head	45
1	Neck	40
6	Trunk	3
6	Arms	3
18	Hands	15
29	Fingers	15
18	Multiple	15
20	Legs	3
16	Feet	3

*Ref 11

Also as part of this clinical trial, blood was drawn in 10 patients during the study and titers were checked on Days 14, 90, and 360. Table 2 shows that all titers remained above 0.5 IU/mL during the study:

TABLE II—ANTIBODY TITRES IN SEVERELY EXPOSED THAI PATIENTS TREATED WITH THAI RED CROSS INTRADERMAL POSTEXPOSURE RABIES VACCINE*

	Days after first dose of vaccine		
Patient	14	90	360
1	4·33	2·22	0·62
2	6·94	2·22	0·83
3	2·77	0·62	0·62
4	1·38	0·62	0·62
5	2·55	0·77	0·55
6	6·94	0·55	0·62
7	1·05	0·55	0·62
8	6·94	0·62	0·62
9	6·94	3·11	3·00
10	2·55	0·62	0·62
No with titre	10/10	10/10	10/10

*Purified Vero cell rabies vaccine.

Chutivongse S, Wilde H, Supich C, Baer G, Fishbein D. 1990. *Lancet* 335:896-8

Over time, additional clinical data proved that the Day 90 dose was not required. That dose was dropped from the Thai Red Cross regimen. Further clinical studies and data have reduced the ID PEP regimen to the currently accepted WHO recommendation of a 1-week 2-site schedule given on Days 0, 3, and 7.

The immune response after pre-exposure vaccination by either IM and ID also has been investigated in several clinical trials. A study by Rescuenco is representative of the clinical data that the WG reviewed among many published studies looking at ID and IM PrEP vaccination. This study was conducted in the US to confirm that the ID route of administration for pre-exposure was as immunogenic as the IM route. It was done to find reliable strategies for administering PrEP to those persons at greatest risk due to their occupation in the event of a human rabies vaccine shortage in the US. Shortage of human rabies vaccines had occurred previously. This study enrolled 128 subjects and the vaccine that was administered was PCECV. Subjects were randomized to 1 of 4 groups. Groups 1 and 2 had not received vaccine previously. Group 1 received 3 doses on Days 0,7,21 and Group 2 received 3 IM doses on Days 0,7,21. Groups 3 and 4 were previously vaccinated and in this study received 1 dose of booster vaccine administered by either the ID or IM route in order to confirm a rapid anamnestic response. Previously unvaccinated subjects in both the ID and IM groups responded with equally high titers after vaccination. All subjects had titers above 0.5 IU/mL by Day 21 as had been reported in almost all published clinical study reports. The IM route of administration gives slightly higher titers than the ID group; however, the slightly lower titers that are produced in the ID group are not clinically significant. all subjects in both the IM and ID PrEP groups had titers above 0.5 IU/mL by Day 21 and all titers remained above that level through the end of clinical trial [Recuenco, S. et al. 2017. *Vaccine* 35:4315-20].

One of the most important reasons for administering PrEP vaccination to patients at risk of exposure to rabies is to eliminate the need for a rabies immune globulin in the event of future exposure, and to elicit a rapid anamnestic response in the patient after they receive booster vaccination. In a study conducted by Wongsaroj et al the Thai Red Cross Institute using PVRV, both Groups A and B received a 2-dose pre-exposure regimen administered on Days 0, 21. Group A received the series using the ID route of administration and Group B received the series by the IM route. The geometric mean titers (GMTs) in both Groups A and B were well above 0.5 IU/mL by Day 35. One year after the primary vaccination was administered and prior to the booster series, the GMT of the ID group was 0.35 IU/mL and the GMT of the IM group was 0.76 IU/mL. On Day 365, both groups received a 2-dose booster series of vaccine administered as 0.1 mL ID in one upper deltoid on each of Days 0, 3. All subjects had an anamnestic response to the booster series by 14 days later and the GMT rose to well above the 0.5 IU/mL level, again confirming that PrEP administered either ID or IM is immunogenic and anamnestic response will occur when these patients receive a booster series of vaccine. Of note, there was no significant difference between the GMT on day 379 in the IM and ID groups after each group received the 2-dose 0.1 mL ID booster series on Day 0, 3 [Wongsaroj P et al. 2013. Rabies neutralizing antibody after 2 intradermal doses on days 0 and 21 for pre-exposure prophylaxis. Vaccine. 31:1748-51]. An anamnestic response in pre-vaccinated subjects also has been confirmed in numerous other studies.

In terms of why additional CCVs are needed when the first one was so efficacious, throughout the decades since the development of CCVs numerous clinical trials have compared the CCVs that have been manufactured according to the WHO prequalification standards. HDCV is expensive to produce and it is very expensive for patients to purchase. There are now other equally efficacious and less expensive cell culture rabies vaccines that have come onto the market, including PCECV and PVRV. These less expensive vaccines have enabled millions of

lives to be saved and have eliminated the production and use of nerve tissue vaccine. Numerous clinical trials have been conducted and data published to confirm that these vaccine, when produced according to WHO prequalification standards, are efficacious, immunogenic, and will elicit a rapid anamnestic response to booster.

Data from a clinical trials conducted by Dr. Madhusudana et al[1] showed that GMTs in patients after receiving the Thai Red Cross ID post-exposure regimen with either PCECV or PVRV were equivalent. Blood was withdrawn on Day 0 prior to vaccination and on Days 14, 30, 90, and 180. Again, all titers were above 0.5 IU/mL. Another study compared PCECV to PVRV. This study was conducted at two hospitals in Thailand by Dr. Wasi and her colleagues[2]. This study enrolled 211 patients with Category II and III wounds who were placed into 3 groups. Groups 1 and 2 received the Thai Red Cross ID PEP Regimen. Group 1 received PCECV and Group 2 received PVRV. Group 3 received the Essen 5-dose IM PEP regimen using PCECV. The GMTs for Groups 1 and 2 are almost exact. Group 3 had slightly higher GMTs as had been reported in numerous other studies with the IM route of administration. Again, this is not clinically significant [[1]Madhusudana et al. 2006. Human Vaccines. 2:200-04; [2]Briggs et al. 2000. Bull WHO.8(5):693-98].

After reviewing the data shown during this presentation and numerous other peer-reviewed published papers, the WG concluded that ID and IM PEP are equally efficacious in patients exposed to confirmed rabid animals. ID and IM PrEP are both highly immunogenic routes of vaccination, with IM producing slightly higher titers in most clinical trials. There is no known clinical relevance attributed to the increased immunogenicity reported with the IM route. CCVs that meet WHO pre-qualification standards will produce equitable immunogenicity responses in both PreP and PEP regimens and when administered IM and ID. Patients who receive PrEP administered IM or ID will both have a robust anamnestic response to booster vaccination when administered either by the IM or ID route. The WG's interpretation from these data is that when using high-quality CCVs, ID and IM routes of administration are equivalent among three clinically relevant immunologic factors: efficacy, immunogenicity, and anamnestic response.

Discussion Points

Dr. Frey emphasized how hard Drs. Moore and Briggs have worked on the WG and that they have been bombarded by endless questions by committee members.

Dr. Sanchez asked what data are available comparing the IM to ID in children specifically, as it seemed all of the articles shown were in individuals 18 years of age and older.

Dr. Briggs indicated that 35% to 60% of the patients in Asia and Africa were children. In Asia, much of the vaccine given post-exposure is given ID and is well-tolerated in children. There is no problem with IM in children either. There is a study of vaccination in malnourished children in India, who also responded very well to the vaccine. The ID route of administration has been used in India, Thailand, and the Philippines. A large percentage of those patients are children and there have been no problems.

Pre-Exposure Prophylaxis Schedule: Grading of Recommendation Assessment, Development and Evaluation (GRADE)

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

Dr. Rao presented the GRADE for the two policy questions the WG developed for rabies PrEP, with the following assumptions:

- Rabies is 100% fatal
- Rabies vaccines are highly efficacious
- Multiple layers of preventing human rabies (e.g., PrEP, animal vaccinations for rabies, PPE while working with rabies virus, PEP)
- Goal of PrEP differs for recognized versus unrecognized exposures:
  - Recognized exposures: Anamnestic response from PrEP + shortened PEP series
  - Unrecognized exposures: Sustained high titers such that "protection" provided by PrEP alone even if PEP is not administered
- ID data can be used to inform IM recommendations
- An increase in the titer cut-off to 0.5 IU/mL has advantages and one potential disadvantage: the booster could be indicated for a titer value that would have been considered acceptable in the past

As shown in Dr. Rao's first presentation regarding the proposed revisions, the WG reorganized the risk groups and labels the Risk Category of the table using risk groups #1, #2, #3, and #4 from highest risk to lowest. The GRADE presentation focused on the last 2 columns of the table, Primary Immunogenicity PrEP and Long-Term Immunogenicity. Primary immunogenicity is the immunogenicity that should be reflected in peak titers which occur about 2-4 weeks after completion of the primary PrEP series. In thinking about primary immunogenicity, the WG considered the goals of primary immunogenicity for each of the 3 risk groups for whom PrEP is indicated. The WG concluded that there is no difference in the goal for ensuring that titers are acceptable 2-4 weeks after completion of the primary series.

The WG thus drafted Policy Question #1 that applies to all 3 risk categories, "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?" In terms of the PICO question, the population is persons for whom rabies vaccine PrEP is recommended, the intervention is [0, 7 days] rabies vaccine PrEP schedule, the comparison is a [0, 7, 21/28 days] rabies vaccine PrEP schedule, and the critical outcome is efficacy defined as primary immunogenicity with peak immunogenicity after completion of the primary vaccine series at 2-4 weeks after completion of the primary series. In terms of safety outcomes, AEs were not included as a critical outcome because these vaccines have a track record for safety over many decades. Summary data about the safety were presented during the February ACIP meeting from RCTs since the 2008 ACIP publication and VAERS data showed no change from previous reporting.

Regarding the second blank column in the table, Long-Term Immunogenicity, the WG thought about whether the goals for long-term immunogenicity should be different for any of the 3 risk groups. Just to recap, those in the #1 risk group can have unrecognized, high-risk, and recognized exposures. That is why they are at highest risk. Those in the #2 risk group can have unrecognized and recognized exposures. Those in the #3 risk group can have only recognized exposures. What differentiates these groups in terms of recommendations is that those in the #1 and #2 risk groups have potential for unrecognized exposures. As mentioned earlier in the day, what this means is that those persons could have exposures for which they do not seek PEP. Thus, the goals for those in the #1 and #2 risk groups and those in the #3 risk group are categorized separately as follows:

- ❑ (Groups #1 and #2) Goal for Unrecognized exposures: Ensure titers are persistently high in case of PEP not being sought.
- ❑ (Group #3) Goal for recognized exposures: Ensure ability to mount an anamnestic response; titers need not be persistently high for anamnestic response.

The ideal way of dealing with long-term immunogenicity would be titer checks. That is already recommended by ACIP for those in the #1 and #2 risk groups listed here. However, for the third risk group, it would be a new recommendation for many. The WG discussed this and recognized that persons in this risk group are not accustomed to having even a single titer drawn, so they wanted to consider a booster for this group as an alternative to ensure the goal of long-term anamnestic response. Data indicate that titer at the 1-year time point is indicative of long-term titers and that the ability to mount an anamnestic response is maintained. In the absence of data confirming that the [0, 7 days] series provides immunogenicity many years later, titers at the 1-year time point could be indicative of a person's long-term immunogenicity. Newer data as recent as a year or two ago found that people can mount an anamnestic response after the [0, 3, 7 days] primary series for as long as 3 years later. Taken together, the WG felt that the titer value at any point during 1-3 years after completion of the primary series could be checked once to ensure long-term immunogenicity and a booster could be recommended if titers are <0.5 IU/mL at the titer check. No further titer checks would be indicated because the persons in the #3 risk group have only recognized exposures, making them very different from the people in the #1 and #2 risk groups.

The WG thus drafted Policy Question #2 to address the booster question, "Should an IM booster dose of rabies vaccine (PCECV or HDCV) be recommended as an alternative to a titer check no sooner than Day 21 and no later than 3 years after the two-dose PrEP series IM [0, 7 days] for those in the #3 risk category who receive PrEP?" In terms of PICO, the population is persons in the #3 risk category, the intervention is a Day 21 to Year 3 rabies vaccine booster after the [0, 7 days] rabies vaccine PrEP schedule, and the comparison is no rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule. The critical outcome is efficacy defined as long-term immunogenicity (i.e., ability to mount an anamnestic response in response to a challenge like a rabies virus exposure or a booster dose of vaccine). Again and for the same reason as stated for the first policy question, a safety outcome was not included.

To retrieve the evidence for both Policy Question #1 and Policy Question #2, the WG performed a literature search of multiple biomedical and interdisciplinary bibliographic databases including Medline, Embase, Cochrane library, and the WHO Index Medicus. A broad and rigorous strategy was used to incorporate terms related to the concept of pre-exposure vaccination against rabies virus using HDCV or PCECV vaccines. The search was limited to 1965-2018, which is a time period well before these CCVs were available. There were no language restrictions. The results were compiled in an Endnote Library and duplicate records were

removed. The search was updated through December 31, 2019 to ensure that records not captured in the original search were included. Records were included if they presented data on human rabies vaccines **and**:

- ❑ Involved immunocompetent adults 18 years of age or older (data from animal or in vitro studies or data from humans <18 years of age were excluded)
- ❑ Included data for intervention of interest (HDCV or PCECV rabies vaccine, pre-exposure, intradermal [1-site or 2 site] or intramuscular [1-site], any PFU)
- ❑ Included data relevant to the outcome measures being assessed
- ❑ Planned categorization of primary data into comparative or single-arm studies; randomized control trials, prospective or retrospective cohort, case-control, cross-sectional studies (records that did not provide primary data [e.g., literature reviews or summaries, editorials, commentaries, opinions, clinical trial registries or protocols] and case reports or case studies were excluded)

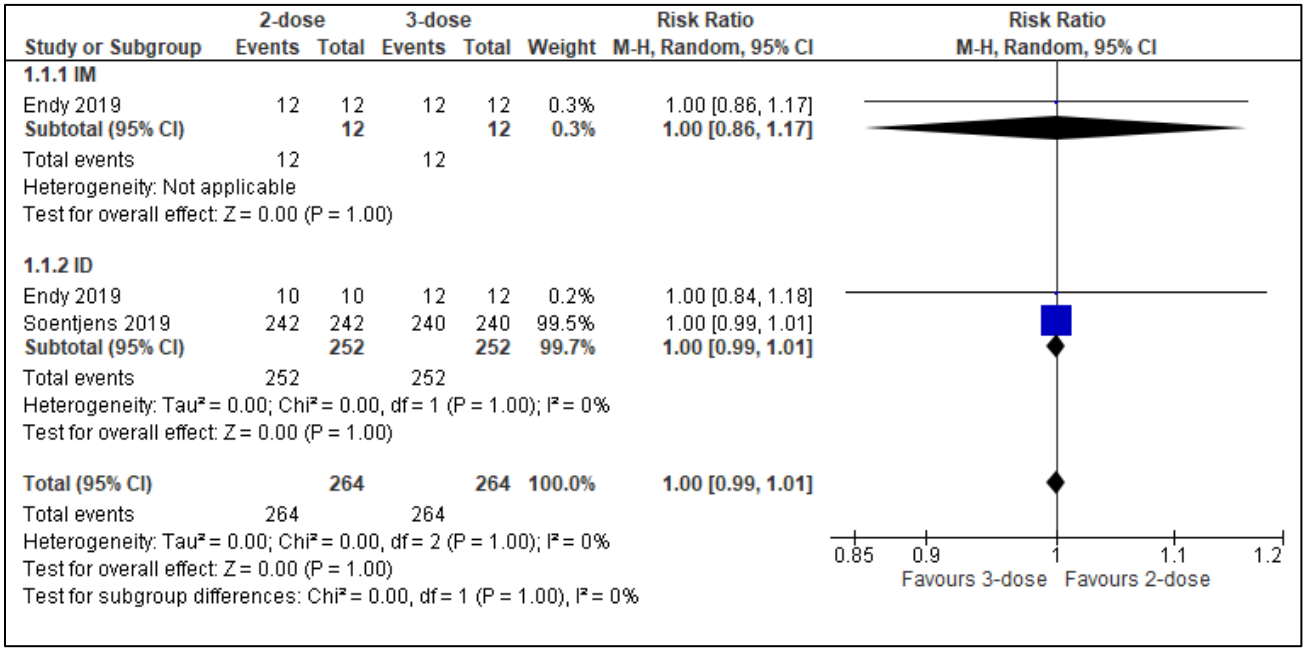
The search identified a total of 258 papers, 142 of which were submitted for critical review. Of those submitted for critical review, 130 were excluded. All 12 of the remaining papers that met the WG's criteria were used for the first policy question and 2 of the 12 were used for the second policy question.

As a reminder, 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 (high certainty) and observational studies as evidence type 3 (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; and *Other Considerations*, including rating upward of the body of evidence from observational studies due to dose-response gradient, large or very large magnitude of effect, or opposing residual confounding.

After assessing on the described criteria, the body of evidence will be assigned an overall evidence type or certainty level. To provide context for interpretation of this, Type 1 or high certainty evidence means that the WG is very confident that the true effect lies close to that of the estimate of effect. Type 2 or moderate certainty evidence means the WG is moderately confident in the effect estimate. Type 3 or low certainty evidence means the WG's confidence in the effect estimate is limited. Type 4 or very low certainty evidence means the WG has very little confidence in the effect estimate. As a reminder, the WG is not measuring how well the individual studies were conducted, but rather how much confidence they have 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.

