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

## Advisory Committee on Immunization Practices (ACIP)

## Summary Report
## February 27-28, 2019
## Atlanta, Georgia

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| Thursday: February 28, 2019 | |
|---|---|
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**Final - February 25, 2019**

**MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)**

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329
February 27-28, 2019

| | AGENDA ITEM | PRESIDER/PRESENTER(s) |
|---|---|---|
| **Wednesday, February 27** | | |
| **8:00** | **Welcome & Introductions** | Dr. Jose Romero (ACIP Chair)<br>Dr. Amanda Cohn (ACIP Executive Secretary; CDC) |
| **8:20** | **Japanese Encephalitis Vaccine** | |
| | Introduction | Dr. Chip Walter (ACIP, WG Chair) |
| | Background and review | Dr. Susan Hills (CDC/NCEZID) |
| | Updated recommendations for U.S. travelers | Dr. Susan Hills (CDC/NCEZID) |
| | Accelerated primary series in adults | Dr. Susan Hills (CDC/NCEZID) |
| | Booster dose recommendations | Dr. Susan Hills (CDC/NCEZID) |
| **9:20** | ***Break*** | |
| **9:30** | **Anthrax Vaccines** | |
| | Introduction | Dr. David Stephens (ACIP, WG Chair) |
| | AV7909 (NuThrax) | Dr. William Bower (CDC/NCEZID) |
| | Preexposure AVA booster dose interval | Dr. William Bower (CDC/NCEZID) |
| **10:30** | ***Break*** | |
| **10:40** | **Influenza Vaccines** | |
| | Introduction | Dr. Chip Walter |
| | Surveillance update | Ms. Lynnette Brammer (CDC/NCIRD) |
| | VE update | Dr. Brendan Flannery (CDC/NCIRD) |
| | Afluria quadrivalent for children aged 6 through 59 months | Dr. Gregg Sylvester (Seqirus) |
| | Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink | Dr. James Donahue (Marshfield Clinic) |
| | Summary and work group considerations | Dr. Lisa Grohskopf (CDC/NCIRD) |
| **12:00** | ***Lunch*** | |
| **1:00** | **Human Papillomavirus Vaccines** | |
| | Introduction | Dr. Peter Szilagyi (ACIP, WG Chair) |
| | Overview and background | Dr. Lauri Markowitz (CDC/NCIRD) |
| | Impact and cost effectiveness of mid-adult HPV vaccination | Dr. Marc Brisson (Laval University) |
| | Overview of health economic results from 4 modeling groups | Dr. Harrell Chesson (CDC/NCHHSTP) |
| | Mid-adult HPV vaccination: patient values and acceptability | Dr. Nancy McClung (CDC/NCIRD) |
| | Program and vaccine provider surveys | Dr. Elissa Meites (CDC/NCIRD) |
| | Work group considerations | Dr. Lauri Markowitz (CDC/NCIRD) |
| **2:30** | ***Break*** | |
| **2:40** | **Combination Vaccines** | |
| | Introduction | Dr. Kelly Moore (ACIP, WG Chair) |
| | Immunogenicity and safety of a pediatric hexavalent vaccine | Dr. Andrew Lee (Merck) |
| | Hib vaccines in AI/AN population | Dr. Laura Hammitt (Johns Hopkins University) |
| | Summary, review of work group considerations | Dr. Sara Oliver (CDC/NCIRD) |
| **3:30** | ***Break*** | |
| **3:40** | **Public Comment** | |
| **4:55** | ***Break*** | |
| **5:00** | **VOTES** | |
| | Japanese Encephalitis Vaccine | Dr. Susan Hills (CDC/NCEZID) |
| | Anthrax Vaccines | Dr. William Bower (CDC/NCEZID) |
| **5:30** | **Adjourn** | |





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## Final - February 25, 2019

**Thursday, February 28**

| | | |
|---|---|---|
| **8:00** | **Agency Updates & Unfinished Business**<br>CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO | Dr. Nancy Messonnier (CDC/NCIRD); *Ex Officio* Members |
| **8:30** | **Pneumococcal Vaccines** | |
| | Introduction | Dr. Grace Lee (ACIP, WG Chair) |
| | PCV13 direct and indirect effects on serotype 3 disease | Dr. Tamara Pilishvili (CDC/NCIRD) |
| | PCV13 direct effects on pneumonia hospitalizations in adults | Dr. Fernanda Lessa (CDC/NCIRD) |
| | Comparison of economic analyses of PCV13 use among adults ≥65 years old | Dr. Andrew Leidner (CDC/NCIRD) |
| | GRADE and Evidence to Recommendations (EtR) for PCV13 use among adults ≥65 years old in the context of indirect effects experience to date | Dr. Almea Matanock (CDC/NCIRD) |
| **10:30** | ***Break*** | |
| **10:40** | **Meningococcal Vaccines** | |
| | Introduction | Dr. David Stephens (ACIP, WG Chair) |
| | Immunogenicity and safety of a MenB-FHbp booster dose | Dr. Paul Balmer (Pfizer) |
| | Immunogenicity and safety of a MenB-4C booster dose | Dr. Phil Watson (GSK) |
| | GRADE and Evidence to Recommendations Framework for MenB booster doses | Dr. Catherine Bozio (CDC/NCIRD) |
| | Work Group interpretation of data, considerations, and next steps | Dr. Sarah Mbaeyi (CDC/NCIRD) |
| **11:55** | ***Lunch*** | |
| **1:00** | **Zoster Vaccines** | |
| | Introduction | Dr. Kelly Moore (ACIP, WG Chiar) |
| | Zoster vaccine uptake and supply | Dr. Kathleen Dooling (CDC/NCIRD) |
| | RZV safety update | Dr. Tom Shimabukuro (CDC/NCEZID) |
| **1:40** | **Hepatitis Vaccines** | |
| | Introduction | Dr. Kelly Moore (ACIP, WG Chair) |
| | Background: HepA vaccines and persons with HIV infection | Dr. Mark Weng (CDC/NCHHSTP) |
| | GRADE: Use of HepA vaccines among persons with HIV infection | Ms. Alaya Koneru (CDC/NCHHSTP) |
| | Evidence to Recommendation Framework: Use of HepA vaccines among persons with HIV infection | Dr. Mark Weng (CDC/NCHHSTP) |
| **2:35** | **Vaccine Supply** | |
| **2:40** | **Adjourn** | |

***Acronyms***

| | |
|---|---|
| AI/AN | American Indian/Alaska Native |
| AVA | Anthrax vaccine absorbed |
| CDC | Centers for Disease Control & Prevention |
| CMS | Centers for Medicare and Medicaid Services |
| DoD | Department of Defense |
| DVA | Department of Veterans Affairs |
| EtR | Evidence to Recommendations Framework |
| FDA | Food and Drug Administration |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| Hib | *Haemophilus influenzae* type b |
| HRSA | Health Resources and Services Administration |
| IHS | Indian Health Service |
| MenB | Serogroup B meningococcal vaccine |
| 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] |
| NVPO | National Vaccine Program Office |
| PCV13 | 13-valent pneumococcal conjugate vaccine |
| RZV | Recombinant zoster vaccine |
| WG | Work Group |





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## Acronyms

| | |
|---|---|
| AAFP | American Academy of Family Physicians |
| AAP | American Academy of Pediatrics |
| ABCs | Active Bacterial Core Surveillance |
| ACA | Affordable Care Act |
| ACHA | American College Health Association |
| ACIP | Advisory Committee on Immunization Practices |
| ACOG | American College of Obstetricians and Gynecologists |
| ACP | American College of Physicians |
| ADVISE | Agent-based Dynamic model for Vaccination and Screening Evaluation |
| AE | Adverse Event |
| AGW | Anogenital Warts |
| AHIP | America's Health Insurance Plans |
| AI/AN | American Indian/Alaskan Native |
| AIGIV | Anthrax Immune Globulin Intravenous |
| AIM | Association of Immunization Managers |
| ALTS | Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study |
| Anti-HAV | Serum Antibody to Hepatitis A Virus |
| Anti-HBsAg | Hepatitis B Surface Antigen |
| Anti-PA IgG | Anti-Protective Antigen Immunoglobulin G |
| AOA | American Osteopathic Association |
| APhA | American Pharmacists Association |
| APN | Advanced Practice Nurse |
| APRN | Advanced Practice Registered Nurse |
| aQIV | Adjuvanted Quadrivalent Influenza vaccine |
| ARFI | Acute Respiratory or Febrile Illness |
| ARI | Acute Respiratory Illness |
| ART | Antiretroviral Therapy |
| ASC-US | Atypical Squamous Cells of Undetermined Significance |
| ASTHO | Association of State and Territorial Health Officers |
| ATS | American Thoracic Society |
| AVA | Anthrax Vaccine Adsorbed |
| BAL | Bronchial Lavage |
| *B. anthracis* | *Bacillus anthracis* |
| BLA | Biologics License Application |
| BMI | Body Mass Index |
| CAIH | Center for American Indian Health |
| CAP | Community-Acquired Pneumonia |
| CAPiTA | Community-Acquired Pneumonia Immunization Trial in Adults |
| CDC | Centers for Disease Control and Prevention |
| CDSi | Clinical Decision Support for Immunization |
| CER | Cost-Effectiveness Ratio |
| CFR | Case Fatality Ratio |
| CIN2+ | Cervical Intraepithelial Neoplasia Grade 2 or Worse |
| CISNET | Cancer Intervention and Surveillance Modeling Network |
| CLD | Chronic Liver Disease |
| CMS | Center for Medicare and Medicaid Services |