Regarding the outcome for PrEP Policy Question #1, the search identified 2 RCTs that compared a 2-dose to a 3-dose primary series (Endy, 2019 & Soentjens, 2019). Across both studies, 100% of participants met the outcome of interest. There was unclear reporting of randomization and allocation concealment in both trials that led to some concerns with risk of bias. This forest plot shows the analysis of the 2 studies reporting on the outcome of immunogenicity comparing the 2-dose to the 3-dose series. The first analysis displays the results from IM administration and the second displays the results from ID administration. The results taken together are listed below these. No heterogeneity due to route of administration is suspected as shown here and the pooled risk ratio is 1.00 with a confidence interval from 0.99 to 1.01, so very tight as shown by the diamond to the right:



The search identified 10 additional studies that compared a 2-dose to a 3-dose primary series. These studies were treated as observational studies, although they were originally designed as randomized trials. In this meta-analysis, the randomization was broken to extract pertinent data and that is why they were considered observation. The quality of the studies was evaluated with the Newcastle-Ottawa Scale (NOS) and minimal concerns were identified in 3 studies and no concerns were identified in the rest:

PrEP Policy Question #1

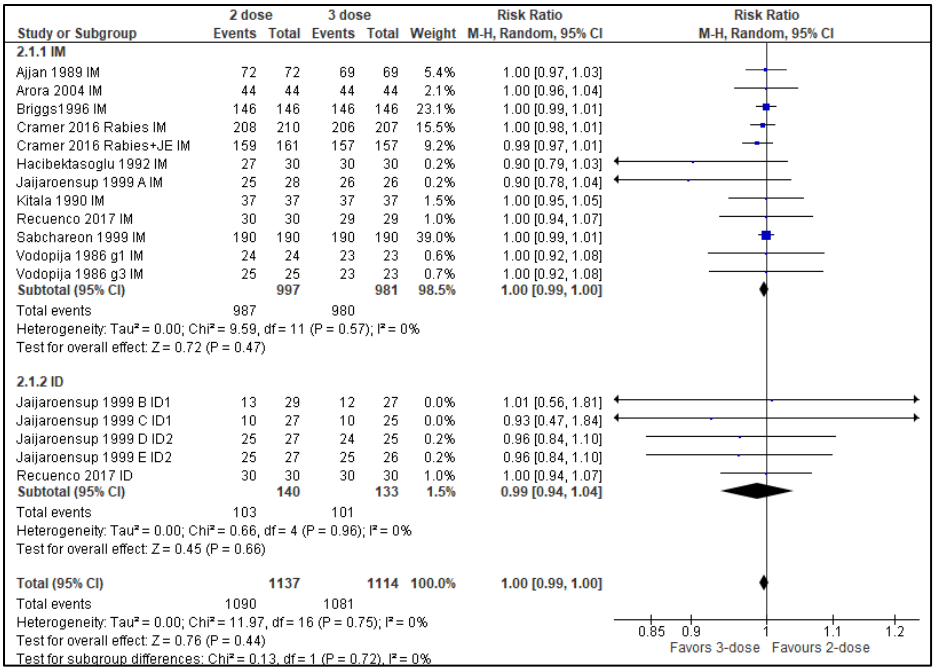
Table 3b: Summary of Observational Studies Reporting Outcome

Authors last name, pub year	Age (years)	N intervention	N comparison	Vaccine	Risk Ratio [95% CI][1]	Study limitations (Study quality[2])
Ajjan, 1989	Mean 22, Range 19-41	72	69	HDCV, IM	1.00 [0.97, 1.03]	9/9 No concerns
Arora, 2004	Mean 26.2, NR	44	44	HDCV, IM	1.00 [0.96, 1.04]	9/9 No concerns
Briggs, 1996	NR	146	146	HDCV, IM	1.00 [0.99, 1.01]	9/9 No concerns
Cramer 2016	Mean 36.7, SD 12.9	371	364	PCEC, IM	0.99 [0.98, 1.01][4]	7/9 Minimal concerns
Hacibektasoglu, 1992	Mean 20, Range 18-24	30	30	HDCV, IM	0.90 [0.79, 1.03]	9/9 No concerns
Jaijaroensup, 1999	NR, Range 17-22	138	129	PCEC, IM, ID	0.94 [0.87, 1.02][4]	9/9 No concerns
Kitala, 1990	NR	37	37	HDCV, IM	1.00 [0.95, 1.05]	8/9 Minimal concerns
Recuenco, 2017	Median 41.0, Range 20-62	60	59	PCEC, IM, ID	1.00 [0.96, 1.05][4]	9/9 No concerns
Sabchareon, 1999	Mean 10, SD 1.3[3]	190	190	HDCV, IM	1.00 [0.99, 1.01]	7/9 Minimal concerns
Vodopija 1986	NR	49	46	HDCV, PCEC, IM	1.00 [0.94, 1.06][4]	9/9 No concerns

[1]Data from observational studies, where intervention and comparison data were taken from the same people at different time points, were analyzed using M-H Risk Ratio random effects procedure. Due to unavailable raw data on pairing, a matched analysis was not possible.
[2]Study quality for observational studies was assessed using the Newcastle Ottawa Scale.
[3]Age for total study population was not reported in this paper. Numbers in this cell are from the study arm from which data were extracted.
[4]Studies contained multiple arms relative to the analysis. Risk ratio reflects pooled analysis from eligible arms.

There were concerns for risk of bias in the 3 studies. The cohort representativeness of the target population was not ideal. The Sabchareon population was predominantly children. Study participants were not demonstrated to be free from the outcome of interest at start of the study in that there were no Day 0 titers for the Cramer and Sabchareon studies. There was inadequate follow-up time to assess the outcome in the Cramer paper, with a follow-up of 1 week after completion of the series rather than 2 to 4 weeks when peak titers would be expected. It is unclear whether anyone was lost to follow-up in the Kitala study based on the manuscript itself, so the assumption had to be made that everyone finished the Day 28 time point. Across these studies, 95.9% of participants met the outcome of interest after a 2-dose series and 97.9% of participants met the outcome of interest after a 3-dose series.

The following forest plot shows the analysis of the 10 studies that were treated as observational reporting on the outcome of immunogenicity comparing the 2-dose to the 3-dose series. Similar to the previous forest plot, the first analysis displays the results from IM administration and the second displays the results from ID administration. No heterogeneity due to route of administration is suspected. The I square is 0% here. The pooled risk ratio is 1.00 with a very tight confidence interval from 0.99 to 1.00:



This is the evidence profile of the GRADE assessment for the outcome of immunogenicity as measured by a titer at or above 0.5 IU/mL:

Table 4: Evidence Table

Immunogenicity after [0, 7 days] PrEP series with HDCV or PCECV

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[0, 7 days] rabies vaccine PrEP schedule	[0, 7, 21/28 days] rabies vaccine PrEP schedule	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (RCTs) (follow up: range 2 weeks to 3 weeks; assessed with: titer level above 0.5)												
2 [1,2]	randomized trials	serious [a]	not serious	not serious	not serious	none	264/264 (100.0%)	264/264 (100.0%)	**RR 1.00** (0.99 to 1.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	Level 2	CRITICAL
Immunogenicity (observational studies) (follow up range: 2 to 3 weeks, assessed with titer level above 0.5)												
10 [3,4,5,6,7,8,9,10,11,1]	observational studies	not serious	not serious	not serious [b]	not serious	none	1090/1137 (95.9%)	1081/1114 (97.0%)	**RR 1.00** (0.99 to 1.00)	**0 fewer per 1,000** (from 10 fewer to 0 fewer)	Level 3	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Method of randomization and allocation not reported in Soentjens 2019 and allocation concealment not reported in Endy 2019. Neither study blinded participants or healthcare personnel; however, unlikely that co - interventions would have influenced the outcome.

b. Sabchareon 1999 study was conducted among children and the response may be more robust than in adults, which would potentially overestim ate the immune response.

The WG assessed the body of evidence from RCTs and non-randomized studies separately. Because of concerns with unclear reporting of randomization and allocation concealment, the RCTs were rated down for risk of bias. The WG had no other concerns of the certainty of the evidence; therefore, they had moderate or level 2 certainty about immunogenicity for the RCTs. In the 2-dose arm and the 3-dose arm, 264 persons achieved 100% seroconversion. RR is 1, CI is 0.99-1.01, and the absolute effect is no fewer/1000 seroconvert in the 2-dose arm compared

to the 3-dose arm. That ranges from 10 fewer persons to 10 more. The second line of this table shows the WG's certainty in the evidence of immunogenicity of the non-randomized studies. The WG had no concerns about the evidence and therefore it remained at low certainty that the observational study started at or Level 3.

For Policy Question #2, the WG abstracted data from the Endy and Soentjens studies. To obtain these data, the WG broke up the randomization and treated them as observational studies. Per Policy Question #2, the comparison group comprises people who did not receive a booster after a 2-dose primary series. In these two studies, no direct comparison group was available. GRADE was performed in the absence of a comparison group. The quality of the studies was evaluated with the NOS. Minimal concerns were identified. Concerns for risk of bias include inadequate follow-up time to assess outcome as titers were drawn 7 days after the booster. This is the evidence profile of the GRADE assessment for the outcome of duration of immunogenicity as measured by a titer at or above 0.5 IU/mL after booster:

Table 4: Evidence Table

Duration of immunogenicity after [0, 7 days]PrEP series with HDCV or PCECV

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Anamnestic response after booster (follow up: range 1 weeks to 3)									
2 [1,2]	observational studies	not serious	not serious	not serious	not serious	none	A historical control of trial participants receiving 2 doses of rabies vaccine resulting in 100% immunogenicity (n=264) at 1 -3 weeks following vaccination schedule (Endy 2019, Soentjens 2019) : 203/203 (100%) seroconverstion with booster	Level 3	CRITICAL

CI: Confidence interval

The best available evidence was informed by the single arms of 2 trials, which demonstrated complete achievement of immunogenicity following a 2-dose primary series, as well as after a booster provided. Therefore, it was treated as non-randomized (observational studies) and started at low certainty or level 3 evidence. The WG had no additional concerns with the body of evidence, so the certainty remained low at Level 3. The WG has low certainty that there is a meaningful difference between the level of immunogenicity achieved between 3 weeks and 3 years among persons who received a booster compared to those receiving a 2-dose primary series.

Discussion Points

Dr. Bell congratulated everyone on these clear and comprehensive presentations about a very complicated and difficult subject with a 100% fatality rate and limited information. She requested further information about the thinking behind Policy Question #2 in terms of why it would be easier to get someone to come in for a booster dose rather than having their blood drawn, or if there was something else about the difference between these two options.

Dr. Rao indicated that there were differences in the opinion on the WG and they vacillated between saying titer only or booster only, and then ultimately settled on giving both options. It is not clear how many people who have the 2-dose series would have a titer less than 0.5 IU/mL and would subsequently require a booster. It is thought that more people would need a booster at the 1-year point than with the 3-dose series, but they cannot say for sure given the lack of data. Even if it was 50% to 60% of people, the discussion on the WG calls was that some people might find it annoying to have to get a titer and then make another appointment to get a booster. They thought that since the current schedule is for a 3-dose series, some people would consider it a preferable option to go straight to the third dose. The reason for the broad time period for the third dose is partly based on the fact that the third dose of the current 3-dose series is at Day 21 or Day 28, which is known to be effective in ensuring long-term immunogenicity. There are data out to 3 years showing that people can continue to have an anamnestic response at 3 years, which is why the WG felt comfortable saying that a booster would be acceptable at any point in that time period. The WG's suspicion is that there probably is long-term immunogenicity beyond 3 years from the 2-dose series. The WHO actually adopted the 2-dose series without any additional requirements for a titer or booster. The WG is taking the most conservative route given the limited data up to 3 years to ensure that people receive either a booster or titer and that people's convenience and preference is honored as much as possible. A titer is paid for out of pocket and costs about $50.00; whereas, going straight to booster can be as high as $1,800.00.

Dr. Poehling asked about the availability of obtaining a titer, given that she thought she heard that KSU was one of only 3 places that perform titers.

Dr. Rao said that KSU, Health Associates, and CDC perform titers. The current 3-dose schedule is for healthy people and they must get a titer repeatedly until that has been achieved. It already is a requirement for people in the continuous and frequent risk groups to have titers drawn serially at certain intervals. For those in the #1 risk group, it is every 6 months. For people in the #2 risk group, it is every 2 years. A huge section of the people who had previously been in the #2 risk group were moved to the #3 risk group, so a good portion of those people already were supposed to be getting titers every 2 years from the people who are now being asked to get a single titer once. The WG does not anticipate that there will be a major increase in the number of titers, given that so many people already are getting titers because they are immunocompromised or because they are in the high risk groups.

Dr. Talbot requested clarity about the cost per dose to receive the series, how much the vaccine costs, and if there are any data available on how compliant people are about getting their booster shot and having their antibody titers drawn.

Dr. Rao indicated that they have been told that the clinic visit and shot together costs about $1,800.00 or so. Ryan Wallace from CDC added that the Medicare reimbursement cost for 1 dose of rabies vaccine is $303.00. Dr. Rao noted that she included some manuscripts that discuss booster shot and titer compliance in the background reading. The WG feels that compliance with titers for those in the #1 risk group is high because they are laboratorians and their jobs require it, so it is an occupational issue that is enforced to continue working in the laboratory. People in the #2 risk group are not as compliant with the ACIP recommendations as they currently stand. Veterinarians in terrestrial regions used to be listed in this group, but they were moved to the #3 risk group. They are good about getting their titer checked immediately because they received the vaccine during veterinary school, partly because it is a requirement for school completion. Subsequently when they are in practice, people are not very compliant with titer checks beyond veterinary school according to the manuscripts and veterinarians on the WG. Animal wildlife workers and others in that group who are supposed to get titers, compliance is even worse and does not seem to be enforced. It does not seem to be forced by their occupations and is left up to the person. Because insurance does not cover PrEP, it is an out-of-pocket cost. Anything that can be done to maintain the protection intended, increase acceptability, and increase the ability to pay for it will be helpful.

Evidence to Recommendations Framework (EtR)

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

Dr. Rao reminded everyone that the Rabies Vaccine WG developed 2 policy questions for PrEP topics the first of which 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. The only outcome was immunogenicity and safety was not included as an outcome given the review of safety data that she presented earlier. Again, the considerations for this recommendation are:

- ❑ Rabies is nearly always fatal
- ❑ PrEP is an important component of preventing human rabies in the US, but it is not the only component
- ❑ PrEP is indicated for persons with a rabies risk greater than that of the general population
- ❑ PrEP is critically important for persons with unusual exposures, unrecognized exposures, and frequent exposure to potentially rabid animals
- ❑ Travel abroad to canine-rabies endemic regions without quick access to PEP

No cases of rabies have occurred among persons who received modern CCV PrEP in the US. ACIP has recommended PrEP for decades. Many persons for whom ACIP recommends PrEP do not receive it. Rabies PrEP is very expensive and insurance typically does not cover the cost and occupations often do not cover the cost. Some occupations do not enforce compliance with ACIP recommendations even though risk is typically because of occupation.

The WG felt that the problem is of public health importance. PrEP is indicated for many persons in the US. All US animal care professionals (e.g., veterinarians, technicians, animal control officers), veterinary students, short-term and volunteer workers with hands-on animal care, persons who frequently handle bats or enter high-density bat environments, various laboratory personnel, and travelers to canine-rabies endemic regions who may not have quick and easy access to PEP if needed). Fewer people receive PrEP than ACIP recommends because the series involves 3 vaccine doses and out-of-pocket costs.

The WG determined that the desirable anticipated effects are minimal, given that they are pretty much equivalent to the 3-dose series. Out of 264 persons receiving 2-dose primary series, 100% achieved titer ≥0.5 IU/mL 2-4 weeks after the second dose. Of the 264 persons receiving the 3-dose primary series, 100% achieved a titer level ≥0.5 IU/mL. Seroconversion is the target outcome of PrEP and is achieved with the proposed 2-dose series just as it is with the [0, 7, 21/28 days] series.

The WG felt that the undesirable anticipated effects are minimal. No expected safety concerns have been associated with US rabies CCVs. Safety data recently compiled from VAERS reports for HDCV and PCECV vaccines, those mentioned in the package insert, and those reported in 25 trials published since the 2008 ACIP recommendations are unchanged from previous reports. These rabies vaccines have been used for decades and are considered to have a favorable safety profile [Moro PL et al. Travel Med Infect Dis. 2019 May - Jun;29:80-81; Moro PL, et al PLoS Negl Trop Dis. 2016 Jul 13;10(7):e0004846; VAERS: Vaccine Adverse Event Reporting System; Dobardzic A et al. Vaccine. 2007;25:4244–51].

With regard to whether the desirable effects outweigh the undesirable effects, both 2-dose and 3-dose primary series achieve complete immunogenicity at 2-4 weeks following completion of the series. Therefore, the WG feels that it favors both. The WG found the overall certainty of the evidence to be moderate, Level 2, due to the concerns for risk of bias.

The WG determined that the target population probably feels that the desirable effects are large relative to the undesirable effects. While no research evidence was identified, the target population would likely appreciate a shorter series that requires fewer vaccines, is less expensive, and provides the same primary immunogenicity as the current 3-dose series. Educational materials may be needed to ensure the target audience understands that the immunogenicity is unchanged from that of the current series for up to 3 years. Knowledge, attitudes, and practices (KAP) surveys may be considered to assess perceptions of the target population. The WG felt that there is no important uncertainty about or variability in how much people value the main outcomes. While again no research was identified, the target population values “protection” from rabies and there is likely no important variability in how people value it. The WG felt that the intervention is acceptable to key stakeholders. A shorter series would be appreciated by clinical providers, public health officials, and patients who all prefer a simpler vaccine schedule that is less expensive than the current schedule. It will be easier to schedule appointments for 2 vaccines than for 3 vaccines.

The WG found the intervention to be a reasonable and efficient allocation of resources. The estimated cost of a 3-dose PrEP series is approximately $1,800 per clinic visit and vaccine dose and these costs are often out-of-pocket. Fewer costs would be incurred by patients with a shorter series, thereby making intervention a reasonable and efficient allocation of resources to all populations for which it is indicated. Rabies vaccine shortages have occurred in the US. A shorter vaccine schedule may prevent an impact of such shortages on PrEP demands.

The WG felt that there probably would be a reduced impact on health equity. While no research evidence was identified, the costs for rabies PrEP is often out-of-pocket so a shorter series could potentially make the PrEP series more accessible to persons who would not otherwise be able to afford it. There are a lot of people for whom ACIP recommends receipt of PrEP who have a higher risk than the general population.

The WG thought that the intervention would be feasible to implement. While no research evidence was identified, no barriers are expected with implementing a shorter series. With a 3-dose series, it is often difficult to ensure that the third dose is administered before someone travels to a canine-endemic region or starts work that requires pre-vaccination. Having to wait until receipt of the third dose at 21 or 28 days is often seen as an inconvenience and people do not see themselves as being previously immunized before receiving the third dose. With the shorter regimen [0, 7 days], they would be considered previously immunized much sooner. As many people in the WG commented, travelers often do not schedule a travel clinic visit soon enough before their travel and this would facilitate that. Implementing a shorter series will be easier and management challenges are expected to be equivalent to those currently faced when deviations occur to the PrEP schedule.

The WG determined that the desirable consequences probably outweigh the undesirable consequences in most settings and that there is sufficient information to move forward with a recommendation. Therefore, the WG proposed the following draft recommendation to ACIP:

Draft recommendation	Work Group Interpretation
In persons for whom rabies vaccine PrEP is indicated, ACIP recommends 2-dose PrEP series IM [0, 7 days] Involving HDCV or PCECV rather than a 3-dose PrEP series IM [0, 7, 21/28 days]	WG preference is for intervention

As a reminder, the second policy question was, “Should an IM booster dose of rabies vaccine (*PCECV or †HDCV) be recommended as an alternative to a titer check no sooner than day 21 and no later than 3 years after the two dose pre-exposure (PrEP) series IM [0, 7 days] for those in the #3 risk category who receive PrEP?” The population is persons in the #3 risk category for whom rabies vaccine PrEP is recommended, the intervention is Day 21/Year 3 rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule, and the comparison is no rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule. It is important to note that this question is applicable only to people who would have sustained risk for rabies beyond the 3-year time point. For instance, this question would not apply a traveler planning a single trip to India who needs a one-and-done series.

The problem is that some persons have sustained risk for rabies (i.e., risk >3 years after completion of the primary series). For those in the #1 and #2 risk groups for rabies, serial titer checks are currently recommended by ACIP because of the risk to those groups for “unrecognized” exposures. In the absence of data to confirm long-term immunogenicity >3 years after primary series, a titer check or booster for those in the #3 risk group can confirm long-term immunogenicity. A single titer check is indicated 1-3 years after the primary series because this value is indicative of long-term immunogenicity. A recommendation for titer checks would be a new ACIP recommendation for those in the #3 risk group. Some persons in the #3 risk group may prefer boosters to titer checks. While a titer is much less costly than a booster, a titer may indicate the need for a booster. Some persons may prefer going straight away to

booster to avoid the inconvenience of multiple clinic visits. Some persons may have the cost of a booster absorbed by occupation. Facilitating the booster dose as soon as when the third dose of the current ACIP [0, 7, 21/28 days] series is administered will amount to no change for those accustomed to that schedule.