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| | |
|---|---|
| COI | Conflict of Interest |
| COID | Committee on Infectious Diseases (AAP) |
| CONACH | Committee on Native American Child Health |
| COPD | Chronic Obstructive Pulmonary Disease |
| CSTE | Council of State and Territorial Epidemiologists |
| DC | District of Columbia |
| DFO | Designated Federal Official |
| DNA | Deoxyribonucleic Acid |
| DoD | Department of Defense |
| DSMB | Data Safety Monitoring Board |
| DTaP | Diphtheria and Tetanus Toxoid and Pertussis |
| DVA | Department of Veterans Affairs |
| EB | Empirical Bayesian |
| ED | Emergency Department |
| ED | Effective Dilution |
| EGL | External Genital Lesions |
| EHR | Electronic Health Record |
| EIS | Epidemic Intelligence Service |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EMA | European Medicines Agency |
| EMR | Electronic Medical Record |
| ESPID | European Society for Paediatric Infectious Diseases |
| EtR | Evidence to Recommendation |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FDA | Food and Drug Administration |
| FFS | Medicare Fee-For-Service |
| FHA | Filamentous Hemagglutinin |
| FQHC | Federally Qualified Health Center |
| FRA | Focus Reduction Assay |
| GAVI | Global Alliance for Vaccines and Immunisation |
| GBS | Guillain-Barré Syndrome |
| GCC | (Tom Harkin) Global Communications Center |
| GEE | Generalized estimating equations |
| GI | Gastrointestinal |
| GMT | Geometric Mean Titers |
| GRADE | Grading of Recommendation Assessment, Development and Evaluation |
| GSK | GlaxoSmithKline |
| HAART | Highly Active Antiretroviral Therapy |
| HBIG | Hepatitis B Immune Globulin |
| HCAP | Healthcare-Associated Pneumonia |
| HCP | Healthcare Personnel / Providers |
| HCW | Healthcare Workers |
| HEDIS | Healthcare Effectiveness Data and Information Set |
| HEMU | Health Economics Modeling Unit |
| HepA | Hepatitis A |
| HepB | Hepatitis B |
| HHS | (Department of) Health and Human Services |
| HI | Hemagglutinin Inhibition |



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| | |
|---|---|
| Hib | Haemophilus Influenzae Type B |
| HPV | Human Papillomavirus |
| HPV-IMPACT | HPV Vaccine Impact Monitoring Project |
| HRSA | Health Resources and Services Administration |
| hSBA | Human Serum Bactericidal Activity |
| HZ | Herpes Zoster |
| ICD | International Classification of Diseases |
| ICER | Incremental Cost-Effectiveness Ratio |
| ICU | Intensive Care Unit |
| IDSA | Infectious Disease Society of America |
| Ig | Immunoglobulin |
| 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 |
| IOM | Institute of Medicine |
| IPD | Invasive Pneumococcal Disease |
| IRB | Institutional Review Board |
| ISD | Immunization Services Division |
| ISO | Immunization Safety Office |
| ITT | Intention-To-Treat |
| IV | Intravenously |
| IVE | Influenza Vaccine Effectiveness |
| IVIG | Intravenous Immunoglobulin |
| JE | Japanese Encephalitis |
| IPV | Inactivated Poliovirus |
| JE-MB | Inactivated Mouse Brain-Derived JE Vaccine |
| JE-VC | Inactivated Vero Cell Culture-Derived JE Vaccine |
| KPNC | Kaiser Permanente Northern California |
| LAIV | Live Attenuated Influenza Vaccine |
| $LD_{50}$ | Median Lethal Dose |
| LLR | Log Likelihood Ratio |
| LMP | Last Menstrual Period |
| LMICs | Low and Middle-Income Countries |
| LSIL | Low-Grade Squamous Intraepithelial Lesions |
| LTFU | Long-Term Follow-Up |
| MAE | Medically Attended Adverse Event |
| MAM | Mid-Adult Men Study |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MenB | Meningococcal B |
| MDHHS | Michigan Department of Health and Human Services |
| MMP | Medical Monitoring Project |
| *MMWR* | *Morbidity and Mortality Weekly Report* |
| mITT | Modified Intent-To-Treat Analysis |
| MSM | Men Who Have Sex With Men |
| NACCHO | National Association of County and City Health Officials |