Some may not know whether they will have risk for long-term immunogenicity and may prefer waiting for 3 years to receive the additional dose. Some may not be able to receive the third dose for an extended time period because of travel and will appreciate having a large time period to receive the booster. The WHO approved [0, 7 days] series without booster in their most recent recommendations in 2018. This idea of ensuring long-term immunogenicity beyond 3 years is something the ACIP WG pursued because of recognizing that rabies is 100% fatal, they wanted to be as conservative as possible, and they wanted to work within the confines of the very limited data available for rabies. Data about immunogenicity will likely be available in the coming years. Given that the WHO has been using this 2-dose series without the option of a booster dose, the hope is that there will be data available from this. If the policy question is recommended by ACIP, the recommendation facilitates collection of data in the US before the next update of ACIP recommendations at 10 years or sooner on those in the #1 risk group among laboratorians at CDC and those in the #3 risk group through collaborations with veterinary schools where PrEP is required. If the data show that the IM [0, 7 days] series provides long-term immunogenicity alone and that there is no need for a titer or booster to ensure long-term immunogenicity, future ACIP updates may easily drop the booster dose requirement. This is an easy change to make and the proposed recommendation would be a step toward a simplified series like WHO's of [0, 7 days] for primary and long-term.

The WG determined the problem to be of public health importance. Many persons in the #3 risk category may require long-term immunogenicity (e.g., career veterinarian). While a 2-dose [0, 7 days] series may provide long-term immunogenicity, in the absence of data to confirm this, a titer check to determine if a booster is needed or a booster straight away provides the added insurance for this nearly 100% fatal illness. Allowing for the option of a booster straight away is important because for some persons in the target population, it is preferable to save time to bypass the titer and go directly to booster. For these persons, the cost is typically absorbed by their occupation.

The WG felt that the desirable anticipated effects would be moderate. An anamnestic response to vaccine challenge, as measured by increase in antibody titer level ≥ 0.5 IU/mL, occurred for 100% of persons who receive rabies vaccine booster at the 1-year time point and 3-year time point. These time points are markers of long-term immunogenicity. The WG suspects that persons who receive a 2-dose [0, 7 days] series will be able to mount an anamnestic response many years later regardless of booster. However, for a high stakes infection, the desirable effects are moderate in the absence of human data to confirm long-term immunogenicity after 3 years.

The WG excepts that the undesirable anticipated effects would be minimal. There are no expected safety concerns associated with a booster dose. Safety data recently compiled from VAERS reports for HDCV and PCECV vaccines, those mentioned in the package insert, and those reported in 25 trials published since the 2008 ACIP recommendations are unchanged from previous reports. These rabies vaccines have been used for decades and considered to have favorable safety profile. The WG found that the desirable effects outweigh the undesirable effects and favors the intervention. There is a 100% response rate among those receiving a booster and there likely will be few additional AEs from receipt of a booster. The WG determined the overall certainty of evidence to be low, Level 3.

The WG thinks that the target population feels that the desirable effects are large relative to the undesirable effects. It is probably that the target population likely wants to ensure long-term immunogenicity. Given limited data that 2-dose series alone will provide long-term immunogenicity, the benefits are expected to outweigh any inconvenience. Persons may experience less anxiety about acquiring this high-mortality infection by having the option of a booster or titer confirming titers ≥0.5 IU/mL. Some persons may experience discomfort or inconvenience from having to get booster.

The WG did not think there would be important uncertainty or variability in terms of the target population's sentiments. While no research evidence was identified, the target population is likely to desire a PrEP series that provides long-term immunogenicity and that there is not likely to be important uncertainty or variability because the target population is at increased risk for exposure to a life-threatening illness. The intervention is likely to be acceptable to the target population because stakeholders are invested in ensuring that the target population has long-term immunogenicity for rabies. Stakeholders are accustomed to accommodating for a third dose of rabies vaccine and will find it acceptable to have titer option or booster dose provided after the proposed [0, 7 days] primary series.

In terms of whether the intervention is a reasonable and efficient allocation of resources, the cost of a clinic visit and rabies booster can be very high at about $1,800 while cost of a titer along is about $50 and figuring in additional costs is about $100. That will still be much less than the booster dose. However, given the added insurance a booster would give for long-term immunogenicity, it would be a reasonable and efficient allocation of resources. Since not all persons who received the primary 2-dose series will require a booster, titer checks confirming titers ≥0.5 IU mL would be less costly and could be used to avoid a booster. Therefore, the WG feels that the intervention is a reasonable and efficient allocation of resources.

Regarding the impact on health equity, no research evidence was identified. However, the costs for rabies PrEP is often out-of-pocket. There is a potential for inequity because of the high costs of vaccine. Because titer is offered as an alternative to booster, the inequity could be resolved by choosing the titer option that is many times less expensive than booster. The WG did not know whether there would be an impact on health equity. However, they did feel that the intervention would be feasible to implement. Administrators of the booster are accustomed to accommodating multiple doses of PrEP beyond a [0, 7 days] series. They will have no difficulty with the feasibility of a booster dose after a 2-dose series. Recommending a booster may improve the feasibility of maintaining occupational compliance with rabies PrEP, including among those who are non-compliant with the current ACIP recommendation for titer checks. The WG determined that the desirable consequences outweigh the undesirable consequences in most settings and that there sufficient information to move forward with a recommendation. Therefore, the WG proposed the following draft recommendation to ACIP:

Draft recommendation	Work Group Interpretation
For those in the #3 risk category for rabies with sustained risk for rabies, ACIP recommends an IM booster dose of rabies vaccine (PCECV or HDCV) as an alternative to a titer check no sooner than day 21 but no later than 3 years after the 2-dose PrEP series IM [0, 7 days]	WG preference is for intervention

Discussion Points

Dr. Bell suggested that it might be useful for the WG to do some more investigating about precisely what the cost of a dose of rabies vaccines is in various settings. In terms of the proposed wording for Policy Question #2, she emphasized the importance of making clear that there are 2 options. One is to get a booster dose and the other is to get a titer. It was not entirely clear to her based on the wording proposed that either is acceptable.

Dr. Rao said that apparently frequency of titer checks does not require a vote, GRADE, or and EtR. That is one of the reasons the WG struggled with this. It is true that only the booster component needs to be voted on and the titer part would be clinical guidance.

Ms. McNally agreed that from a consumer perspective, it would be helpful to be clearer regarding the options.

Dr. Sanchez asked about ID administration. Dr. Rao indicated that ID has not been recommended in the US for a very long time. As Dr. Briggs presented in her talk, ID was licensed briefly in the US but companies pulled out of providing it for ID purposes. If not licensed by FDA, so this introduces infection control issues in terms of using a single use vial for multiple people. It makes sense from a cost-saving perspective internationally, which is why the WHO endorses it. No ACIP recommendations are being provided for ID use due to how rarely it will be used in the US population, the risks from an infection control standpoint, and the fact that it is not FDA-licensed or packaged currently for the US. The purpose of Dr. Briggs's study was more to explain why ID studies were included in the GRADE assessment.

Titer Frequency, Clinical Guidance, and Next Steps

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

Dr. Rao presented the revised recommendation table shown earlier with the WG's PrEP preferences added, including guidance for titers, to the last 2 columns as shown here:

Risk category	Nature of Risk	Typical Population	Disease Biogeography[†]	Primary Immunogenicity PrEP	Long-term immunogenicity
#1: Elevated risk for unrecognized and recognized exposures and	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized. Direct and indirect exposures.*	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)	Laboratory	IM [0, 7 days]	Titers every 6 months
#2: Elevated risk of both unrecognized and recognized exposures	Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized and is greater than for those in the Infrequent risk group. Direct exposures and rarely indirect exposures	Persons who frequently handle bats or at frequent risk for coming into contact with bats because of entrance to high density bat environments (e.g., bat biologist)	All geographic regions where bats are a reservoir for rabies**	IM [0, 7 days]	Titers every 2 years
#3: Elevated risk of recognized exposures	Risk of virus exposure greater than population at large. Exposure is a recognized one. Direct exposures.	Persons who work with animals • Animal care professionals (e.g., veterinarians, technicians, animal control officers) • Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) • Spelunkers • Veterinary students • Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods*	All geographic regions where terrestrial and non-terrestrial mammals are reservoirs for rabies	IM [0, 7 days]	Titer once at 2 years after primary series (booster if titer <0.5 IU/mL) **OR** Booster no sooner than day 21 and no later than year 3.
		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 area). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler's Health destination pages)*	• Geographic regions internationally with canine rabies		
#4: Low risk of exposure / (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	U.S. population at large	• Nationwide	• No pre-exposure prophylaxis • No serologic monitoring	n/a

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

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

†Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock). **Bats are reservoirs for rabies in all US states except Hawaii

WG's preference for primary immunogenicity is now completed with the IM [0, 7 days] schedule, which addresses Policy Question #1. The long-term immunogenicity column for the booster dose for those in the #3 risk category is now filled in, which addresses Policy Question #2. The item that still has to be filled in is the frequency of titer checks in the long-term immunogenicity column. Dr. Rao reminded everyone that in her earlier presentation, she explained that the ideal way of ensuring long-term immunogenicity is through serial titers. That is something already recommended for those in the #1 and #2 risk groups because they can have unrecognized exposures. ACIP currently recommends the frequency of those titers to be every 6 months for those in the #1 risk group and every 2 years for those in the #2 risk group. The WG's preference is for that to remain unchanged to ensure long-term immunogenicity for those in the #1 and #2 risk groups.

The last piece of the table to consider is the titer option for those in the #3 risk group. As mentioned earlier, a titer check for persons in this risk group is not something that some of the people in this group are accustomed to. The WG was concerned that instituting a titer check as the only option for ensuring long-term immunogenicity beyond 3 years may not be followed by this group, which is why the booster option was proposed. For those for whom a titer would be preferrable as opposed to going straight away to a booster, the WG considered the available data. The data from the Strady et al article in 1998 showed that titers at the 1-year time point are a marker for long-term immunogenicity. New data from the paper that was included in the GRADE shows an anamnestic response occurs for 100% of people in the RCTs for up to 3 years after the primary series. Since there are no data beyond the 3 year time point, out of an abundance of caution, the WG proposed a booster or titer check at the 2 year time point. No further titers would be needed for those in the #3 risk group because the reason for PrEP for those in this group is the ability to mount an anamnestic response.

To summarize the clinical guidance that was presented during all of the day's presentations, the table was updated for the risk groups. The WG reorganized the risk groups for PrEP and titles of three risk groups based on changing rabies landscape, included biogeography information for each risk group to make it easier to navigate and to clear up questions that have been problematic for clinicians and public health, and provided more examples of occupations for each risk group so that there is as little confusion as possible. To ensure long-term immunogenicity, a titer was introduced as an option for persons in the #3 risk group at 2 years. This clinical guidance, so it is not something for which GRADE, EtR, or a vote would be needed. The WG also is proposing changing the ACIP cutoff for minimal acceptable antibody titer to 0.5 IU/mL. Moving on to the proposed changes the WG is suggesting that would require a vote is the suggestion for primary immunogenicity that the 3-dose series be shortened to a 2-dose series and that in addition to the titer option, an option be given for booster once to the people in the #3 risk category no sooner than Day 21 and no later than 3 years.

Dr. Rao explained that the advantages of the proposed change to 2 versus 3 doses is that the #1 risk group would receive 1 less dose of pre-exposure vaccine, they would be assured that they would have completed vaccination much sooner than if they had to get a third dose at 21 or 28 days, and there would be no change to the fact that they would be getting titers every 6 months. These are benefits for laboratorians. The #2 risk group would receive fewer vaccine doses in the primary series and titers every 2 years, which is the same as currently recommended. If anything, this would decrease the number of people who have to get this because the #2 risk group would be limited to people who have unrecognized exposures such as those handling bats or entering high-density bat environments. This represents a very small number of people. The #3 risk group is the IM [0,7 days] 2-dose series. Those who do not have sustained risk for rabies would not have to get a titer or booster beyond that initial 2-dose series. Those who do have risk for longer-term exposure because of their careers or recreational activities would have the option of getting a booster as soon as they would have with the 3-dose series or the option of a titer for people who would prefer the lower costs.

The WG considerations throughout their discussions about the approach to PrEP were very mindful of the concerns raised by the ACIP during the February 2020 meeting about making any change to the ACIP recommendations for rabies. Notably, the ACIP recommendations have changed quite a lot over time as more data have been provided and CCVs have become widely used. The 2008 ACIP recommendations have been effective and rabies is 100% fatal, so the WG understood that ACIP's request was to ensure that any proposed changes are supported by robust data, address the evolving rabies landscape, reflect new data and increase confidence in modern CCVs, and do not result in suboptimal immunogenicity compared to the current PrEP. It also is important to note that the WHO and ACIP recommendations do not have to align. Dose and cost-sparing options are the top priority for the WHO. The WG did not feel that the increased cost associated with the titer or the booster in the #3 risk group would not be much, given that many of those people were in the #2 risk group and were supposed to be getting titers anyway.

Depending upon what ACIP thinks about the WG's proposed revisions to the recommendations, there potentially could be a vote on the two PrEP policy questions during the February 2021 ACIP meeting. In addition, the WG anticipates beginning to present on PEP to ACIP in February 2021 as well.

Discussion Points

Dr. Lee emphasized the importance of being thoughtful about how the dynamic of the benefit/risk balance can change. She thinks it is great step forward that they are trying to streamline and continue to improve maximum effectiveness while minimizing any harms and/or challenges.

Dr. Poehling requested clarity regarding the #3 risk group in terms of whether their only choice is a booster if they do not get the titer at 2 years, or if it should read a titer once between 2 and 3 years.

Dr. Rao recalled that the reason they made it a specific timepoint was because the table was beginning to be confusing and the ranges were somewhat out of control. The only reason they chose 2 years was because it was the same as for the #2 risk group. They certainly could change that.

Dr. Frey added that it is known that if a person has an elevated titer at 1 or 2 years, it typically will last out to 3 years or longer.

Dr. Kimberlin (AAP Redbook) asked whether any sensitivity analyses have been performed to determine whether the 100% seroconversion that was seen in the two studies with 263 or 410 subjects holds up in larger trials. For instance, they would not necessarily put a lot of stock in an N=3 and 100%. He wondered about people's comfort level making this kind of a change based on a few hundred people.

Dr. Rao responded that sensitivity analyses were not performed, but the confidence interval was extremely tight for the 2 studies that were demonstrated.

Dr. Cohn indicated that costs will be re-checked and presented during the next ACIP meeting if the companies allow it.

Dr. Talbot emphasized how fragile the healthcare system is and that she was struggling with this recommendation versus just giving the third shot in case they do not get it again in the future. She wondered whether there is any way to get serology data beyond 3 years.

Dr. Rao said they are hoping that because the WHO has instituted this recommendation for the 2-dose series that there will be data for that soon. The thought was that going forward, CDC would be able to collect data if this recommendation is accepted by ACIP and then they would know whether this titer or booster is even needed for the #3 risk group. The idea of long-term immunogenicity was not of concern to the WHO. It is really the ACIP WG who, out of an abundance of caution and wanting to ensure that there are definitely data, did not feel comfortable making the recommendation without the data.

Dr. Talbot questioned why they were in a hurry to make the change rather than waiting for the WHO data, particularly given that this is a 100% fatal disease.

Dr. Rao said that with the option for the #3 risk group, they are allow them to get the booster dose as soon as Day 21, which is the same as the current 3-dose series. What that amounts to is that if people want to get the 3-dose series, they can. However, it is not always convenient for people to get the third dose and it is not always needed because they are not going to have a risk beyond 3 years. The cost is such that people are not being compliant with recommendation

to get PrEP because it is so expensive and is out-of-pocket for them. The WG's thought was that they are allowing people to continue to get the vaccine the way they current are, but they are also being given other options with the hope of improving the number of people who get the vaccine and accommodate for different preferences.

Dr. Frey added that there are scheduled titer checks that people are supposed to be getting done.

Bryan Baxter (Bavarian Nordic) indicated that based on some general market research conducted in major cities in the US, the average cost for PrEP per dose was about $450.00. These data can be shared with the ACIP. That was the cost for vaccine only in non-ED settings and not including the visit and consumables.

Dr. Romero said that rather than taking a deep dive into the cost and factoring everything in during the meeting, they can work with Dr. Rao to obtain this information offline.

Dr. Bell suggested checking in with the WHO rather than waiting for data, given that presumably they would know whether there have been any breakthrough infections in the intervening time. The advantage/disadvantage of the WHO environment is that people are getting exposed to rabies every day, most of whom presumably have not gotten PrEP. With the anticipation of coming to a vote at some point, the attempt to simplify the table may set them up for numerous questions when people miss the 2-year time point for the titer check.

Dr. Lee asked why there are out-of-pocket costs if this is a recommendation and someone has insurance.

Dr. Cohn indicated that they would present information on the cost summaries, reimbursement, et cetera during the next meeting.

Friday: October 30, 2020

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

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the October 30, 2020 emergency meeting of the Advisory Committee on Immunization Practices (ACIP) focused solely on the topic of coronavirus disease 2019 (COVID-19) vaccines. He emphasized that faced with a crisis of historic proportion, basic scientists, clinical scientists, clinical investigators, and volunteers have worked with unprecedented speed to develop, test, evaluate, and manufacture a plethora of potential vaccines against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The mandate given to the ACIP has been to develop equitable, just, and fair policy guidelines for the use of those vaccines that are proven to be safe and effective in preventing and mitigating SARS-CoV-2 disease. The volume of data that have been compiled, analyzed, synthesized, and

presented to the ACIP voting members, liaisons, *ex officio* representatives and the public has possibly been more than ever presented for any other vaccine that has come before the ACIP. It can be said without hyperbole or exaggeration that no other national COVID-19 vaccine advisory group has dedicated as much time to addressing questions posed to the ACIP regarding the use of those COVID-19 vaccines.

Over the 7 months since its creation, the ACIP's COVID-19 Vaccine Work Group (WG) has met more times than any other non-standing ACIP WG. Dr. Romero publicly acknowledged the extraordinary work in terms of time, effort, and quality that the members of the COVID-19 Vaccine WG have dedicated to this effort. In addition to the official WG members, all ACIP members have given of their time to prepare for, attend, and meaningfully participate in the equivalent of 2 years' worth of open public meetings in a 10-month timeframe. Dr. Romeo also acknowledged the extraordinary leadership of Dr. Nancy Messonnier, Director of the National Center for Immunization and Respiratory Diseases (NCIRD); Dr. Amanda Cohn, ACIP Executive Secretary; and Jessica McNeil, Assistant Executive Secretary for ACIP. In addition, he acknowledged the important support work provided by Ms. Stephanie Thomas and Ms. Natalie Greene who have provided much of the materials to be reviewed prior to the meetings. In closing, he thanked all who have dedicated, are dedicating, and will continue to dedicate their time to ACIP's efforts to provide guidance for the use of safe and effective COVID-19 vaccines, emphasizing that he believed history would not forget their dedication to this task.

During the first day of the regular ACIP meeting on October 28, 2020, Dr. Cohn welcomed everyone and indicated that copies of the slides being presented during this meeting were available on the ACIP website and had been made available through a ShareFile link for ACIP Voting, Liaison, and *Ex-Officio* members; videos of the live webcast would be posted on the ACIP website approximately 1 week after the meeting; and that meeting minutes also would be posted on the ACIP website, generally within 90-120 days of the meeting. She reviewed meeting logistics and reminded everyone that ACIP members 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 those 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 that company.

Dr. Romero conducted a roll call of ACIP members. During the roll call of the regular ACIP meeting on October 28, 2020, ACIP members stated any COIs. These remained unchanged during the October 30, 2020 emergency ACIP meeting:

- Dr. Robert Atmar is serving as the Co-Director of the Clinical Operations Unit (COU) of the National Institutes of Health (NIH)-funded Infectious Diseases Clinical Research Consortium (IDCRC) that is working within the COVID-19 Prevention Network (CoVPN) to evaluate Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccine candidates in Phase 3 clinical trials, including those produced by Moderna, AstraZeneca, Janssen, Novavax, and Sanofi.