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| | |
|---|---|
| NACI | National Advisory Committee on Immunization |
| NAP | National Action Plan |
| NAPNAP | National Association of Pediatric Nurse Practitioners |
| NAS | National Academy of Sciences |
| NBPP | Non-Bacteremic Pneumococcal Pneumonia |
| 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 |
| NCI | National Cancer Institute |
| NCIRD | National Center for Immunization and Respiratory Diseases |
| NCVIA | National Childhood Vaccine Injury Act |
| NF | Neutralizing Factor |
| NFID | National Foundation for Infectious Diseases |
| NHANES | National Health and Nutrition Examination Survey |
| NHIS | National Health Interview Survey |
| NHP | Non-Human Primate |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NIPP | Non-Bacteremic Pneumococcal Pneumonia |
| NIS-Child | National Immunization Survey-Child |
| NIS-Teen | National Immunization Survey—Teen |
| NIS | National Inpatient Sample |
| NNDSS | National Notifiable Diseases Surveillance System |
| NNV | Number Needed to Vaccinate |
| NP | Nasopharyngeal |
| NVAC | National Vaccine Advisory Committee |
| NVPO | National Vaccine Program Office |
| NVSN | New Vaccine Surveillance Network |
| NVT | Non-Vaccine Types |
| NYC | New York City |
| OASH | Office of the Assistant Secretary for Health |
| OB-GYN | Obstetrician-Gynecologist |
| OID | Office of Infectious Disease |
| OMPC | Outer Membrane Protein Complex |
| OP | Oropharyngeal |
| PA | Protective Antigen |
| PCR | Polymerase Chain Reaction |
| PCV | Pneumococcal Conjugate Vaccine |
| PEP | Post-Exposure Prophylaxis |
| PRP | Polyribosyl Ribitol Phosphate |
| PICO | Population, Intervention, Comparison, Outcomes |
| PIDS | Pediatric Infectious Disease Society |
| PK | Pharmacokinetics |
| PNP | Pediatric Nurse Practitioner |
| PrEP | Pre-Exposure Prophylaxis |
| PREVENT | Pregnancy Influenza Vaccine Effectiveness Network |
| PRNT | Plaque Reduction Neutralization Test |
| PT | Preferred Terms (MedDRA) |
| PWHIV | Persons Living With HIV |



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| | |
|---|---|
| PWID | People Who Inject Drugs |
| QALY | Quality-Adjusted Life-Year |
| QIV | Quadrivalent Influenza Vaccine |
| RCA | Rapid Cycle Analysis |
| RCT | Randomized Controlled Trial |
| RIV | Recombinant Influenza Vaccine |
| ROA | Route of Administration |
| RN | Registered Nurse |
| RNA | Ribonucleic Acid |
| RR | Relative Risk |
| RSV | Respiratory Syncytial Virus |
| RT-PCR | Reverse Transcriptase Polymerase Chain Reaction |
| rRT-PCR | Real-Time Reverse Transcription Polymerase Chain Reaction |
| RZV | Recombinant Zoster Vaccine |
| *S. pneumoniae* | *Streptococcus pneumoniae* |
| SAB | Spontaneous Abortion |
| SAE | Serious Adverse Event |
| SAGE | Strategic Advisory Group of Experts on Immunization (WHO) |
| SAHM | Society for Adolescent Health and Medicine |
| sBLA | Supplemental Biologics License Application |
| SC | Subcutaneous |
| SCC | Squamous Cell Carcinoma |
| SES | Socioeconomic Status |
| SFHR | Small Fragment Homologous Replacement |
| SIDS | Sudden Infant Death Syndrome |
| SMD | Standardized Mean Difference |
| SME | Subject Matter Expert |
| SNiPP | Surveillance for Non-invasive Pneumococcal Pneumonia |
| SNS | Strategic National Stockpile |
| SSUAD | Serotype-Specific Urinary Antigen Detection |
| TBE | Tick-Borne Encephalitis |
| Tdap | Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis |
| TNA | Toxin Neutralization Assay |
| TND | Test Negative Design |
| TIV | Trivalent Influenza Vaccine |
| UAD | Urinary Antigen Detection |
| UAT | Urinary Antigen Test |
| UK | United Kingdom |
| US | United States |
| USPHS | US Public Health Service |
| USPI | US Product Information |
| US Flu VE | US Influenza Vaccine Effectiveness Network |
| UTD | Up-To-Date |
| VA | (US Department of) Veteran's Affairs |
| VAERS | Vaccine Adverse Event Reporting System |
| VE | Vaccine Effectiveness Efficacy |
| VE | Vaccine Efficacy |
| VFC | Vaccines For Children |
| VICP | Vaccine Injury Compensation Program |



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|---|---|
| VLP | Virus-Like Particles |
| VRBPAC | Vaccine and Related Blood Products Advisory Committee |
| VSD | Vaccine Safety Datalink |
| VT | Vaccine Type |
| VT-CAP | Vaccine-Type Community-Acquired Pneumonia |
| WG | Work Group |
| WHO | World Health Organization |
| VE | Vaccine Effectiveness |
| YF | Yellow Fever |
| ZVL | Zoster Vaccine Live |



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

**José Romero, MD, FAAP**
**ACIP Chair**

**Amanda Cohn, MD**
**Executive Secretary, ACIP / CDC**

Dr. Romero called to order the February 2019 Advisory Committee on Immunization Practices (ACIP) and thanked everyone for their attendance.

Dr. Cohn welcomed everyone to the February 2019 ACIP meeting. She indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She pointed out that multiple Centers for Disease Prevention and Control (CDC) staff were present at the entrance to the room and at the desk outside the room to assist members of the public with questions.

She noted that handouts of the presentations were distributed to the voting ACIP members and were made available for others on the tables outside of the auditorium. Additionally, slides were made available through a ShareFile link for liaison and *ex-officio* members. Slides presented during this meeting will be posted on the ACIP website approximately three to four weeks after the meeting. The live webcast also will be posted in about four weeks following the meeting, and the meeting minutes are posted to the ACIP website generally within about 120 days following the meeting. Minutes from the October 2018 meeting were scheduled to be posted shortly after the February 2019 meeting.

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

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

The next ACIP meeting will be convened at CDC on Wednesday and Thursday, Wednesday and Thursday, June 26-27, 2019. Registration for all meeting attendees is required and will open on the ACIP website shortly. Registration is not required for webcast viewing.



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Dr. Cohn announced the following Liaison and *Ex Officio* member substitutions:

Liaison Representatives

- Susan Lett MD, MPH would be representing Association of Immunization Managers (AIM) and Council of State and Territorial Epidemiologists (CSTE)
- Dr. Linda O'Neal Eckert will serve as the new American College of Obstetricians and Gynecologists (ACOG) member

*Ex-Officio* Members

- Lori Hoffman Hōgg MS, RN, CNS would be representing the Department of Veterans Affairs (DVA)

Dr. Cohn then introduced the incoming ACIP Chair and Dr. Romero introduced the four new ACIP members and guest attendees:

**José Romero, MD**

Dr. Romero is the incoming ACIP Chair and will serve in this role for the next 3 years. He was an ACIP member from 2014-2018. He is a pediatrician and pediatric infectious disease specialist at the University of Arkansas. He brings extensive administrative, vaccine policy, clinical, teaching, and research perspective to the ACIP. He has done a remarkable job over the years leading several ACIP Work Groups (WGs) as Chair. Dr. Romero responded that this was a unique honor and that he was very grateful to have this position.

**Kevin Ault, MD**

Dr. Ault is a Professor of Obstetrics and Gynecology at the University of Kansas School of Medicine. He was a Liaison representative to ACIP from ACOG from 2013-Present. He currently is a member of ACIP Influenza WG.



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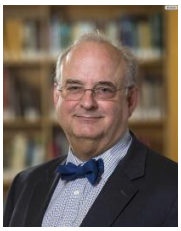

**Stephan Gravenstein, MD, MPH**

Dr. Gravenstein is an Academic and Clinical Geriatrician at Brown University School of Medicine and School of Public Health. He has extensive immunization research experience across the lifespan, with a special focus on immunization issues in older adults.

**Veronica Valentine McNally, JD**

Veronica Valentine McNally will serve as the Consumer Representative to ACIP. She is President and CEO of the Franny Strong Foundation, which was established in memory of her infant daughter and provides education about vaccinations.

**H. Keipp Talbot, MD, MPH**

Dr. Keipp Talbot is an Internist and Infectious Disease Specialist at Vanderbilt University. She also brings to ACIP immunization research experience across the lifespan, with a special focus on immunization issues in older adults. Previously, she was a member of the ACIP Pneumococcal WG.

Guest Attendees at This Meeting

- ❑ Dr. Alejandro Cravioto, Chair, World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE)
- ❑ Dr. Jon Abramson, Chair, Global Alliance for Vaccines and Immunisation (GAVI) Vaccine Investment Strategy Steering Group

Dr. Cohn indicated that as stated in the ACIP charter, the purpose of the ACIP committee is to deliberate on the use of vaccines to control disease in the United States (US), including considerations of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, economic analyses, and implementation issues:



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- "The committee may revise or withdraw their recommendations regarding a particular vaccine as new information on disease epidemiology, vaccine effectiveness of safety, economic consideration or other data become available."
- "Under provisions of the Affordable Care Act (ACA) . . . immunization recommendations of the committee that have been adopted by the Director of the CDC must be covered by applicable health plans"

ACIP is, at its heart, a public body. Engagement with the public and transparency in ACIP's processes is vital to the Committee's work. As part of ACIP's commitment to continuous improvement, this meeting features changes to strengthen ACIP's oral and written public comment process. These changes are designed to accommodate increased public interest in ACIP's work, maximize opportunities for comment, make public comment more transparent and efficient, and create a fair process for assigning limited oral public comment time. Dr. Cohn took a couple of minutes to outline these changes for this meeting. As always, ACIP is dedicated to continuous improvement and welcomes feedback on ways they can continue to strengthen ACIP's processes and maximize engagement with the public.

First, Dr. Cohn addressed changes to ACIP's oral public comment process. In previous meetings, ACIP would hold multiple, short public comment periods over the course of the meeting's two days and people would sign up for public comment on site at the day of the meeting. With increased public interest in commenting at ACIP meetings, ACIP wanted to improve this process to provide more time for public comment, make the process for signing up for comment more efficient, and create a fair way to determine public speakers when there were more people requesting to speak than could be accommodated in the meeting's limited time. For this meeting, the following improvements to ACIP's public comment process were made:

- More Time: Rather than multiple short periods across two days, there is now a single, 75-minute public comment period at the end of the first day of the meeting and before any scheduled votes. This change reserves more time for public comment than in previous meetings, and allows speakers to hear all the presentations related to an ACIP vote before their comments.