- Dr. Sharon Frey is employed by Saint Louis University (SLU), which has a Vaccine Treatment Evaluation Unit (VTU) that is part of the IDCRC. She is currently serving as the Site PI for the Moderna and Janssen Phase 3 COVID-19 vaccine clinical trials.

- Dr. Paul Hunter owns a small amount of stock in Pfizer and has received a small grant from Pfizer to conduct a quality improvement (QI) project on pneumococcal vaccines.

Given that no specific vaccine products were being recommended during this meeting, all voting ACIP members were permitted to participate in the discussion.

A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the October 30, 2020 ACIP emergency meeting.

Coronavirus Disease 2019 (COVID-19) Vaccines

Introduction

Beth Bell, MD, MPH
ACIP, COVID-19 Vaccine WG Chair
Clinical Professor, Department of Global Health
School of Public Health, University of Washington

Dr. Bell thanked Dr. Romero for his leadership, incredible assistance and support, and vision in the context of the ACIP's work in addressing the COVID-19 pandemic and working on COVID-19 vaccine policy. She then introduced the session for the October 30, 2020 emergency ACIP meeting, which focused on ACIP's continued response to the ongoing pandemic and accelerated vaccine development. She reminded everyone that during the September 22, 2020 meeting, ACIP reviewed the following topics:

- Overview of COVID-19 Vaccine Safety
- Enhanced Vaccine Safety Surveillance
- Vaccine Implementation
- Disparities Among COVID-19 Epidemiology
- Overview of Vaccine Equity and Prioritization Frameworks
- Phase 1 Allocation for COVID-19 Vaccine: WG Considerations

The COVID-19 Vaccine WG continues to meet on a weekly business. The topics this group has covered during October include the following:

- Review of Available Information on Reinfection of COVID-19
- Post-Infection Immunity
- Discussions to Finalize the Outcomes for GRADE (Grading of Recommendation Assessment, Development and Evaluation)
- Modeling Data for Initial Allocation of Vaccine
- Current Epidemiology of COVID-19 in Pregnant Women
- Review of Ethical Principles to Inform Initial Allocation of Vaccine
- Clinical Development Program for Two COVID-19 Vaccines, Including Data From Phase I/II Clinical Trials and Plans for Phase III Clinical Trials
- Further Discussions Regarding COVID-19 Vaccine Allocation

Dr. Bell indicated that during this session, presentations would be provided in the following topic areas:

Vaccine Development & Regulatory
- ❑ Update from VRBPAC meeting
- ❑ NVX-CoV2373 Vaccine Candidate
- ❑ Janssen's SARS-CoV-2 Vaccine Program

Implementation
- ❑ Update on Vaccine Implementation Planning
- ❑ Vaccinate with Confidence

Safety
- ❑ FDA Safety Surveillance Systems
- ❑ Post-Authorization Safety Monitoring Plans

Allocation and Epidemiology
- ❑ Modeling Strategies for the Initial Allocation of COVID-19 Vaccines
- ❑ Updates to Immunity and Epidemiology to Inform COVID-19 Vaccine Policy
- ❑ Ethical Principles for Early Vaccine Allocation

WG Interpretation
- ❑ WG Interpretation of Data
- ❑ Policy Questions, Evidence to Recommendation (EtR) Framework, and Outcomes

Dr. Bell reported that over 200 COVID-19 vaccines are currently under development. Within the US, 4 vaccines are in active Phase III clinical trials and 5 are in active Phase I/II clinical trials. In terms of the Phase III clinical trials in the US, AstraZeneca announced the removal of an FDA hold on its AZD1222 vaccine on 10/23/2020 and are resuming Phase III trials. Janssen announced the lifting of its safety pause for its Ad26.COV2.S vaccine on 10/23/2020 and is resuming Phase III trials. The Pfizer/BioNTech BNT162b2 vaccine trial reported having enrolled 42,133 participants as of 10/26/2020. Of these, 35,771 participants have received their second vaccination. In addition, Pfizer/BioNTech reported that approximately 30% of US participants enrolled have "diverse backgrounds." Enrollment is complete for Moderna's messenger ribonucleic acid (mRNA)-1273 vaccine. As of 10/22/2020, approximately 30,000 participants have been enrolled and 25,654 of those participants have received their second vaccination.

In terms of the distribution of demographic characteristics of the participants in Moderna's Phase III clinical trials in the US taken from their website, 63% of participants are White, 20% are Hispanic/Latinx, 10% are Black/African American, 4% are Asian, and 3% are Other Racial/Ethnic Groups. Approximately 8000 participants are ≥65 years of age. Of the participants, 22% are healthcare personnel (HCP) and 27% report living with comorbidities (e.g., diabetes, cardiac disease, lung disease, and obesity). Dr. Bell shared a table of the COVID-19 vaccines in human clinical trials in and outside of the US, pointing out that there are additional inactivated vaccines in Phase I/II/III, 10 protein subunit vaccines candidates in Phase I/II, 7 non-replicating viral vector vaccine candidates in Phase I/II, and 7 RNA vaccine candidates in Phase I/II.

Food and Drug Administration (FDA) Update

Doran Fink, MD, PhD
Deputy Director-Clinical, Division of Vaccines and Related Products Applications
Center for Biologics Evaluation and Research, Food and Drug Administration

Dr. Fink provided an overview of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on October 22, 2020 during this session. He first reminded everyone that the VRBPAC reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products. VRBPAC is a committee of experts external to FDA that provides input upon request by FDA on certain regulatory actions (e.g., licensure of new vaccines) and on more general topics critical to advancing regulatory science. VRBPAC recommendations are non-binding, but are usually followed by FDA.
The VRBPAC met on October 22, 2020 for a general discussion of the development, authorization, and/or licensure of vaccines to prevent COVID-19. This was an open meeting with a live webcast that was accessible to the public. There was no discussion of specific COVID-19 vaccine candidates or any votes on recommendations. The agenda included the following topics:

- ❑ FDA Introduction and Presentation of Discussion Points
- ❑ Epidemiology, Virology, and Clinical Features of COVID-19 (CDC)
- ❑ NIH Activities in the Development of Vaccines Against COVID-19
- ❑ Biomedical Advanced Research and Development Authority (BARDA) Activities in the Development of Vaccines Against COVID-19
- ❑ CDC Plans for Safety/Effectiveness Monitoring & Evaluation During Emergency Use Authorization (EUA) Use and Post-Licensure FDA Surveillance Systems and Plans for Post-Marketing/Post-Authorization Evaluation
- ❑ Operational Aspects of COVID-19 Vaccine Distribution and Tracking (CDC)
- ❑ COVID-19 Vaccine Confidence (Reagan-Udall Foundation)
- ❑ Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19: Manufacturing and Clinical Considerations (FDA)
- ❑ Open Public Hearing
- ❑ Committee Discussion and Recommendations

During that VRBPAC meeting, the FDA explained the considerations for manufacturing and clinical information needed to support licensure for EUA of COVID-19 vaccines, as described in two recent FDA guidance documents. The purpose of the guidance documents is to provide reassurance that FDA will rely on sound science, established regulatory standards, and a transparent process for evaluating COVID-19 vaccine candidates.

Dr. Fink first explained the clinical considerations for an EUA in detail, which are summarized as follows:

- ❑ EUA for a COVID-19 vaccine may be requested to allow for the vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people, following a planned interim analysis in an ongoing Phase 3 trial

- ❑ A favorable benefit/risk determination to support issuance of an EUA in this scenario would require the following, in addition to adequate manufacturing information:

- Efficacy data showing protection against SARS-CoV-2 infection or disease with a point estimate of least 50% versus a placebo comparator and an appropriately alpha-adjusted confidence interval lower bound >30%
- At least half of Phase 3 study subjects followed for both safety and efficacy for at least 2 months following completion of the full vaccination regimen
- Safety data from throughout clinical development (including well over 3,000 Phase 3 vaccine recipients) to evaluate reactogenicity, serious adverse events (SAEs), and AEs of special interest (AESI)
- Sufficient cases of severe COVID-19 to assess for signals of enhanced disease

- Reasons for a median follow-up of at least 2 months after completion of the full vaccination regimen to support issuance of an EUA for a COVID-19 vaccine:

  - Allows time for potential immune-mediated adverse reactions to be evaluated (uncommon but clinically significant immune-mediated adverse reactions to preventive vaccines generally have onset within 6 weeks following vaccination)
  - Ensures that vaccine efficacy is assessed during the time period when adaptive/memory immune responses (rather than innate responses) are mediating protection
  - Allows for early assessment of waning protection and signals of enhanced disease

- Following a successful efficacy analysis that supports issuance of an EUA, further evaluation of a COVID-19 vaccine would be needed:

  - For ongoing benefit/risk assessments for continuation of the EUA
  - To accrue additional data to support licensure and/or to inform labeling

- Continued evaluation of a COVID-19 vaccine made available under EUA would include:

  - Longer-term follow-up for safety, including in larger numbers of vaccine recipients and in populations with lower representation in clinical trials
  - More precise estimation of vaccine effectiveness
  - More robust assessment of effectiveness against specific aspects of SARS-CoV-2 infection or disease
  - Characterization of duration of protection
  - Investigation of immune biomarkers that might predict protection
  - Ongoing monitoring for signals of enhanced disease

- Issuance of an EUA for a COVID-19 vaccine would be contingent upon the ability to conduct further vaccine evaluation through a combination of:

  - Active follow-up of vaccine recipients under the EUA
  - Passive monitoring for clinically significant adverse reactions using established reporting mechanisms (e.g., VAERS)
  - Observational studies, including those that leverage healthcare claims databases
  - Continuation of blinded, placebo-controlled follow-up in ongoing clinical trials for as long as is feasible and strategies to handle loss of follow-up

- ❑ FDA does not consider issuance of an EUA for a COVID-19 vaccine to necessitate immediate unblinding of ongoing clinical trials or offering vaccine to all placebo recipients
    - ➢ Trial participants may choose to withdraw from follow-up for any reason, including to receive vaccine made available under EUA

A number of specific topics were posed during the meeting for VRBPAC discussion, including the following:

- ❑ Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.
- ❑ Please discuss strategies for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- ❑ Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to further evaluate safety, effectiveness, and immune markers of protection and evaluate the safety and effectiveness in specific populations.

To summarize the discussion from the meeting, VRBPAC expressed concerns about public vaccine confidence, consistent with those described in the Reagan-Udall Foundation presentation. Hesitancy around acceptance and use of COVID-19 vaccines will continue to be driven by speed of vaccine development and the perception of uncertainty and limitations of data. Issues with COVID-19 vaccine deployment could adversely impact public confidence in vaccines in general. Regulatory actions to make COVID-19 vaccines widely available therefore need to be transparent, effectively communicated, and above all supported by adequate data.

There was broad agreement that data to support issuance of an EUA for a COVID-19 vaccine should not be less than the standards outlined by the October 2020 FDA guidance. Some VRBPAC members expressed concerns that a median follow-up of 2 months after completion of the vaccination regimen would not be sufficient to support an EUA for rapid and widespread deployment, in particular for vaccines manufactured for novel platforms. A successful interim efficacy analysis, with more limited COVID-19 cases and wider confidence intervals compared to a final analysis, would not be sufficient to support an EUA for rapid and widespread deployment. Other VRBPAC members considered 2 months medium follow-up to be sufficient to support issuance of an EUA. They felt that rare AEs and waning immunity could be monitored by surveillance during vaccine use under an EUA.

Some VRBPAC members were concerned about COVID-19 of any severity as the primary efficacy endpoint in current Phase 3 trials, given that there may be limited information on severe disease. FDA and some VRBPAC members discussed that primary endpoints were selected based on feasibility and prior experience with preventive vaccines. Vaccines are typically approved based on data showing prevention of laboratory-confirmed disease, regardless of severity. Experience supports that vaccine effectiveness increases with more specific (e.g., more severe) case definitions. While analyses to support EUA will include some information on severe disease, insisting on an adequately powered analyses of severe disease (which has a lower incidence than less severe disease) could delay the availability of an impactful vaccine.

VRBPAC members expressed concern about clinical trial recruitment of, and accrual of data, in the populations most affected by COVID-19 (e.g., racial and ethnic minorities, elderly individuals, and individuals with medical comorbidities). FDA reported that published guidance and advice to COVID-19 vaccine manufacturers has advocated for inclusion of these populations in trials. While there is no regulatory mechanism for mandating trial recruitment, vaccine manufacturers have been publicizing enrollment demographics for their trials. This is important given that demographic and medical history data from trial participants will be considered in regulatory decisions and will be reflected in vaccine labeling to inform HCP and vaccine recipients. Vaccine manufacturers have been publicizing enrollment demographics for their trials.

There also was discussion regarding considerations for pediatric development and data to support use in pediatric populations, particularly with respect to careful evaluation of immune-mediated reactions or enhanced disease and immunobridging approaches. There is a need for safety assessments that include careful evaluation for immune-mediated reactions or enhanced disease (e.g., MIS-C/MIS-A) to support benefit/risk considerations for pediatric enrollment in clinical trials and for vaccine authorization or approval in pediatric age groups. Immunobridging approaches to infer vaccine effectiveness in pediatric populations will benefit from an evolving understanding of natural and vaccine-elicited immunity.

There was broad agreement among VRBPAC members that blinded, placebo-controlled follow-up in ongoing trials should continue for as long as is feasible, including after an EUA. Concern was expressed that if a COVID-19 vaccine were widely deployed under EUA based on limited data, it could harm further accrual of critical data from placebo-controlled follow-up. There was agreement with the need for robust strategies for vaccine evaluation following licensure or EUA to complement, and replace once it becomes infeasible, placebo-controlled follow-up.

VRBPAC raised questions about expanded access as an alternative to EUA. FDA explained that expanded access is another regulatory mechanism for making investigational products to address serious diseases available outside of clinical trials. An expanded access treatment protocol could be considered to allow for deployment of a COVID-19 vaccine. It is important to note that the benefit/risks considerations are similar to EUA, other considerations such as planning and implementation differ from EUA, and an expanded access treatment protocol would be conducted under Investigational New Drug (IND) regulations that require informed consent, Institutional Review Board (IRB) oversight, and investigator responsibilities for vaccine providers.

In terms of next steps, FDA will consider the October 22nd VRBPAC feedback provided in continuing to balance the public health goal of safe and effective vaccines to address the COVID-19 pandemic and the obligation to ensure that authorization or approval of any COVID-19 vaccine complies with regulatory requirements for sufficient safety, effectiveness, and manufacturing information to support favorable benefit/risk for vaccine recipients. The VRBPAC will be reconvened prior to any FDA action to approve or issue an EUA for a COVID-19 vaccine to evaluate and discuss data submitted in support of the licensure application/EUA request and vote on recommendations as to whether the data support vaccine licensure/proposed use of the vaccine under EUA.

Discussion Points

Dr. Romero asked what the considerations are for unblinding individuals who withdraw from a study with regard to whether they receive placebo or vaccine.

Dr. Fink indicated that FDA cannot mandate that any vaccine manufacturer conducting a clinical trial unblind or not unblind the trial, or that unblind or not unblind any individual participant. This is a matter of ethical and scientific consideration and FDA would like the vaccine manufacturers who are conducting a trials to think very carefully about balancing the ethical and scientific implications of their decision to unblind.

Dr. Ault asked whether there is a video archive of the VRBPAC meeting that is available to the public, and for the expanded access whether there ever has been one of this order of magnitude with millions of doses of vaccine.

Dr. Fink indicated that there is a YouTube video recording of the VRBPAC available at the following link: https://www.youtube.com/watch?v=1XTiL9rUpkg&feature=youtu.be. There are recent examples of expanded access treatment protocols that have been used to provide vaccine to thousands of individuals or tens of thousands of individuals. One example was to address the meningococcal B disease outbreak on several college campuses prior to FDA licensure of the meningococcal group B vaccines. More recently, there has been an expanded access protocol for the non-US licensed yellow fever (YF) vaccine Stamaril® due to a shortage of the US-licensed YF vaccine YF-VAX® in travel clinics across the US. Having said that, these examples pertain to thousands and tens of thousands of vaccine recipients versus millions of vaccine recipients. The IND requirements for an expanded access treatment protocol certainly would add some complexities and feasibility concerns to using that regulatory mechanism.

Dr. Frey pointed out that safety may be a major driving factor for vaccine hesitancy. There have been two very nice examples of pause or halting rules to the studies that have occurred already. While this may be novel to the general community, it is actually a positive thing when people pause a study or hold a study from further enrollment until there are discussions and people are comfortable with the decision-making. She asked whether all of the studies being initiated are being scrutinized with the same rigorous standards of safety.

Dr. Fink responded that all of the Phase 3 studies underway have very close oversight from a DSMB that regularly reviews safety data and meets on an ad hoc basis to review, discuss, and consider whether any change in trial conduct is warranted following a safety signal, such as a SAE for which causal relationship to the study vaccine cannot be excluded. Furthermore, some studies in addition to the DSMB oversight have pre-specified study pausing rules that are triggered based on certain safety events.

Ms. McNally requested additional background on expanded access and how it differs from the traditional FDA approval process and the EUA, how a person who wanted to obtain a COVID-19 vaccine would go about receiving it under expanded access, and whether the Reagan-Udall Foundation had any discussions with consumers regarding expanded access during its listening session.

Dr. Fink clarified that expanded access is not an approval process. The only approval process is licensure. There are several regulatory mechanisms for making an investigational product, including investigational vaccines, outside of clinical trials. An EUA is one of those mechanisms and it is dependent upon declaration of a public health emergency, such as COVID-19.

Expanded access does not require a declaration of a public health emergency, but it does have additional requirements for use of the investigational product as compared with an EUA. Expanded access is conducted under the IND regulations and can be of a range of sizes spanning from just 1 patient to hundreds or thousands of patients depending upon the need and data available to support its use. An idea was raised by the VRBPAC about use of COVID-19 vaccine under expanded access, and the FDA is in the process of considering whether this would be an appropriate mechanism for deployment of a COVID vaccine. If that is considered, the vaccine manufacturer that has an active IND on file with the FDA would submit a protocol for use of the vaccine under expanded access regulations and potentially would work with other governing agencies, as was the case with the YF vaccine expanded access experience, to organize and implement the expanded access protocol. In terms of the Reagan-Udall Foundation, this was a question that was raised during the end of a VRBPAC meeting and he did not think that expanded access was addressed by the foundation's efforts.

Dr. Lee expressed gratitude for all of the work FDA and VRBPAC have done to get them to this place. She asked how often FDA anticipates the continuing evaluations of COVID-19 vaccines data under an EUA to occur, and whether there have been discussions around potential thresholds that would change decisions as data continue to accumulate. In terms of Dr. Fink's mention that an EUA would be contingent on follow-up on safety and effectiveness and specifically observational studies that leverage healthcare claims databases, she wondered whether there are plans to use Sentinal as one of the options for that versus manufacturer led studies.

Dr. Fink responded that continued evaluation of vaccine following deployment under either an EUA or licensure would include assessments that are made at scheduled intervals, as well as continuous assessments that would include passive reporting as well as mechanisms such as rapid-cycle analyses (RCA). He noted that further information would be provided about some of these systems later in the day in a presentation on FDA and CDC plans for post-licensure or post-authorization surveillance. He clarified that observational studies, including those that leverage healthcare claims data, would not necessarily in and of themselves be a requirement for an EUA, but the FDA does see these as a very important part of continued follow-up during deployment.

Dr. Bernstein expressed appreciation for Dr. Fink's concise and detailed summary of VRBPAC's ongoing extraordinary and challenging work. Regarding the clinical considerations for EUA and why 2 months was chosen, he recalled that Dr. Fink mentioned that the median time was 2 months. He requested clarity about whether it was the median or at least 2 months for all subjects.