- Clearer Registration Process: To create a fairer and more efficient process for requesting to make an oral comment, ACIP now asks that people interested in making an oral comment submit a request online in advance of the meeting. Priority is given to these advance requests. If more people request to speak than can be accommodated, a blind lottery will be conducted to determine who the speakers will be. Speakers selected in the lottery will be notified in advance of the meeting. Public comment speakers for this meeting were instructed to sign in with Noah Aleshire at the information table outside the main auditorium so that ACIP would know they were present.

Some elements of the previous process have been maintained. As with previous comment periods, speakers will be limited to three-minutes to make their comments. It is critical that speakers stay within this time to ensure that all public commenters have an opportunity to speak. A lighted timer will be displayed on the screen so that the speakers will know when their time has expired. As with previous meetings, the ACIP Chair has discretion to recognize individuals to provide scientific and technical information that is relevant to the Committee's deliberations at any time during the meeting. This is not an alternative to the public comment process. Rather, it is an opportunity for the Committee to obtain relevant scientific and technical information from individual experts and stakeholders to inform its discussions.



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Substantial improvements also have been made to ACIP's written comment process. These changes were made based on feedback from the public asking for more time and the ability to submit more detailed written comments. Previously, public comments were submitted via email to CDC, with length limited to one-page and comments required to be submitted before to the meeting. For this and subsequent meetings, ACIP is using a docket on regulations.gov where any member of the public can submit a written comment. This is a substantial improvement, as this new process allows for the ability to submit longer comments and the ability to include attachments, visibility of the comments to the public, and a longer window for comment submission. Comments may now be submitted up to 48 hours following the end of the meeting. All comments submitted within 72 hours prior to the meeting will be made available to the ACIP members prior to the meeting.

At the time of this meeting, the docket was still open. Using docket ID CDC-2019-0002, those interested were invited to submit a comment at regulations.gov. Dr. Cohn indicated that the docket would remain open for 48 hours following the end of the meeting. This information also can be found in the *Federal Register* notice announcing ACIP meetings and on the ACIP meeting website. She encouraged everyone to access and read the public comments posted.

As noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to these vaccines, but are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the provision that he/she abstains on all votes related to the vaccines of that company. At the beginning of each meeting, ACIP members state any COIs.

Detailed instructions for submission of names of potential candidates to serve as ACIP members will be added to the ACIP website shortly. A transition is being made to an online application process, which is anticipated to make the process more efficient and easier for members to apply for nomination. Applications for ACIP membership are due no later than July 1, 2019 for the 4-year term beginning July 2020.

Dr. Romero conducted a roll to determine whether any ACIP members had COIs. Dr. Gravenstein declared COIs related to Sanofi, Seqirus, and Merck. Dr. Romero then requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaisons is included in the appendixes at the end of the full minutes from the February 2019 ACIP meeting.



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# Japanese Encephalitis Vaccine

## Introduction

**Chip Walter, MD**
**Chair, ACIP Flavivirus Vaccines WG**

Dr. Walter reminded everyone that the Japanese Encephalitis (JE) Vaccine WG's objectives are to: 1) review newly available safety and immunogenicity data for inactivated Vero cell culture-derived JE vaccine (JE-VC); 2) review epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated data; and 4) update *Morbidity and Mortality Weekly Report (MMWR) Recommendations and Reports*.

WG presentations to ACIP during the October 2018 session included the following topics:

- Evidence to Recommendations (EtR) framework for updated JE vaccine recommendations
- Accelerated dosing schedule data in adults
- Booster dose recommendations
  - Strengthen current permissive recommendation
  - Expand to include children aged <17 years

Dr. Walter indicated that this session would include the following presentations in anticipation of taking a final vote:

- Background and review of JE and JE vaccine
- Review and vote on
  - Updated recommendations for U.S. travelers
  - Accelerated primary series in adults
  - Booster dose recommendations
- Conclusion and next steps

## Background and Review of JE and JE Vaccine

**Dr. Susan Hills, MBBS, MTH**
**Arboviral Diseases Branch**
**Division of Vector-Borne Diseases**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**
**Fort Collins, Colorado**

Dr. Hills began her presentation with a brief background and review of JE and JE vaccine. JE is caused by a mosquito-borne flavivirus that occurs in most of Asia and parts of the Western Pacific, and is the leading vaccine-preventable cause of encephalitis in Asia. Most JE virus infections are asymptomatic with fewer than 1% of infected people developing neurological disease. However, when disease does occur it is often severe. Overall, about 20% to 30% of patients die and 30% to 50% of survivors have significant neurologic, cognitive, or behavioral sequelae. There is no specific antiviral therapy, and treatment consists of supportive care[1]. Currently, even with national vaccination programs in some endemic countries, there are still an



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estimated 68,000 JE cases annually in Asia, with an overall incidence for all age groups of approximately 1.8 cases per 100,000 population. The highest risk for infection is in rural, agricultural areas because the primary breeding site for the main vector is rice fields[2] [[1]Vaughn DW. Epidemiol Rev 1992; [2]Campbell GL, et al. Bull World Health Organ 2011].

For most travelers to Asia, the risk for JE is very low but varies based on travel destination, duration, season, activities, and accommodations. A JE vaccine was first licensed in the US in 1992. In the 25 years from 1992 through 2017, only 12 JE cases were identified among US travelers or expatriates. Based on these 12 reported JE cases and 4 to 5 million US citizen trips to Asia annually, the estimated risk for travelers is less than 1 case per million trips to Asia. Travelers with longer trips or increased rural and outdoor exposures are at higher risk of acquiring JE virus infection. Among the 12 US traveler cases, 8 (67%) had traveled for a month or longer, 3 (25%) had traveled for less than a month but spent at least one night in a rural area, and 1 (8%) traveled for less than one month but there was no information on this individual's itinerary or activities [Hills et al. CDC Yellow Book 2018].

JE-VC, manufactured by Valneva as IXIARO®, is the only JE vaccine currently licensed and available in the US. The vaccine was licensed for adults 17 years of age and older in 2009, and the licensure was subsequently extended to children ages 2 months and older in 2013. The primary series is 2 doses administered 28 days apart. ACIP recommendations for a booster dose for adults at least 1 year after the primary series were approved in 2011. Dr. Hills noted that she would discuss booster doses for children later in the session.

There are no efficacy data for IXIARO®. However, there is an established immunologic correlate of protection which is a JE virus 50% plaque reduction neutralization test ($PRNT_{50}$) titer of ≥10. The vaccine was licensed based on a non-inferior neutralizing antibody response compared with a licensed mouse brain-derived JE vaccine [Hombach J. *Vaccine* 2005; Markoff L. Vaccine 2000].

Following licensure of JE-VC for adults in 2009, ACIP approved recommendations for use of JE vaccine in US travelers. In 2013, following licensure of JE-VC for children, a Grading of Recommendation Assessment, Development and Evaluation (GRADE) analysis was performed and JE vaccine recommendations were reviewed. The recommendations were extended to children, but no other changes to the recommendation were considered necessary [CDC. *MMWR* Rec Rep 2010; CDC. *MMWR* Morb Mortal Wkly Rep 2013].

The current review of the JE vaccine recommendations for travelers is a routine review in consideration of new safety, immunogenicity, and traveler risk data. As part of this review, the JE Vaccine WG has prepared an updated *MMWR Recommendation and Reports* document that incorporates previously published policy notes and new data indications and dosing schedules.



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## Updated Recommendations for US Travelers

**Dr. Susan Hills, MBBS, MTH**
**Arboviral Diseases Branch**
**Division of Vector-Borne Diseases**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**
**Fort Collins, Colorado**

Dr. Hills indicated that as Dr Walter mentioned earlier, ACIP would be asked to vote on three topics in regard to JE vaccine during this meeting, the first of which would be the updates to the JE vaccine recommendations for US travelers. The changes from the current JE-vaccine recommendations are minor. In summary they are as follows:

- ❑ Inclusion of additional information on the factors that increase JE risk to help healthcare providers identify travelers who might be at high risk of JE virus infection based on their planned itinerary and to assist with decision-making regarding who should be vaccinated
- ❑ Longer-term travel is no longer defined as a specific cut-off of 1 month or longer
- ❑ Consideration of vaccination for travelers to an area with an ongoing JE outbreak has been removed
- ❑ Minor wording changes have been made to address questions that have been raised about the wording of the existing recommendations, such as changing “expatriates” to “persons moving to a JE-endemic country to take up residence”

ACIP would be asked to vote on these slightly modified JE vaccine recommendations for US travelers. However, the WG felt that the additional information provided as part of the overall JE vaccine recommendations would be essential for providing context. Although ACIP members reviewed this information in the background materials that were sent around, Dr. Hills reviewed the complete JE vaccine recommendations section of the *MMWR* document. The recommendations section begins with the following:

> “JE is a very low risk disease for most US travelers to JE-endemic countries. However, some travelers will be at increased risk of infection based on their planned itinerary. Factors that increase the risk of JE virus exposure include: 1) longer duration of travel; 2) travel during the JE virus transmission season; 3) spending time in rural areas; 4) participating in extensive outdoor activities; and 5) staying in accommodations without air conditioning, screens, or bed nets.”