Dr. Fink clarified that it is a median. At least half of the subjects will have at least 2 months of follow-up. It is expected that a high proportion of enrolled subjects will have at least 1 month of follow-up. They do recognize that the trials will continue to enroll, so it will not be feasible to demand that all subjects have a certain amount of follow-up to enable regulatory action and allow for deployment of the vaccine, especially in the face of very convincing efficacy data. The Phase 3 trials that are currently underway have enrolled very large numbers of subjects very rapidly, so they do not expect there to be any issues with the proportion of subjects who have safety follow-up.

Dr. Sanchez asked what the timeline for FDA approval is after VRBPAC makes a recommendation for a vaccine, and whether expanded access would pertain to a vaccine studied in persons 18 years of age being expanded to others like the pediatric population.

Dr. Fink replied that for a vaccine to be made available under expanded access to a large number of recipients, there needs to be sufficient data to support a favorable benefit-risk determination in a population. He would not envision a scenario in which a vaccine would be made available to pediatric populations outside of anything other than a clinical trial without data to support favorable benefit-risk in the pediatric population. That would include safety and immunogenicity data to at least support effectiveness specifically in pediatric populations of the age groups that would be under consideration. Expanded access would not be a mechanism for offering vaccine to pediatric populations outside of a clinical trial in the absence of data in pediatric populations. Regarding timing, FDA expects EUA reviews and reviews of licensure applications to be fairly expedited to address the needs of the ongoing pandemic. While he could not provide a definitive answer about how many days or weeks between a VRBPAC meeting and vote that includes recommendations to authorize or include the vaccine and when that vaccine is actually made available through FDA action, it will be as expediently and as quickly as possible.

NVX-CoV2373 Vaccine Candidate

Filip Dubovsky MD, MPH
Chief Medical Officer
Novavax

Dr. Dubovsky reported on the Novavax NVX-CoV2373 vaccine candidate in terms of vaccine design, the non-human primate (NHP) protection study, Phase 1 Day 35 safety and immunogenicity data, Phase 2 Dose 1 and Dose 2 reactogenicity data, and plans for Phase 3. In terms of the NVX-CoV2373 vaccine design, this is a baculovirus-expressed recombinant protein. This is a full-length spike, including transmembrane domain and the usual 2P mutations. It self-assembles into a native conformation trimer and is further processed into a stable nanoparticle. The adjuvant is saponin-based and is a natural product from the bark of a tree. It is processed into purified form into cage-like structures. The antigen and adjuvant are co-administered into a vial of ready-to-use liquid that is stable at 2^0-8^0 C.

In a protection study sponsored by Operation Warp Speed (OWS) that was conducted at Texas Biomedical Research Institute, rhesus macaques were vaccinated at Day 0 and Day 21 and were then challenged with 10^6 wild-type virus at Day 38. Subgenomic RNA was detected on Day 2 and Day 4 in the lower airway in the placebo group, which indicates that viral replication was ongoing. For both dose levels that were taken into clinical study, no RNA was detected indicating that no replication was detected. In the upper airway, replication was seen on days 2, 4, and 7 in the placebo group. No viral replication was detected in the vaccine groups. This is consistent with the other data collected from other NHP studies, as well as in small animals.

Regarding the clinical development plan, the first human Phase 1 study was conducted in Australia with 131 subjects 18 to 59 years of age. Based on the results from this study, Novavax launched 3 studies. One was a Phase 2 study in the US and Australia in 1288 subjects 18 to 84 years of age. At the same time, a Phase 2b study was launched in South Africa that was recently expanded to 4400 subjects and includes a small human immunodeficiency virus (HIV)-positive cohort. A 15,000 Phase 3 study was started in the United Kingdom (UK), which includes a small sub-study with inactivate influenza vaccine (IIV) co-administration to ensure that there are no safety or immunogenicity issues with that. Based on confirmation of the dose and safety from the Phase 2 study, Novavax is launching a large Phase 3 study in the US and Mexico with over 30,000 individuals.

The Phase 1 study, which was published in September 2020, is fully enrolled and safety and immunogenicity follow-up is ongoing. This is the study of the 131 subjects ages 18 to 59 years of age. There were 5 dose groups: placebo, 25 µg with no adjuvant given twice, 25 µg with adjuvant given twice, a high-dose adjuvant group, and a group that had 2 doses of 5 µg and 2 doses of 25 µg given twice. The study sites, investigators, contract research organization (CRO), and participants are blinded to individual vaccine/placebo allocation. Day 35 (14 days after Dose 2) safety and immunogenicity data, which is the basis of the publication, were reviewed by an independent Safety Monitoring Committee (SMC) and submitted to the FDA in advance of the Phase 2 study. The Day 35 safety summary for NVX-CoV2373 is consistent with previous nanoparticle vaccine with Matrix-M1. No SAEs were identified for NVX-CoV2373.There were no AESIs, including potentially immune-mediated medical condition AESIs, and no confirmed COVID-19 AESIs. All AEs were mild and moderate and were balanced in active arms.

In terms of the local reactogenicity symptoms collected 7 days after each dose, the majority of symptoms were none or mild. Pain and tenderness were the most commonly reported. The mean duration was less than 2 days for each of these events. Regarding reactogenicity symptoms, the majority of subjects reported none or mild and the mean duration was less than 2 days for both local and systemic reactogenicity symptoms. There were more systemic symptoms after Dose 2 versus Dose 1 in the placebo and active groups. The most common symptoms reported were headache, fatigue, and myalgia. Once again, the mean duration was less than 2 days.

Regarding the anti-spike immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) kinetics, after 2 doses delivered on Day 0 and Day 21 there was pretty much no response. After the 2 doses with no adjuvant, there was a bump after Dose 2 that was stable throughout the observation period. The single dose of adjuvanted vaccine had a nice response after dose 1, which stabilized. There was a nice bump after Dose 2 that remained at high levels. From this data, Novavax concluded that adjuvanted vaccine is better than non-adjuvanted vaccine and furthermore, the 2 doses are superior to a single dose. There is a large dose-sparing effect with the adjuvant, because the 5 µg and 25 µg dose groups are comparable.

Regarding the peak immune responses on Day 35 anti-S IgG ELISA and 100% wild-type neutralization responses, the 2 dose groups with adjuvants performed quite well in terms of the IgG. Convalescent sera was donated by Dr. Pedro A. Piedra of Baylor College of Medicine. This is an un-curated panel serum that has the same samples on both the IgG and the neutralization responses. Seroconversion of 100% was achieved for IgG and neutralization. Furthermore, in a post-hoc analysis IgG was 5-fold to 7-fold higher than for convalescent sera and 3- to 4-fold for the neutralization. In addition, the confidence intervals do not overlap. To determine the quality of the immune response, a correlation between the neutralization response and the IgG response was assessed. For the Baylor convalescent serum, there is a nice correlation between IgG and neutralization. This indicates that when people get sick with wild-type infection, they generate antibodies and those antibodies neutralize the virus. For the 25 µg group with no adjuvant, the correlation breaks down. The adjuvanted dose groups recapitulated the pattern seen with wild-type seroconversion and the correlation is tight again. To Novavax, this indicated that the Matric-M1 adjuvant is important in generating desired immune responses, with a functional immune response against a broad range of antibody titer. This is thought to be important from a safety perspective because some people have postulated that antibody does not neutralize and may lead to enhanced illness in the future.

Turning to the intracellular immune response among the placebo, 2-dose 5 µg + Matrix-M, and 2-dose 25 µg + Matrix-M groups. In the placebo group, the Th1 immune response was flat. However, a signal was detected for IL2, IFNg, and TNFa in the other two groups. On the Th2 cytokines, they probed for IL5 and IL13 and found a small increase in those cytokines. This recapitulates what they have seen in small animal models, indicating that this adjuvanted platform is capable of generating a Th1-bias immune response. This is consistent with previous evaluation of this platform in humans. Looking at polyfunctional CD4 T-cells, there was a relatively large proportion of CD4 cells that generate double and triple cytokines for both dose groups, especially when compared to the double cytokines for the Th2 analysis. The beginning strategy was to look for CD45+ CCR7- CD4 cells. They postulated that this would help with the memory response going into the future.

Novavax Phase 1 study conclusions are that reactogenicity and safety profiles are reassuring for both the 5 µg and 25 µg dose groups when formulated with Matrix-M1 adjuvant. In terms of immunogenicity, the Matrix-M1 adjuvant is required to induce an optimal functional immune response, 2 doses of vaccine administered 21 days apart are superior to a single dose, 5 µg and 25 µg induce comparable immune responses when formulated with Matrix-M1, and Matrix-M1 induces a Th1 biased immune response with high levels of neutralizing antibody. The safety and immunogenicity profile of both 5 µg and 25 µg formulated with Matrix-M1 and administered on Day 0, 21 is acceptable for further clinical evaluation.

The Phase 2 study of 1288 adults ages 18 to 84 in the US and Australia is fully enrolled, Dose 2 has been administered, and safety and immunogenicity follow-up is ongoing. The study sites, investigators, CRO, and participants are blinded to individual vaccine/placebo allocation. Reactogenicity data were reviewed by the SMC and the FDA in advance of the Phase 3 study. Regarding local reactogenicity events in 2 Dose adjuvanted groups, pain and tenderness were reported most frequently. Increased rates were seen in the adjuvanted groups, especially after Dose 2, and reactogenicity was attenuated in adults ≥60 years of age. In terms of local reactogenicity events in the 2-dose adjuvanted groups compared to placebo, pain and tenderness were reported most frequently. Increased rates are seen in adjuvanted groups, especially after Dose 2. Reactogenicity events were attenuated in adults >60 years of age, which was exactly as expected based on previous experience. The aggregated terms were the same as previously (e.g., pain, tenderness, erythema, swelling). In terms of systemic reactogenicity events in the 2-dose adjuvanted groups, fatigue, headache, and myalgia were reported most frequently. Increased rates were seen in the adjuvanted groups, especially after Dose 2. Reactogenicity was attenuated in adults >60 years of age.

The Phase 3 pivotal safety and efficacy study will be conducted in the United States (US) and Mexico. This is a randomized, observer-blinded, placebo-controlled study in which participants are randomized 2:1 to receive 5 µg + Matrix-M1 vaccine or placebo with 2 doses 0.5ml administered on Day 0 and Day 21. The study will include up to 30,000 adults >18 years of age across the US and Mexico. The plan is to target at least 25% participants ≥ 65 years of age, at least 25% with high-risk co-morbidities, at least 15% black/African Americans, 10% to 20% LatinX, and 1% to 2% Native Americans. This is an endpoint-driven study with efficacy evaluations at 72, 108, and 144 cases. The primary endpoint is prevention of PCR-confirmed mild, moderate, or severe COVID-19 illness occurring 7 days after Dose 2 in baseline seronegative adults. Safety follow-up will be conducted through 2 years.

In summary, the NVX-CoV2373 vaccine candidate is based on the baculovirus/nanoparticle platform technology. The safety database includes over 12,100 nanoparticle vaccinees (RSV, influenza, Ebola) and over 2,500 nanoparticle vaccinees adjuvanted with Matrix-M1. Vaccine presentation will be in 10-dose vials with transportation and storage at 2^0-8^0 C. The vaccine is preservative-free and no admixing or reconstitution is required. A 0.5 ml dose is administered intramuscularly 21 days apart. The preliminary safety profile is reassuring with a favorable reactogenicity profile. A peak immune response is observed 14 days after Dose 2. There is a favorable immunologic phenotype, with a robust neutralizing antibody response and polyfunctional CD4+ Th1-biased cellular immune response. Efficacy evaluation is ongoing.

Discussion Points

Dr. Romero requested further information about when in the patients' illness the convalescent serum was obtained. In addition, he asked whether the protein is locked into the pre-binding or post-binding conformation in the vaccine.

Dr. Dubovsky indicated that the details of the convalescent serum are highlighted in the publication. In general, they were a median of 19 days after diagnosis. A small number were hospitalized, a small number were asymptomatic, and the vast majority were those who were considered to have moderate illness who presented to the emergency department (ED) for care, which is where they were recruited. The full-length protein has the stabilizing 2P mutations, which locks it into conformation.

Dr. Glenn added that it is in the pre-binding conformation and that the structure was published recently in *Science*.

Dr. Frey asked what the thinking was about the mechanism that would cause the AEs or local and systemic events post-vaccination to increase after the second dose, whether both vaccines are being given in the same arm, and whether that and/or the use of the adjuvant might play a role in this.

Dr. Dubovsky indicated that they recommend, but do not mandate, that the vaccine be given in alternate arms so that they can follow the local events. It is very typical for AEs to increase after Dose 2 because the immune response also bumps after Dose 2. These local reactogenicity events are thought to be related to the immune responses generated with vaccination, which is consistent with what has been seen previously and with what was seen in the Novavax Phase 3 influenza program. The unadjuvanted groups had a lower level of reactogenicity.

Regarding the Phase 3 planned trial, Dr. Szilagyi inquired as to what proportion of the 30,000 adults will be in the US.

Dr. Dunkle indicated that the estimate is that roughly 10% of the population will be in Mexico and 90% will be in the US.

Dr. Lee observed that with all of these vaccines, it seemed that local and systemic reactions were extremely common and should be anticipated regardless of COVID vaccine type. She recalled that one of Dr. Dubovsky's slides showed a Grade 4 reaction for which she requested further information.

Dr. Dubovsky said that they think the Grade 4 reaction was a fever of $>40^0$ that occurred in the placebo group. They are blinded to the individual, but that is what was indicated by the SMC.

Given that saline is not believed to cause high fevers, the current opinion is that this is likely to be a data entry error. These are uncleaned live data, so this may be resolved as the cleaning progresses. Based on the reactogenicity profile. This is quite favorable as there was not a fever signal in the Phase 1 study at all. This is comparable to other licensed vaccines.

Dr. Fryhofer (AMA) observed that on Slides 18 and 19, reactogenicity is noted as being attenuated in adults 60 years of age and older and she wondered whether that was an indication that this vaccine may not work as well in older individuals.
Dr. Dubovsky indicated that this is a response that is seen with most vaccines. It is known that immune responses are attenuated in older adults, given that immunosenescence is part of what occurs in life and the impact on efficacy is unknown. The immunogenicity data are not yet available to them, but may help to understand what is going on.

Dr. Whitney-Williams (NMA) noticed in the Phase 2 trials that there were 240 HIV+ patients and wondered whether there are any plans to include that group in the Phase 3 trials.
Dr. Dubovsky indicated that the 240 HIV+ patients are in the South African study where HIV rates are extremely high, so part of the discussion with the regulators and the society groups there was the need to include those because that is the population that will be vaccinated in the future. Once safety and immunogenicity in that population are understood, they will be better positioned to make future plans. Those cohorts are being vaccinated currently, so there should be data soon.

Dr. Dunkle added that the Phase 3 trial does not exclude stable HIV-infected individuals.

Dr. Ault asked whether Novavax has any plans for Phase 2 or 3 trial in pregnancy. They recently published results in the *New England Journal of Medicine* (*NEJM*) for a respiratory syncytial virus (RSV) vaccine that uses the same platform in pregnant women.

Dr. Dubovsky indicated that they are in discussions with regulatory agencies about how to best go forward. The data that were published were not with the Matrix adjuvant, so there are other considerations that need to be assessed. They are concluding their development and reproductive toxicology (DART) study and will base decisions on that.

Janssen Investigational COVID-19 Vaccine Program

Jerald Sadoff, MD
Lead Clinical Investigator
Senior Advisor, Clinical Development
Janssen Infectious Diseases and Vaccines

Dr. Sadoff presented an update on Janssen's investigational COVID-19 vaccine program. The foundation of Janssen's investigational COVID-19 vaccine is its proprietary AdVac® Technology Platform. Janssen uses a replication incompetent human adenovirus 26 (Ad26), which expresses the target antigen. They have taken out a region of the virus so that it cannot replicate. It invades the cells and makes the transgene and its own antigens, but it cannot assemble them into a replicating virus. The antigen is not on the surface of the virus. It is only on the surface of the cells that the virus enters and is membrane bound. This vaccine has induced very good humoral and cellular antibody responses against structural proteins with neutralizing activity and/or other unique functionalities, as well as cellular CD4-T cell responses with a Th1 signature and CD8 T-cell responses. There has been no sign of vaccine-associated enhanced respiratory disease (ERD) in pre-clinical models after breakthrough infection. Janssen

has extensive clinical experience with its Ad26-based vaccines, with over 110,000 participants vaccinated. These Ad26-based vaccines have shown to have a favorable safety and tolerability profile in the populations studied to date. On July 1, 2020, Johnson & Johnson received approval from the European Medicines Agency (EMA) for Janssen's Ad26-based preventive Ebola vaccine.

Janssen took the approach of looking at a number of vaccine constructs because of instability problems that were noted before, and of looking at theoretical considerations. Janssen has had a lot of experience with its RSV and HIV programs on how to construct stable expression vectors, so they assessed stabilization, signal peptide, expression of antigen, manufacturability of vaccine, and immunogenicity in pre-clinical animal models. Based on that, they were able to find a vaccine candidate that was clearly superior in terms of its immunogenicity and the other considerations, Ad26.COV2.S. It encodes a full length membrane-bound S-protein with stabilization mutations and a native initial signal sequence. After a single dose of Ad26.COV2.S, they were able to show protection in the lower and upper respiratory tract of SARS-CoV-2 challenged NHP. In other data, they have done down dosing studies and have shown that even when the vaccine is reduced, they have still been able to get substantial protection. This leads to the belief that the immunogenicity achieved will be protective.

Based on that, Janssen began a Phase 1/2a study, COV1001, to assess the safety, reactogenicity, and immunogenicity of this investigational vaccine in healthy adults 18 to 55 years of age (Cohort 1; N=400) and adults 65 years of age and older (Cohort 3; N=375) at 2 different dose levels ($5x10^{10}$ viral particles and $1x10^{11}$ viral particles) administered as a 1 dose or 2 dose regimen. They have the data on the 1 dose regimen and are currently accumulating the data on the 2 dose, so Dr. Sadoff focused mainly on the data after 1 dose. Cohort 2 is comprised of 270 participants 18 to 55 years of age in whom duration of the immune response, the ability to boost at various times if necessary, and anamnestic responses will be examined. There were very good seroconversion rates with the ELISA at 99% at a slightly lower dose and a similar 99% with very reasonable geometric mean titers (GMTs) for neutralizing antibody levels. There were very few differences between the elderly and younger adults in terms of immune response, and there was a rise between Day 15 and Day 29. The wild-type virus neutralizing antibodies (wtVNA) showed very good response rates as well of 92% at both doses, with a similar response in the elderly with comparable GMTs and overlaps. The GMTs rose quicker for the neutralizing antibodies, with a very good response at Day 14. Therefore, in the Phase 3 trial, they will start counting cases 2 weeks after single dose immunization. From this data, it is clear that there are no differences in immunogenicity between the younger and elderly groups in terms of ELISA or wtVNA, and they seem to be at the flat part of the dose response curve, which allows them to pick the lower dose as a single dose regimen going forward.

There was also a very good T-cell response in both groups of 76% and 83% for the 2 different doses in the younger age group and slightly lower in the older age group at 60% and 67%. These are Th1 responses measured by IFNg and/or IL-2. Only 2 individuals responded with Th2 and the rest were completely negative. The ratio in those 2 between the Th1 and Th2 was 28.9 and 20.2. Clearly, a Th1-type response dominated in both younger adults and the elderly with practically no Th2 response at all. With this vector, they also are able to induce fairly high percentages of CD8 T-cell functional responses that express gamma interferon and may play a role in protection as well, although they have yet to prove that. The CD8 responses are 51% and 65% in the younger age group and slightly lower at 36% and 24% in the older age group, which reflects a fairly high percentage of CD8 T-cell responses. They have a stringent test for discriminating between background and the higher responses compared to some other techniques that have been used, so these GMTs might be somewhat lower than normally seen.

This vaccine does cause some systemic AEs based on blinded data between the groups. Among the 402 subjects in Cohort 1, approximately 50% to 60% overall had systemic AEs. All were transient and lasted no more than 1 to 2 days before resolving completely. In terms of pyrexia, there was some fever in Cohort 1 that was considered Grade 3. These were very responsive to anti-pyrectics and they did not judge that any-pyrectics needed to be used prophylactically. In Cohort 3, there were far fewer systemic reactions and fever rates were very low with no Grade 3 fevers. Once again, reactogenicity was much lower in the older cohort than the younger cohort but the immunogenicity seemed comparable. Based on this, Janssen designed a Phase 3 efficacy trial, COV3001.

COV3001 is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study evaluating the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19. The primary endpoint is moderate to severe illness. The study is being conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the US with a target of about 50% of the subjects being in the US. From the beginning, there has been a plan to enroll a diverse population. This study does not have a fixed stop interim analysis. A continuous, sequential monitoring technique is used for safety and efficacy instead. This study is being conducted in healthy adults 18 years of age and above. The estimated enrollment is 60,000 and participants will receive a single dose of $5x10^{10}$ of Ad26.COV2.S or placebo. The endpoints are the number of participants with first occurrence of molecularly confirmed moderate to severe COVID-19 with seronegative status. The hope is to have a planned follow-up of up to 2 years. Janssen will attempt to follow participants as long as possible regardless of what happens, but there are plans for how analytically to deal with dropouts and people who want to receive the vaccine or knowing whether they received vaccine or placebo.

In terms of the Phase 3 pause, pauses are not uncommon in these types of studies. Janssen is dedicated to the safety of its participants. This particular pause was in an individual who had a safety event and was subject to automatic stopping or pausing rules. This was judged by the DSMB to be appropriate. Janssen evaluated this case extensively with the DSMB and outside experts. It is a complicated case that had multiple potential causes, which have not completely been determined. However, it is believed that there is no relationship between vaccination and the event. In consultation with the FDA, the DSMB agreed to restart the trials. The trial has restarted in the US and enrollment is continuing. Janssen plans to disclose the clinical data for its COVID-19 trials once those data are presented or published at prespecified milestones, and will proactively disclose the regulated trial holds as requested by health authorities. Janssen is planning to deploy this vaccine widely once a signal is reached and there is approval from the FDA and other regulatory agencies. The plan is to put it in a 2R glass vial that has 5 doses per vial, 10 doses per carton, and 8 cartons per shipper. The anticipated storage conditions under an EUA would be storage by Janssen at -20^0 C for up to 2 years, in end-user storage at 2^0 to 8^0 C for up to 3 months, and after first use at 2^0 to 8^0 C for up to 6 hours. More data are evolving with the hope that there will be much longer stability of up to 9 months or longer like Janssen's other vaccines in this platform.

Discussion Points

To respond to Dr. Ault's question regarding pregnancy trials, Dr. Sadoff reported that Janssen is currently conducting studies in its Ebola program in pregnant women. As soon as the toxicology data are available within the next month, they will be planning to start studies in pregnant women because they understand how important it is in this age group to be able to vaccinate.

Dr. Poehling recalled that the data on the AE profile had both doses combined, but she wondered whether there was a plan to assess those data by the dose. She also requested that Dr. Sadoff expand on the discussion that the vast majority of the CD4 T-cells were in the Th1 biased response with the exception of the 1 subject in each age group who had a ratio of Th1/Th2.

Dr. Sadoff said that on the Th1/Th2, they feel that the Th1 bias in the animals models may be strongly indicative of not being the type of pattern seen with ERD based on vaccine. That in combination with antibody is a telling signal of this. If there is a Th2 response with a predominantly Th1-type response in that individual in combination with neutralizing antibody, seems to be the type of immune response that is not associated enhanced disease. In terms of the AE profile, the FDA and other regulatory agencies have seen unblinded data on the limited number of individuals and there is a trend for less reactogenicity in the lower dose group. The plan is to publish these data after they have the second dose safety data from the 2-dose regimen of the ongoing study. They would then publish the safety data in the two groups in terms of the lower and higher dose, which should be available fairly soon. They want to maintain blinding in the Phase 1 study until they have looked at the safety data in the elderly age group at the second dose.

Dr. Szilagyi was interested that the primary outcome in the Phase 3 study is moderate to severe disease in healthy adults and wondered whether that meant that adults with diabetes, cardiac disease, lung disease, obesity, et cetera are excluded. In addition, he asked what percentage of enrollees would be in the US.

Dr. Sadoff indicated that the primary endpoint of the trial is moderate to severe disease. In the safety run in, comorbidities associated with accelerated disease are excluded. That will include the first 2000 participants in the younger age group and the first 2000 in the older age group. They can have other comorbidities. After those first 4000 are enrolled, in each age group separately, the plan is to enroll individuals with all of the comorbidities associated with accelerated disease. Diabetes, hypertension, et cetera will be a major part of the trial. The moderate definition was picked primarily based on their experience with vaccines against respiratory diseases, with vaccines having a better chance of working with more severe disease and a lower level of protection against mild upper respiratory disease. This provides two reasons to go from a moderate to severe endpoint, including a better chance for the vaccine to show its true effectiveness and a more clinically relevant endpoint to some extent. They are looking very carefully at mild disease. They have built 3, 6, and 12 month blood draws into the trial to look for seroconversion against the virus. This is an assay that does not include the S protein so that it is not interfered with by the vaccine to look for asymptomatic disease, so they should have a very good understanding of the vaccine's effectiveness against asymptomatic and all other forms of the disease. Furthermore, they are monitoring every case that they find by collecting nasal swabs and saliva samples every other day until two consecutive samples are negative. Then, they will compare the control to the vaccine group to determine whether the vaccine has an effect on the viral load even in the breakthrough cases. They are doing this because in a recent RSV challenge study conducted, they showed very good effectiveness of the vaccine in the upper respiratory tract to prevent infections. In the breakthrough cases, the number of viral particles and live virus in the recipients of the vaccine were dramatically lower than in the non-vaccine group. So, there may be an effect on transmission even if there is not complete protection in the upper respiratory tract. Therefore, they are measuring that as well. At least 50% of participants are intended to be from the US.

Dr. Kimberlin (AAP Red Book) commended the manufacturers on their rapid yet deliberative approaches to this unprecedented situation and the need for a safe and effective vaccine. Toward that end, transparency as they all have done with their Phase 3 protocols is critically important. He expressed interest in knowing more about the subject halt for the Phase 3 study that was discussed in very broad terms. He thought everyone would benefit more by knowing what system that was related to.

Dr. Sadoff indicated that they have been very transparent about the case with the regulatory agencies, IRBs, and investigators. They have been reluctant to discuss the case in public because the study is still blinded and there is a matter of patient confidentiality that they are very concerned about. At this point, they have not felt it appropriate to disclose the nature of the AE other than to mention that it has been fully discussed with independent consultants, the IRBs, the IBMC, and the regulatory agencies, including the FDA, and that have all agreed that the study should go forward. They will be disclosing as much information as they can in a timely manner when it is appropriate, but fully respecting the patient's confidentiality. That is basically why they have not given information that might lead to speculation, which is not warranted based on the data they have.

Dr. Fryhofer (AMA) asked whether the diversity data of the trial participants will be posted on the website. She expressed the hope that Janssen understands how important transparency is in terms of developing vaccine confidence and asked if they could share the age of the person who had the safety event. In terms of the Th1 T-cell response and vaccine enhanced respiratory problems, she asked whether they are looking at thrombotic or inflammatory responses in the study.

Dr. Sadoff indicated that they will be posting the diversity figures just like the other companies and will be very transparent about that. They agree that transparency is very important for many reasons, so they will disclose as much information as possible that does not in any way violate patient confidentiality. This was a young individual in the younger age group. Thrombotic events are not AESI, but they are assessing this very closely. Every individual in the trial receives an electronic device, pulse oximeter, and thermometer. There is a broad trigger for symptoms that may be anything related to COVID. Patients can immediately begin taking their temperature and oxygenation levels, even for the mildest cases. Any thrombotic event is considered a trigger to immediately call the site or their own doctor. That is electronically triggered automatically when something similar to a thrombotic event occurs.

Dr. Lee noted that in comparison to the convalescent sera, the slide showing the ELISA and the neutralizing antibody assays looked somewhat lower and she wondered whether that was thought to be meaningful in any way. Secondly, she asked how convalescent sera could be standardized and if this is comparable across trials since assumably these all come from different lots and locations.

Dr. Sadoff said that while he did not go into the technical details, on that slide there was a dotted line across the top for the neutralizing antibody. That line represents the upper level quantitation. That means that there were quite a few sera in both the younger and elderly group that could have higher dilutions that had not been measured yet. The GMTs will go up somewhat, but he would say that they were slightly lower than the convalescent sera. He strongly agreed with the need standardization of these sera so that they can directly look from a comparison point of view to learn how relevant it is. They have looked at several panels and have different results from different panels. One was higher and another was lower, so they think that standardization would be useful for the field and would encourage that to occur. As far

as implications, they think that the convalescent sera is probably adequate. It is not yet known how difficult this virus is to neutralize and whether extremely high titers or low titers are needed.

Given the abbreviated timeline, Ms. McNally asked whether Dr. Sadoff could be more specific about the timely manner for disclosing more information about the unexplained illness in the study pause.

Dr. Sadoff indicated that they will be disclosing the database on the dose ranging. The blinded data on doses versus safety and immunogenicity would be done fairly shortly when the second dose evaluations are completed. In terms of evaluating more information about the pause and the case, that will be determined based on confidentiality and unblinding considerations. It may turn out that they will be able to disclose more information in a short period of time, depending on how the case evolves and also whether confidentiality issues may not be an issue at some point.

Dr. O'Leary (PIDS) echoed the sentiments that confidence in these vaccines is so crucially important, transparency takes on extra weight in the current environment. While the confidentiality concerns may very well be justified, from the perspective of the public in a trial of thousands of people, that will be hard to accept. Therefore, he encouraged them to be as transparent as possible.

Dr. Sadoff said that they understand that the dynamic between the two is a very delicate balance that has to be judged and continuously judged. They will take the comments into consideration and appreciate them. There has been some discussion about pediatric trials. Their view is that they would like to start pediatric trials in at least 12 to 18 year olds as soon as possible. Based on the safety and immunogenicity seen in that age group, they will move into the younger age groups as well because they think the pediatric population is very important to consider for vaccination, with safety being a very important consideration.

Dr. Kimberlin (AAP Red Book) asked how many subjects were enrolled before the halting event occurred in one subject.

Dr. Sadoff said he would have to acquire that number and report back. The trial just began in September, so there are not yet many thousands of subjects.

Dr. Maldonado (AAP) voiced very strong support for transparency, especially with regard to pediatrics. While she recognized that children under 18 years of age are considered to be in tier 3, it is critical during this time given the sentiments around vaccines in general and the downstream impact of vaccine confidence in all immunizations that these particular trials will have on pediatric populations and the ability to control preventable infectious diseases. Families want to make sure that their healthy children are going to be protected not only from this devastating illness, but also from others. Every single family and pediatrician must be confident in this vaccine. While it is known that the populations with highest risk are not children, in order to reduce the ultimate goal of reducing transmission and achieving herd immunity, pediatric populations must be engaged. This is a critical group. Pediatricians know how to vaccinate. They do this all of the time and they depend upon the AAP and CDC for their guidance and that guidance is always dependent upon transparency.

Dr. Sadoff stressed that Janssen plans studies in children as soon as possible and very carefully in terms of safety.

COVID-19 Vaccine Implementation Planning Update

Janell Routh, MD, MHS CAPT, USPHS
Deputy, Implementation Planning Unit Vaccine Task Force
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Routh provided an update on vaccine implementation planning. She reminded everyone that the overarching objectives for the COVID-19 vaccination program are to: 1) ensure the safety and effectiveness of COVID-19 vaccines in order to build and maintain confidence in this program; 2) reduce mortality, morbidity, and incidence of COVID-19 disease; 3) help minimize disruption to society and the economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution in a multisectoral fashion. These objectives help to frame the work in which CDC is engaging with its jurisdictional partners in order to confirm their readiness to receive and administer vaccine product. These principles guide the planning efforts and push everyone toward readiness for the implementation of this program.

She shared an illustrative scenario for planning purposes, explaining that it would be adapted based on clinical and manufacturing information and that distribution would adjust as the volume of vaccine doses increases. Final prioritization will be decided by ACIP. On September 16, 2020, CDC published the "COVID-19 Vaccination Program Interim Playbook for Jurisdiction Operations." All 64 jurisdictions returned a COVID-19 vaccination plan and federal agency plans have been received from the Veteran's Affairs (VA), Indian Health Services (IHS), Department of Defense (DoD), Department of State (DOS), and the Bureau of Prisons (BOP). The plans were reviewed by at least three CDC subject matter experts (SMEs) and feedback was returned. Information about plans will be updated on the CDC website.

Not surprisingly, jurisdictional plans showed strengths and challenges. In terms of strengths, jurisdictions have organized their planning around the allocation phasing assumptions, set out clear plans to train and equip providers on the Vaccine Adverse Event Reporting System (VAERS), laid out deep operational details for second dose reminders (e.g., text, email, automated call) some of which are already live. Challenges include ensuring that public health messaging plans and expedited procedures for emergency communications are in place, that all data systems to administer and track vaccine have been identified, and that additional planning is in place to ensure equitable access to vaccine distribution in later phases.

In terms of next steps for vaccine implementation now that the plans have been returned and feedback incorporated, the goal is for jurisdictions to be ready by November 15, 2020 based on projections of vaccine availability. This includes having signed Data Use Agreements (DUAs) to ensure tracking of uptake, identifying pockets of low vaccination, identifying and intervening in coverage disparities, and allocating vaccine product. By this time, vaccination provider sites should be identified and enrolled, especially of those sites that can administer vaccine product to Phase 1 populations and that can position ultra-cold product after possible EUA. Jurisdictions are to confirm that the selected facilities are enrolled in the Vaccine Tracking System (VTrckS) to order and receive product. State capacity will be augmented through federal pharmacy partnerships to support vaccination in long-term care facilities (LTCFs). Microplanning will continue to ensure readiness across various scenarios. Pharmacies can help to increase access to vaccines. Almost 90% of Americans live within a 10-mile radius of a pharmacy.

For Phase 2, a general pharmacy partnership strategy has been developed for the COVID-19 Vaccine Program. Once there is an adequate supply of COVID-19 vaccine to support broader vaccination efforts, it will be important to help jurisdictions increase access to COVID-19 vaccine for the general population in Phase 2. The federal government is partnering with pharmacies nationwide to increase access to vaccine. Partners who enroll in this program will receive a direct allocation of COVID-19 vaccine when supply is sufficient and vaccine is recommended for use beyond the initial critical populations. Pharmacy partners under consideration include national chains, large regional chains, and networks of independent pharmacies and regional chains. Of the eligible US pharmacies, 55% have already enrolled. A list of partners will be shared with jurisdictions shortly. Leveraging all resources and public and private partners will allow for the successful administration of the COVID-19 vaccination program. The CDC vaccine website contains information and resources for the general public, providers, and jurisdictions.

Vaccinate with Confidence for COVID-19 Vaccines

CAPT Amanda Cohn, MD
Chief Medical Officer (Acting), Office of Vaccine Policy, Preparedness, and Global Health
Office of the Director, National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention
Executive Secretary, Advisory Committee on Immunization Practices

Dr. Cohn provided an update on CDC's *Vaccine with Confidence* strategy. There has been a considerable decline in COVID-19 vaccine acceptability in the past 4 months due to concerns about side effects, efficacy, risk perception/need for vaccine, and associated costs. Attributes that make COVID-19 vaccine more acceptable include HCP saying that the vaccine is safe, making the vaccine free of cost, having high potential for the vaccine to help get people back to work and school, and ensuring easy access to the vaccine. Individuals across the demand continuum will have concerns, which are understandable and must be addressed with empathy and transparency. Concerns among HCP is a risk for overall vaccine confidence, given that HCP are the most trusted source for health information. Various communities will have unique experiences informing COVID-19 vaccine perceptions, which can be addressed through engagement with community organizations and leaders to communicate clear and accurate information about COVID-19 vaccines.

Vaccinate with Confidence is a national strategy to reinforce confidence in COVID-19 vaccines with the key priorities to protect communities, empower families, and stop myths. The objectives are to: 1) regularly share clear and accurate COVID-19 vaccine information and take visible actions to build trust in the vaccine, the vaccinator, and the system; 2) promote confidence among HCP in their decision to get vaccinated and to recommend vaccination to their patients; and 3) engage communities in a sustainable, equitable and inclusive way—using two-way communication to listen, increase collaboration, and build trust in COVID-19 vaccine. There are tactics, sample products, and tools for each objective.

Vaccinate with Confidence is not an advertising, marketing, or communications campaign. Instead, it is a cohesive framework to support health departments, healthcare providers, immunization partners, and community partners and leaders' promotion of COVID-19 vaccines. This national strategy includes evidence-based content to amplify messages that enable an individual to make the decision to vaccinate, which is critical to ensuring that safe and effective COVID-19 vaccines can help control and reduce the impact of this pandemic. CDC is seeking feedback from a wide range of partners on the *Vaccinate with Confidence for COVID-19*

Vaccines Framework, and will send a short email to share with colleagues to review and provide input in addition to the input collected during this meeting.

Discussion Points (Routh & Cohn)

- From the broader healthcare perspective, there has been under-investment in vaccine implementation planning:

  - → ACIP expressed hope that going forward, CDC and others would be fully supported in this endeavor versus adding one more task to the already complex delivery system. Funding investments in this type of work is critical.
  - → Assuming that COVID-19 vaccine implementation will ramp up from January through March with more to do in April, there is concern that the Coronavirus Aid, Relief, and Economic Security (CARES) Act Provider Relief Fund that has paid for increases in the workforce will run out on December 31, 2020. Consideration must be given to what can be done at the state and local health department levels in terms of implementing COVID-19 vaccine activities if additional funding is not forthcoming.
  - → State and local jurisdiction funds are likely to depend upon local legislatures.
  - → There are major deficits in the healthcare delivery system, especially in primary care. More targeted support is needed for private practice to continue to deliver all types of vaccines.
  - → Implementation is where actual impact will happen or not. The same level of investment that has been made in vaccine development must be made in implementation. There must be national investment. While state support is important, federal support is crucial. This cannot be done in everyone's "free time." In order for implementation to be successful, the federal government must make a significant investment.
  - → Typically, ACIP approves a vaccine and then leaves implementation up to the states. This situation offers a good opportunity for ACIP to permanently change the model by which it operates.

- The planning process for delivering vaccines to children will be very different from the process for adults, given that the majority of children's vaccines are given in pediatric offices and many providers do no participate in Vaccines for Children (VFC). Although children are likely to be the last in line and pediatric trials are just beginning, planning for delivery to children should be done now.

- Much can be learned from influenza vaccines (e.g., make vaccination simple and easy, use reminders, use already planned visits, fund and support these activities where possible).

- While each of the 64 jurisdictions presented creative and unique plans based on their own jurisdictional issues that should be beneficial, it is crucial to keep in mind that different communities have different issues regarding vaccine acceptance, such as communities of color and Tribes:

  - → Many communities of color experience issues due to ongoing systemic racism and disparities that lead them to have distrust. Therefore, it is critical to work with communities of color to engender and earn trust, while being completely up front. It is particularly important to engage with community-based organizations (CBOs) and doctors of color who practice in these communities.

- → Concerns from Tribes focus on the very compressed timeline that does not allow for the IHS to engage in meaningful conversations. Tribes are being asked to make decisions about distribution, prioritization, et cetera without having all of the information they feel they need. Despite efforts to address these concerns, issues remain about how vaccine will be distributed, ordered, and reported on. Many Tribes want to be ready, but they are challenged by whether to choose distribution through states or through IHS. It is preferable to have both doors open.

- ❑ Confidence in receiving COVID-19 vaccine must be increased within the HCP workforce. If the group they trust the most will not take these vaccines, patients are not going to want to take them either:

  - → Lack of confidence among HCPs can be boosted by providing them with language that helps them answer questions about such topics as how vaccine was licensed so quickly when other vaccines take 15 years.
  - → HCPs are constantly being asked whether they trust COVID-19 vaccines, to which some respond that when CDC and FDA say they trust it, HCPs will recommend it.
  - → Given that HCPs are the most trusted vaccine administrators, perhaps language should be included that permits them to be vaccinated in the first phase. Many private practitioners do not have access to personal protective equipment (PPE), yet they are the ones on the frontline to whom patients turn.

- ❑ Workers Compensation must be addressed.

- ❑ CDC is producing content that will be shared with partners in the near future. It is imperative for partners, HCP organizations, and community partners to amplify these messages as this will be much more powerful than messages coming just from CDC or HHS.

- ❑ Private practitioners have expressed interest in being able to order and receive vaccines through VTrckS. CDC encouraged them to speak with their local jurisdictions to enroll as providers in VTrckS, through which they can also order/receive vaccine.

- ❑ The two components of DUAs, identified and de-identified data, need to be separated in order to move quickly as vaccines become available.

- ❑ Many COVID-19 vaccines will require 2 doses, making it critical to be able to ascertain what vaccine was given for Dose 1 and when Dose 2 is needed:

  - → Efforts to determine this information with existing Immunization Information Systems (IIS) can be frustrating.
  - → State IIS for adults have lagged behind.
  - → Ensuring that people received both doses and the correct products is very important to CDC, so immunization cards will accompany ancillary kits in order to have both IIS records and paper and pen solutions.

CBER Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness

Steve Anderson, PhD, MPP
Director, Office of Biostatistics & Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Anderson reviewed FDA's active post-licensure safety surveillance systems and Center for Biologics Evaluation and Research (CBER) plans for monitoring COVID-19 vaccine safety and effectiveness. FDA and CDC have weekly and bi-weekly coordination meetings on VAERS and pharmacovigilance activities between the CBER Office of Biostatistics and Epidemiology (OBE) and the OBE Division of Epidemiology (DE) and the CDC Immunization Safety Office (ISO). CBER DE physicians will be reviewing the SAE reports from VAERS for COVID-19 vaccines. This will include review of individual reports, death reports, aggregate analyses, case-series, et cetera. FDA will utilize statistical data-mining methods to detect disproportional reporting of specific vaccine AE combinations to identify AEs that are more frequently reported.

COVID-19 vaccine monitoring data considerations include rapid data access for near real time surveillance, large databases comprised of tens of millions of patients for evaluating vaccine rare SAEs, data representing the integrated care spectrum (e.g., outpatient, physician, inpatient, et cetera), high quality data to assess and confirm potential AEs or safety concerns for COVID-19 vaccines, and data with significant clinical detail or medical chart access. The FDA Biologics Effectiveness and Safety (BEST) system includes several partners, represents a variety of healthcare settings, and has an emphasis on inclusion of electronic health records (EHR), some claims, and linked claims-EHR data. BEST is a modern surveillance system that is able to perform a diversity of queries and studies. There has been an ongoing FDA-CMS partnership on vaccine safety since 2002. CMS data cover a very large population of approximately 55 million elderly US beneficiaries ≥65 years of age. Given that over 92% of US elderly individuals use Medicare, this database represents the elderly population and not a sample. It represents a variety of healthcare settings and consists of claims data with access to medical charts. Not all claims and EHR data systems can be used to address a vaccine safety or effectiveness regulatory question, and each data system has its limitations in terms of the populations, healthcare settings, clinical detail, necessary parameters, data lag, exposures, and outcomes that are captured.

In terms of COVID-19 vaccine safety surveillance planning, the FDA will utilize RCA to monitor 10 to 20 safety outcomes of interest to be determined based on: 1) pre-market review of sponsor safety data submitted to the FDA; 2) coordination with federal partners, international regulatory partners and organizations, academic experts, and others; and 3) literature and regulatory experience with similar vaccines, novel vaccine platforms, and using other relevant data. Dr. Anderson shared the following draft working list of possible AE outcomes:

• Guillain-Barré syndrome • Acute disseminated encephalomyelitis • Transverse myelitis/encephalitis/ myelitis/ encephalomyelitis/meningoencephalitis/meningitis /encepholapathy • Convulsions/seizures • Stroke • Narcolepsy and cataplexy • Anaphylaxis • Acute myocardial infarction • Myocarditis/pericarditis • Autoimmune disease • Deaths	• Pregnancy and birth outcomes • Other acute demyelinating diseases • Non-anaphylactic allergic reactions • Thrombocytopenia • Disseminated intravascular coagulation • Venous thromboembolism • Arthritis and arthralgia/joint pain • Kawasaki disease • Multisystem Inflammatory Syndrome in Children • Vaccine enhanced disease

In terms of experience, the FDA has conducted near real-time surveillance for annual influenza vaccine and Guillain-Barre Syndrome (GBS) since 2007 and Sentinel rapid surveillance for the 2017-2018 seasonal influenza vaccine to evaluate 6 health outcomes of interest.

Epidemiological analyses will require the capability to resolve potential safety signals identified from near real-time surveillance, TreeScan® signal detection efforts, and other sources. This may involve rapid queries and small epidemiological studies and/or larger self-controlled, cohort, comprehensive protocol-based studies. There may be limited information available at the time of licensure on the level and duration of effectiveness. Manufacturers may conduct certain COVID-19 vaccine effectiveness (VE) post-licensure studies. FDA may conduct COVID-19 general effectiveness studies, including subpopulations of interest; duration of protection studies; or other types of studies. FDA is coordinating COVID-19 VE efforts with the CDC/NCIRD through monthly and bi-monthly meetings.

The FDA, CMS, and CDC have extensive experience with the data and methods needed to conduct VE studies having produced several VE and relative VE for influenza and zoster vaccines and duration of effectiveness analysis of Zostavax® vaccine. Dr. Anderson emphasized that COVID-19 vaccine monitoring is a large US government effort that involves regular meetings, planned sharing of protocols, discussion of safety and effectiveness outcomes of interest, and coordinated planning and conduct of surveillance activities between the FDA, CDC, CMS, VA, and DoD.

Post-Authorization Safety Monitoring Plans

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Vaccine Safety Team
CDC COVID-19 Vaccine Planning Unit (VPU)
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro provided an overview and continued the discussion of post-authorization/post-licensure safety monitoring of COVID-19 vaccines. He reported that ACIP has established a COVID-19 Vaccine Safety Technical Sub-Group (VaST) to advise CDC and other federal partners on planning and preparation for post-authorization/post-licensure safety monitoring of COVID-19 vaccines and independently review and evaluate safety data. Post-authorization/post-licensure safety data on COVID-19 vaccines will be presented regularly during public ACIP meetings. During this meeting, he provided updates on Vaccine Safety Datalink (VSD) monitoring, the CISA Project clinical consult service, HCP's role in reporting AEs to VAERS, and HCP's role in facilitating patient enrollment into the V-SAFE smartphone-based active surveillance system. VSD planned monitoring and evaluation for COVID-19 vaccine safety includes: 1) near real-time sequential monitoring using RCA; 2) monitoring for vaccine-mediated enhanced disease (VMED); 3) studies to evaluate COVID-19 vaccine safety during pregnancy, including fetal death and infant outcomes; tree-temporal scan data mining; and 4) a variety of projects to assess changes in healthcare utilization during COVID-19 and impact on AE monitoring; utility of smartphone technology to enhance vaccine safety monitoring; multisystem inflammatory syndrome in children and adults (MIS-C and MIS-A) as vaccine AEs; safety in an expanded underserved VSD population; and knowledge, attitudes, and beliefs around acceptance/refusal of COVID-19 vaccination.

CISA Project clinical consult service supports US HCP and health departments on complex clinical vaccine safety questions and assists with evaluations of patients with AEs after receiving COVID-19 vaccine or in making clinical decisions about administering COVID-19 vaccine to a person who may be at increased risk for an AE. Advice from CDC and the CISA Project is meant to assist in decision-making versus providing direct patient management and is available to US healthcare providers and health departments by contacting CDC-INFO. HCPs have been CDC's longstanding partners for reporting vaccine AEs to VAERS. VAERS depends upon HCPs to identify and report suspected AEs, even if they are not sure if a vaccine caused an AE. The Health Insurance Portability and Accountability Act (HIPAA) permits reporting of vaccine AEs and medical documentation to VAERS for public health purposes. HCP participation in VAERS reporting will enable public health officials to have accurate and timely information on the safety of COVID-19 vaccines. Specific guidance on VAERS reporting for vaccines authorized for use under EUA will be forthcoming.

V-SAFE is a new smartphone-based active surveillance program for COVID-19 vaccine safety that uses text messaging to initiate web-based survey monitoring and conducts electronic health checks on vaccine recipients. Health checks are conducted daily for the first week post-vaccination and weekly thereafter until 6 weeks post-vaccination. There are additional health checks at 3, 6, and 12 months post-vaccination. V-SAFE includes active telephone follow-up through the VAERS program with vaccine recipients reporting a clinically important event during any V-SAFE health check. A VAERS report will be taken during telephone follow-up, if appropriate. V-SAFE captures information on pregnancy status and enables follow-up on pregnant women as well. V-SAFE will allow for estimation of rates of local and systemic reactogenicity and rates of clinically important AE following COVID-19 vaccination and symptoms and conditions associated with these AEs. HCPs will play an important role in V-SAFE enrollment by providing a one-page information sheet to patients at the time of vaccination (to be created by CDC) and counseling patients on the importance of enrolling in V-SAFE. CDC will provide information on how to briefly counsel patients on V-SAFE. Of note, V-SAFE will be translated into at least 5 other languages.

ACIP COVID-19 Vaccine Safety Technical Sub-Group

Melinda Wharton, MD, MPH
Director, Immunization Services Division
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wharton described the ACIP COVID-19 VaST in more detail. VaST was organized in June 2020 and is comprised of independent expert consultants, ACIP members, liaison representatives, and federal agency SMEs. The focus of VaST is to prioritize AESI, develop USG plans for safety monitoring, and create a communication framework. VaST was built off of lessons learned from H1N1 vaccine safety monitoring. There was consensus that a Federal Advisory Committee Act (FACA)-chartered subgroup would ensure transparency, independence, and public accountability. VaST is currently comprised of ACIP and National Vaccine Advisory Committee (NVAC) representation, 7 independent expert consultants, ACIP *ex officio* members (NIH, FDA, OIDP, CMS, HRSA, IHS), and a VA and DoD liaison. The VaST's post-implementation objectives are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical SMEs from federal agencies conducting post-authorization/approval safety monitoring to share vaccine safety surveillance data; 3) advise on analyses, interpretation, and data presentation; and 4) liaise with the ACIP COVID-19 Vaccines WG on issues of safety data presentation to the

ACIP and application of safety data to policy decisions. The VaST's deliverables include development of frequent COVID-19 vaccine safety technical reports for internal ACIP and CDC and federal partner use, and frequent COVID-19 vaccine safety data summaries for public release.

Discussion Points (Anderson, Shimabukuro, Wharton)

Given that safety surveillance is critical, this immense and collaborative effort is impressive.

While the EHR can be a useful tool for data mining, finding AEs, and ensuring vaccines are distributed, it also has pitfalls that need to be stressed. Confidentiality goes without saying, but the biggest concern is that the use of the EHR is burdensome in terms of implementation and use when data registration or data mining are involved. For private practice, this is burdensome and costly. If this is required and there is a cost to integrate it into the health record, it could fail in the community setting.

The emphasis on collaboration among government agencies and groups working on vaccine safety in terms of harmonizing outcomes of interest, regular communication, and sharing data is very important and is applauded. This type of collaboration and coordination should continue through the entire process so that signals are investigated. This also should help to ensure that communicating to the public is well-coordinated, transparent, and consistent.

It was observed that safety monitoring may be difficult in settings outside of VAERS and registries, such as monitoring vaccines administered in workplaces where employers have their own health insurance plans. This is an area that FDA is exploring.

Concern was expressed about the ability of the systems described to monitor for MIS-C, wild-type or vaccine-induced, particularly with respect to the case definition requirement of a positive test or exposure to a suspected or confirmed case within 4 weeks prior to symptom onset.

Concern was expressed about access to V-SAFE in under-served areas. It is important to be mindful that while most people have access to some form of communication, indigent populations may not have ongoing access to care. In addition, V-SAFE communication must be culturally sensitive.

Lessons learned from children being at home and not in school is that there are many barriers. As hard as it may be to believe, not everybody has internet access and many people purchase phone minutes for phones that are not smartphones. It would be beneficial to track or record V-SAFE use, perhaps by Zip Code, to ensure that it is inclusive of all communities in terms of access and recording long-term effects from the vaccine.

Consideration should be given to modernizing VAERS to accept data from EHRs and/or registries.

Modeling Strategies for the Initial Allocation of SARS-CoV-2 Vaccines

Matthew Biggerstaff, ScD, MPH
Data, Analytics, and Modeling Task Force
Centers for Disease Control and Prevention

Dr. Biggerstaff presented modeling strategies for the initial allocation of SARS-CoV-2 vaccines. The question posed to the group to model was, "What is the potential impact, in terms of preventing COVID-19 infections and deaths, of initially allocating vaccine to one of the following groups after vaccinating HCP in Phase 1A: Adults aged 65+, adults with high-risk medical conditions, and essential workers?" He described in detail the population stratification, vaccine product assumptions, completeness of protection, vaccine allocation assumptions for Phase 1a and Phase 1b, epidemic dynamics, administration assumptions, and approximate timing of vaccine rollout (before incidence rises, as incidence rises, as incidence falls). In terms of findings, initially vaccinating high-risk adults or essential workers in Phase 1B averts approximately 1% to 5% more infections compared to targeting age 65+. This difference is greatest in the scenario in which the vaccine is introduced before incidence rises. The findings are robust to assumptions of reduced VE in older populations. Initially vaccinating age 65+ in Phase 1b averts approximately 1% to 4% more deaths compared to targeting high-risk adults or essential workers. As before, this difference is greatest in the scenario in which the vaccine is introduced before incidence rises. The percentage of deaths averted changes if VE is reduced in older populations. Initially vaccinating high-risk adults, age 65+, or essential workers in Phase 1b averts a similar percentage of deaths across the scenarios. Initially vaccinating age 65+ in Phase 1b averts approximately 2% to 11% more deaths compared to targeting high-risk adults or essential workers. Again, this difference is greatest in the scenario where the vaccine is introduced before incidence rises. The findings are robust to assumptions of reduced VE in older populations, but the percentage averted drops.

There are limitations to the study. The efficacy and ability of the vaccine candidates to prevent transmission, as well as the time vaccine may become available, is currently unknown. Modeled epidemic trajectories are only for illustration and are not forecasts. Overall averted burden should be interpreted cautiously, given that it will be sensitive to the future trajectory of the epidemic; findings reflect an idealized rollout with minimal delays and 100% uptake; and the aim of this study was to demonstrate the relative impact of different initial vaccine allocation strategies. The following inputs were assumed and will require reassessment as more information becomes available: 1) all infections confer protective immunity; 2) immunity, either naturally- or vaccine-acquired, does not wane significantly within a year of infection or immunization; 3) given exposure, younger age groups are just as likely to become infected as older age groups (susceptibility independent of age); 4) individuals with comorbidities are just as likely as their peers to practice social distancing and other protective behaviors; and 5) there was no reduction in VE among those with high-risk medical conditions. The findings are consistent in sensitivity analyses where the percentage of the population infected prior to vaccine introduction was varied. In terms of consistency with external literature, a review of peer-reviewed and pre-publication studies that model the impact of vaccination under different initial allocation strategies shows general agreement with the results presented here.

Discussion Points

This is an incredible, elegant, and impressive analysis and enormous amount of work.

From a clinical and public health medical consultant point of view, the assumptions in the model make sense. VE may be somewhat high, but it is reasonable.

Consider modeling the impact of poor nutrition, falling behind in school, and possible abuse and neglect if older adults are vaccinated first and schools remain closed. The modeling team noted that this is possible but may require a more complex framework such as agent-based models that model people and societal parameters.

Consider modeling hospitalizations and not just deaths. The modeling team noted that they started with infections and deaths because those estimates are easier to obtain, but infections and hospitalizations can be incorporated in future versions.

Consider modeling congregate care settings. The modeling team indicated that this was already done and was presented by Dr. Slayton during the August 2020 ACIP meeting. The take-away from that study was that vaccinating staff in these settings may be more beneficial than just vaccinating residents, likely because of infection-blocking such that the infection is not introduced into the congregate setting.

It is critical for ACIP to address equity and disproportionate impact on disadvantaged populations. Approaching this from a race/ethnicity standpoint is probably not the best approach.

Updates to COVID-19 Immunity and Epidemiology to Inform Vaccine Policy

Megan Wallace, DrPH, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wallace provided updates to COVID-19 immunity and epidemiology to inform vaccine policy, including an overview of US COVID-19 epidemiology, COVID-19 post-infection immunity, COVID-19 reinfection, and epidemiology of COVID-19 in pregnant women. As of October 29th, there were 8,834,393 cases of COVID-19 and 227,045 COVID-19 deaths. From March 1, 2020 through October 17, 2020, the number of specimens tested and percent positive for SARS-CoV-2 from combined laboratories reporting to CDC was 6.3% at Week 42. In terms of what happens to anti-SARS-CoV-2 antibodies after infection, Rhesus macaques challenged with SARS-CoV-2 developed binding and neutralizing antibody responses. Re-challenge of rhesus macaques boosted SARS-CoV-2 antibody responses. In humans with SARS-CoV-2 infection, serum antibodies decline between the acute phase and 2 months post-discharge. In HCP with a history of mild SARS-CoV-2 infection, serum antibodies waned 2 months post-infection. Among hospitalized persons with SARS-CoV-2, neutralizing antibody titers demonstrated little to no decrease over 75 days since symptom onset. Pertaining to whether persons infected with SARS-CoV-2 mount cellular immune responses, in symptomatic COVID-19 patients, SARS-CoV-2 memory B-cells did not wane at the same rate as serum antibodies. Recovered COVID-19 patients have SARS-CoV-2-specific CD4+ T-cells and CD8+ T-cells. In conclusion, repeat exposure to SARS-CoV-2 may cause boosting of immune response. Several studies have now observed waning of serum antibodies in COVID-19 patients after a few months. However, the implications for protection are unknown. Neutralizing antibody titers demonstrated little or no

decrease at 75 days post-symptom onset. SARS-CoV-2 specific cellular B- and T-cell responses have been detected in COVID-19 patients. Memory B cells did not wane as fast as serum antibody titers.

Discussion Points

Pregnant and lactating women should not be excluded from high priority populations for COVID strategies and treated separately. More than 75% of the HCP workforce are females. For instance, pregnant HCP and first responders who are pregnant should be prioritized alongside their non-pregnant peers.

Though reinfection appears to be uncommon at this point, it will be beneficial to have further guidance on this as soon as possible.

The summary about what is known and unknown about reinfection was phenomenal. However, using language such as reinfection is “likely uncommon within 3 months” suggests more is known that actually is. Perhaps “may be uncommon within 3 months” would be less challenging for management.

It is imperative for messaging around vaccine to emphasizes that vaccines are not likely to be 100% effective and that other measures must be utilized in combination with vaccines. The vaccine is not a panacea and will not result in immediate full herd immunity.

Dr. James Lee invited health care institutions and local/state public health entities interesting in discussing more about reinfections to email eocevent461@cdc.gov.

Ethical Principles for Phased Allocation of COVID-19 Vaccines

Mary E. Chamberland, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Chamberland discussed ethical principles for phased allocation of COVID-19 vaccines, which the COVID-19 Vaccine WG developed to assist ACIP in the identification of groups for early allocation of COVID-19 vaccine in the setting of a constrained supply. During the September 2020 ACIP meeting, 5 interim ethical principles were endorsed: Maximizing Benefits and Minimizing Harms, Equity, Justice, Fairness, and Transparency. During the July through August ACIP meetings, possible groups for Phase 1 vaccination were explored, including HCP in Phase 1a and essential workers (non-HCP), persons with high-risk underlying medical conditions, and adults aged ≥65 years in Phase 1b. The WG reviewed COVID-19 vaccine allocation frameworks including those from Johns Hopkins University (JHU), National Academies, and the World Health Organization (WHO). In addition, they reviewed the ethical literature and consulted with experts in health equity, ethics, and Grading of Recommendation Assessment, Development and Evaluation (GRADE). The interim ethical principles were updated to guide phased allocation and a manuscript was drafted on ethical principles to address key questions to guide allocation planning, and a health equity domain was incorporated into the Evidence to Recommendations (EtR) Framework. There are now 4 ethical principles (Maximizing Benefits and Minimizing Harms, Promote Justice, Mitigate Health Inequities, and Promote Transparency), and updates to the interim version included folding fairness into justice and styling the principles as action phrases. A series of Key Questions was developed to: 1) facilitate “translation” of the ethical principles; 2) assist ACIP in developing its

national recommendations for early phase COVID-19 vaccine allocation; and 3) serve as a tool for State, Tribal, Local, and Territorial (STLT) health authorities as they develop vaccination implementation plans. Although ethical principles are fundamental for stewardship of a limited supply of vaccine, they also will be applicable when COVID-19 vaccines are more widely available. Dr. Mary Chamberland described in detail each Key Question for COVID-19 vaccine allocation planning stratified by ethical principles.

Application of the principle of transparency across the entirety of the allocation decision-making process is essential for building public trust and confidence and being clear about the level of certainty in available evidence. Methods and data used for ACIP recommendations are publicly available and include public participation. ACIP meetings are open to the public and are available on-line. Comments can be made to the *Federal Register* and/or during ACIP meetings and when ACIP engages with stakeholders and partners. Allocation of a limited supply of vaccine is complicated by efforts to address multiple goals, most notably reducing morbidity and mortality and minimizing disruption to society, the economy, and healthcare capacity. If the goals of a vaccination program are not clearly prioritized, it will be difficult to draw distinctions between groups for early phase allocation. There is increasing consensus among allocation frameworks for early vaccination of HCP, suggesting that maintenance of healthcare capacity as the highest priority. If vaccine supply remains constrained, ethical principles can help to guide identification of subsets of other groups for subsequent early phase allocation. The next steps for the WG are to seek ACIP's views on the updated ethical principles and key questions, publish ACIP's ethical principles, and engage in further discussion about application of the ethical principles to help inform Phase 1 allocation recommendations. The WG requested feedback on how application of these principles and key questions could be made more useful to STLT health authorities for COVID-19 vaccine allocation planning.

Discussion Points

While there was agreement with and endorsement of the principles, some members were struggling with how they fit into the overall pandemic response—especially having seen projections earlier showing that it seems to matter less *who* gets the vaccine first as far as numbers of infections and deaths. That is, the principles seem less important than how soon the vaccine gets deployed.

The WG pointed out that the modeling work measured only one dimension of the impact, aversion of cases and deaths. The ethical principles takes a more holistic view of several dimensions in the context of limited vaccine supply being guided by ethnical, scientific, and implementation considerations.

The Key Questions to help guide and integrate the process seem beneficial and are greatly appreciated.

One thing that will go a long way with the general population, especially in terms of trust and disparities, is a mechanism for reporting how vaccine products are actually being allocated.

One decision with which ACIP will be faced will be assessing the data in terms of benefits and risks for various groups once a vaccine is available. If a vaccine becomes available in the next month or two, this will be a relatively short timeframe for efficacy and safety data. With no long-term safety data, it will be difficult to balance the benefits versus long-term issues that historically have arisen. Balancing the scientific and ethnical aspects is going to be difficult.

The slide on promoting transparency harkens back to the earlier comments about Tribes and the dynamic tension that a compressed timeline is going to create.

WG's Interpretation of the Data

Sara Oliver MD, MSPH
Co-Lead ACIP COVID-19 Vaccine WG
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Oliver presented the ACIP COVID-19 Vaccine WG's interpretation of the data. In terms of COVID-19 vaccine and prior infection, data from Phase 3 trials for any possible vaccine-associated enhanced disease or reactogenicity after prior infection are not yet available. In the absence of concerning data from Phase 3 trials, having positive PCR, antigen, or antibody results is not a contraindication to receive COVID-19 vaccine. Any vaccine recommendations that rely on knowledge of prior immunity/antibody testing would be difficult to implement. In terms of COVID-19 vaccine and breastfeeding women in Tier 1a, most WG members agreed that breastfeeding would not be a contraindication to receive a COVID-19 vaccine. However, this needs to be evaluated for each vaccine, especially if any live virus/vector vaccines are authorized/licensed. Regarding pregnant women in Tier 1a, limited data on pregnancy are expected from Phase 3 trials. The WG did not reach a consensus. The majority felt that if a woman is recommended to receive the vaccine in an early allocation phase, pregnancy should be a precaution but not a contraindication to receive a COVID-19 vaccine. The WG emphasized the need to allow women to make an informed decision, providing all current knowledge of COVID-19 vaccines/platforms with pregnancy and risk of disease. Concerning pregnancy diagnosed after receipt of the first dose of COVID-19 vaccine, the majority of the WG felt that the second dose could be given at the recommended interval. A minority of the WG felt that the second dose should be postponed until the second trimester or until after pregnancy, emphasizing the need to allow women to make an informed decision.

Regarding the WG's interpretation of the modeling data, the differences among the 3 strategies are thought to be minimal. Ethical principles and implementation considerations may greatly contribute to selecting the optimal sequence in Phase Ib. The largest impact in averted deaths and infections is the timing of vaccine introduction in relation to increases in COVID-19 cases. It is important to emphasize the need to continue non-pharmaceutical interventions (e.g., wearing a mask, social distancing) while awaiting available vaccine. Many factors will inform interpretation of modeling data and allocation decisions, such as VE in older adults, a vaccine's ability to prevent severe disease or transmission, and whether the goal is to prevent the greatest number of infections or greatest number of deaths. For vaccine candidates, both Novavax and Janssen are planning and enrolling large Phase 3 efficacy trials of 30,000 to 60,000 people. The primary endpoints include symptomatic, virologically confirmed COVID-19 disease. Both companies are attempting to enroll diverse populations in terms of race and ethnicity, age (<65 years and ≥65 years of age), and underlying medical conditions.

Concerning implementation and distribution, the WG's interpretation is that Phase 2/3 data from the vaccines show induction of binding and neutralizing antibodies as well as T-cell responses, favorable safety/reactogenicity profiles, supporting advance to Phase 3 trials. Both platforms have prior experience from other vaccines. Safety pauses are expected with large clinical trials, indicating the process is working appropriately. For the current Phase 3 clinical trials, the WG stressed the importance of enrolling diverse study participants, the importance of harmonizing safety and efficacy endpoints across all Phase 3 trials to the extent possible, and the need to report maternal and fetal outcomes for women who become pregnant during the clinical trials. The WG supports FDA's guidance for ensuring that Phase 3 trials conduct ongoing assessment of long-term safety and efficacy, and that issuance of an EUA is not grounds to unblind follow-up in an ongoing clinical trial.

Discussion Points

The American College of Obstetricians and Gynecologists (ACOG) urged ACIP to incorporate pregnant and lactating women clearly and explicitly in the prioritization framework should an EUA be issued.

The American Academy of Pediatrics (AAP) agreed with the ACOG statement and defers to them on matters of pregnancy and pregnant women. AAP also emphasized the need to move to pediatric trials when the data suggest that it is safe to do so and should monitor fetal outcomes. It is important for pregnant and lactating women to make an informed decision. CDC is engaging ACOG and AAP and is working with colleagues with expertise in this area to develop materials that can be provided at the time of vaccination.

Related to the unblinding of clinical trials should an EUA become available, particularly for participants in vaccine trials in which efficacy and safety are demonstrated, it is troubling that participants potentially will not have the benefit of receiving vaccine once efficacy is demonstrated. These volunteers have assumed the risk of study participation and in most clinical trial circumstance would be among the first to potentially benefit once efficacy is demonstrated. It is recognized that this is an issue that must be dealt with by the FDA and VRBPAC.

Policy Questions, EtR Framework

Kathleen Dooling, MD MPH
Co-Lead ACIP COVID-19 Vaccine WG
Medical Officer, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Dooling reviewed the COVID-19 vaccine policy questions for the EtR framework and critical and important outcomes. As a reminder, the goals of the COVID-19 vaccine program are to: 1) ensure the safety and effectiveness of COVID-19 vaccines; 2) reduce transmission, morbidity, and mortality of COVID-19 disease; 3) help minimize disruption to society and economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution. The two ACIP policy questions proposed by the WG are: 1) Should COVID-19 Vaccine "A" be recommended to adults in the US?; and 2) Who should be recommended to receive COVID-19 Vaccine "A" during Phase 1? The EtR framework assesses the domains of Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. Dr. Dooling reviewed the population, intervention, comparison, outcomes (PICO) for vaccine policy for Question #1, including the critical and important benefits and harms identified

by the WG. The WG's next steps for Policy Question #1 (Vaccine Recommendations) are to populate the EtR framework, start GRADEing the vaccine evidence and incorporating Phase 3 data when available, and discuss clinical guidance for special populations, concomitant administration, and scheduling. For Policy Question #2 (Allocation Recommendations), the WG's next steps are to publish the ethical principles manuscript and incorporate the latest information regarding science, implementation, and ethics to further refine Phase 1 allocation. For the health equity domain criterion question, the following sub-questions were posed: 1) Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?; 2) Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?; 3) Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?

Discussion Points

There was support for the two policy questions being evaluated separately and the important and beneficial outcome of serial PCRs for asymptomatic infection.

This is an unprecedented situation in which consideration may need to be given to conditional recommendations, which should incorporate the principles of informed consent and some higher level of clinical decision-making.

Perhaps consideration should be given to getting the vaccine out as quickly as possible in response to the modeling data suggesting that the faster vaccines are administered, the more deaths that will be prevented.

This does not take into consideration any time-phased protection or safety other than the data that will be provided should an EUA come through in a relatively short period of time. This is a virus like nothing they have seen previously, so the unknown and negative possibilities are always a consideration. They can look at objective information and arrive at a conclusion to move forward with allocation, but that presumes that there is not going to be some later problem.

Following participants for a mean of 2 months after the second dose as a timepoint to start making final decisions about safety is troubling. Concerns prevailed on making quick decisions on safety. While it is true that most AEs of interest will be captured in the first 6 weeks, there will be a need for long-term studies, particularly due to the potential for vaccine-enhanced disease. This highlights the need for a dynamic decision-making process.

The WG has considered mortality, morbidity, and preventing spread in a lumped manner. In the context of unknowns, perhaps those should be disaggregated.

The questions fit the PICO perfectly, with the caveat that there may be changes. There must be flexibility over time and flexibility in implementation. Local areas will have to deal with the reality of whether to save doses for Dose 2.

Given the uncertainties, perhaps the WG should review the data on a monthly basis and update the recommendations to account for concerns in balance with benefits and harms.

While the focus on safety is very important, it is also crucial to understand durability of the immune response.

The ethical principles will be very important to local jurisdictions. Concrete guidance will be needed in terms of equity and a sense of fairness in terms of how allocations actually are implemented.

Frequent messaging of information about COVID-19 vaccines will be very important to public confidence.

Certification

Upon reviewing the foregoing version of the October 28, 29, & 30, 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

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2019 – December 31, 2020

CHAIR
ROMERO, José R., MD, FAAP
Professor of Pediatrics
Horace C. Cabe Endowed Chair in Infectious Diseases Director,
Pediatric Infectious Diseases Section
University of Arkansas for Medical Sciences and Arkansas Children's Hospital
Director, Clinical Trials Research
Arkansas Children's Hospital Research Institute
Little Rock, AR
Term: 10/30/2018-06/30/2021

EXECUTIVE SECRETARY
COHN, Amanda, MD
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS
ATMAR, Robert L., MD
John S. Dunn Clinical Research Professor in Infectious Diseases
Departments of Medicine and Molecular Virology & Microbiology
Baylor College of Medicine
Chief, Infectious Diseases Service
Ben Taub General Hospital, Harris Health System
Houston, TX
Term: 7/1/2016 – 6/30/2020

AULT, Kevin A., MD, FACOG, FIDSA
Professor and Division Director
Department of Obstetrics and Gynecology
University of Kansas Medical Center
Kansas City, KS
Term: 10/26/2018 – 6/30/2022

BAHTA, Lynn, RN, MPH, CPH
Immunization Program Clinical Consultant
Infectious Disease, Epidemiology, Prevention & Control Division
Minnesota Department of Health
Saint Paul, Minnesota
Term: 7/1/2019 – 6/30/2023

BELL, Beth P., MD, MPH
Clinical Professor
Department of Global Health, School of Public Health
University of Washington
Seattle, WA
Term: 7/1/2019 – 6/30/2023

BERNSTEIN, Henry, DO, MHCM, FAAP
Professor of Pediatrics
Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center
New Hyde Park, NY
Term: 11/27/2017-06/30/2021

FREY, Sharon E., M.D.
Professor and Associate Director of Clinical Research
Clinical Director, Center for Vaccine Development
Division of Infectious Diseases, Allergy and Immunology
Saint Louis University Medical School
Saint Louis, MO
Term: 11/27/2017-06/30/2021

HUNTER, Paul, MD
Associate Professor of Family Medicine and Community Health
University of Wisconsin School of Medicine and Public Health
Associate Medical Director
City of Milwaukee Health Department
Milwaukee, WI
Term: 7/1/2016 – 6/30/2020

LEE, Grace M., MD, MPH
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine
Stanford, CA
Term: 7/1/2016 – 6/30/2020

MCNALLY, Veronica V., JD
President and CEO
Franny Strong Foundation
West Bloomfield, Michigan
Term: 10/31/2018 – 6/30/2022

POEHLING, Katherine A., MD, MPH
Professor of Pediatrics and Epidemiology and Prevention Director,
Pediatric Population Health
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC
Term: 7/1/2019 – 6/30/2023

SÁNCHEZ, Pablo J., M.D.
Professor of Pediatrics
The Ohio State University – Nationwide Children's Hospital
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio
Term: 7/1/2019 – 6/30/2023

SZILAGYI, Peter, MD, MPH
Professor of Pediatrics
Executive Vice-Chair and Vice-Chair for Research
Department of Pediatrics
University of California, Los Angeles (UCLA)
Los Angeles, California
Term: 7/1/2016 – 6/30/2020

TALBOT, Helen Keipp, MD
Associate Professor of Medicine
Vanderbilt University
Nashville, TN
Term: 10/29/2018 – 6/30/2022

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification
Centers for Medicare and Medicaid Services
Baltimore, MD

Food and Drug Administration (FDA)
FINK, Doran, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Health Resources and Services Administration (HRSA)
RUBIN, Mary, MD
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
WEISER, Thomas, MD, MPH
Medical Epidemiologist
Portland Area Indian Health Service
Portland, OR

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
KIM, David, MD CAPT,
US Public Health Service Director Division of Vaccines
Washington, DC

National Institutes of Health (NIH)
BEIGEL, John, M.D.
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases (NIAID) Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
ROCKWELL, Pamela G, DO
Associate Professor, Department of Family Medicine,
University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine Ann
Arbor, MI

American Academy of Pediatrics (AAP)
MALDONADO, Yvonne, MD
Senior Associate Dean for Faculty Development and Diversity
Professor of Pediatrics and Health Research and Policy
Chief, Division of Pediatric Infectious Diseases
Stanford University School of Medicine
Stanford, CA

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C Senior
Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
CHAI, Thevy S, MD
Director of Medical Services
Campus Health Services
University of North Carolina at Chapel Hill
Chapel Hill, NC

American College Health Association (ACHA) (alternate)
MCMULLEN, Sharon, RN, MPH, FACHA
Assistant Vice President of Student & Campus Life for Health and Wellbeing
Cornell Health
Ithaca, NY

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH Lead
Clinician
Clinical Quality Compliance and Management
Planned Parenthood Southeast
Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

American College of Obstetricians and Gynecologists (ACOG)
ECKERT, Linda O., MD, FACOG
Professor, Department of Obstetrics & Gynecology
Adjunct Professor, Department of Global Health
University of Washington
Seattle, WA

American College of Physicians (ACP)
GOLDMAN, Jason M. MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science, Florida Atlantic University, Boca Raton, Florida
Private Practice
Coral Springs, FL

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics
Geriatrics Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
GLUCKMAN, Robert A., MD, MACP
Chief Medical Officer, Providence Health Plans
Beaverton, OR

American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
Executive Director, AIRA
Washington, DC

American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN
Assistant Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E., DO
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
FOSTER, Stephan L., PharmD CAPT (Ret)
U.S.P.H.S.
Professor, College of Pharmacy
University of Tennessee Health Sciences Center
Memphis, TN

Association of Immunization Managers (AIM)
HOWELL, Molly, MPH Immunization Program Manager
North Dakota Department of Health
Bismarck, ND

Association for Prevention Teaching and Research (APTR)
McKINNEY, W. Paul, MD
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

Association of State and Territorial Health Officials (ASTHO)
SHAH, Nirav D, MD, JD
Director
Maine Center for Disease Control and Prevention
Augusta, ME

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A., MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD State
Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

Council of State and Territorial Epidemiologists (CSTE) (alternate)
LETT, Susan, MD, MPH
Medical Director, Immunization Program
Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Boston, MA

Canadian National Advisory Committee on Immunization (NACI)
QUACH, Caroline, MD, MSc
Pediatric Infectious Disease Specialist and Medical Microbiologist
Medical Lead, Infection Prevention and Control Unit
Medical Co-director – Laboratory Medicine, Optilab
Montreal-CHUM
Montreal, Québec, Canada

Infectious Diseases Society of America (IDSA)
BAKER, Carol J, MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD
Professor of Pediatrics
Boston University School of Medicine
Boston, MA

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and Chief, Communicable Disease Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine, Division of Allergy and Infectious Diseases
University of Washington School of Medicine and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A., RN, MS, CPNP
Director, Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases (NFID)
Bethesda, MD

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD
Professor and Chair
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

Pediatric Infectious Diseases Society (PIDS)
O'LEARY, Sean, MD, MPH
Associate Professor of Pediatrics
Pediatric Infectious Diseases
General Academic Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine

Pediatric Infectious Diseases Society (PIDS) (alternate)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pharmaceutical Research and Manufacturers of America (PhRMA)
ROBERTSON, Corey, MD, MPH
Senior Director, US Medical, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine Sidney Kimmel Medical College at Thomas Jefferson University
Philadelphia, PA