Accompanying the recommendations is a box that provides more information on these five risk factors to assist healthcare providers in advising patients on what factors increase their risk. The first two sections of the box explain “Duration” and “Season.” The “Duration” section provides an explanation that in terms of duration, the highest incidence of disease occurs in longer-term travelers, there is not a specific duration that puts a traveler at risk, but longer-term travel increases the likelihood of exposure to infected mosquitos, and that longer-term travel includes cumulative periods in endemic areas. It then describes that JE virus transmission can be seasonal or year-round and points to resources to assist in understanding this further. The “Location” section outlines the settings where the highest risk occurs and other potential concerns related to the location of travel, the “Activities” section discusses the higher risk with outdoor activities and provides examples, and the “Accommodations” section provides more details on accommodations that are likely to increase the risk of mosquito exposure:



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| |
|---|
| **Duration**<br>• Highest incidence of disease has been reported among longer-term travelers.<br>• Although no specific duration of travel puts a traveler at risk for JE, longer-term travel increases the likelihood that a traveler might be exposed to an infected mosquito.<br>• Longer-term travel includes cumulative periods in endemic areas, such as frequent travelers, and persons residing in urban areas who are likely to visit higher risk rural areas. |
| **Season**<br>• JE virus transmission occurs seasonally in some areas, and year-round in other areas.<br>• Information on expected JE virus transmission by country is available on the CDC website (see Japanese encephalitis chapter in CDC Health Information for International Travel [the Yellow Book]). These data should be interpreted cautiously because JE virus transmission varies within countries and from year to year. |
| **Location**<br>• Highest risk occurs from mosquito exposure in rural or agricultural areas.<br>• Mosquitoes that transmit JE virus typically breed in flooded rice fields, marshes, and other stagnant collections of water.<br>• Some cases have been reported among travelers to coastal areas or resorts located in or adjacent to rural or rice growing areas.<br>• JE can occur in large, focal outbreaks indicating extensive active JE virus transmission in those areas. |
| **Activities**<br>• The mosquitoes that transmit JE virus feed most often in the outdoors, particularly from sunset through dawn, so examples of activities that increase risk include:<br>  o Outdoor recreation such as camping, hiking, trekking, biking, rafting, fishing, hunting, or farming.<br>  o Spending substantial time outdoors, especially during the evening or night. |
| **Accommodations**<br>• Accommodations without air conditioning, screens, or bed nets increase risk of mosquito exposure. |

The recommendations section then moves on to say:

> "Healthcare providers should assess each traveler's risk for mosquito exposure and JE virus infection based on their planned itinerary, and discuss ways to reduce their risk. All travelers to JE-endemic countries should be advised to take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms.
>
> For some people who might be at increased risk for JE based on travel duration, season, location, activities, and accommodations, JE vaccine can further reduce the risk for infection. The decision whether to vaccinate should be individualized and weigh the: 1) risks related to the specific travel itinerary, 2) likelihood of future travel to JE-endemic countries, 3) high morbidity and mortality of JE when it occurs, 4) availability of an effective vaccine, 5) possibility, but low probability, of serious adverse events following vaccination, and 6) traveler's personal perception and tolerance of risk."

Dr. Hills noted that this is the wording ACIP members would be asked to vote on, although she emphasized that it is important to consider this language in the broader context of the information she just presented, which also will appear in the recommendations section of the *MMWR* document. The wording is:

> "JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g., ≥1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas.



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JE vaccine also should be considered for shorter-term (e.g., less than 1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations . Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities.

JE vaccine is not recommended for travelers with very low risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside of a well-defined JE virus transmission season."

## JE-VC Accelerated Primary Series for Adults Aged 18-65 Years

**Dr. Susan Hills, MBBS, MTH**
**Arboviral Diseases Branch**
**Division of Vector-Borne Diseases**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**
**Fort Collins, Colorado**

The second topic Dr. Hills reviewed during this session for an ACIP vote was the accelerated schedule for JE-VC for adults aged 18 through 65 years. Although these data were presented to ACIP during the October 2018 and previous ACIP meetings, she briefly reviewed them before the vote.

In terms of the timeline of relevant events in regard to this topic, the Food and Drug Administration (FDA) approved JE-VC for use as a 2-dose primary series administered in the standard schedule at 0 and 28 days in March 2009. In October 2015, the manufacturer presented data to ACIP for an alternate accelerated primary series at 0 and 7 days in adults. In December 2017, the manufacturer submitted the Biologics License Application (BLA) amendment to the FDA. In October 2018, the FDA approved the accelerated primary series and the WG re-presented these data to ACIP.

The primary data supporting the accelerated schedule came from a randomized trial among adults aged 18 through 65 years. The study was conducted at seven study sites in Europe. JE-VC was administered with rabies vaccine in an accelerated or conventional schedule, and non-inferiority of the accelerated 0 and 7 day schedule compared with the 0 and 28 day conventional schedule was assessed[1]. Some additional data on a shorter primary series schedule came from a previous Phase 2 study in adults. In this trial, JE-VC was administered on a day 0, 14 and 28 day schedule or a 0 and 28 day schedule. For participants randomly assigned to the group that received the 0, 14 and 28 day schedule, blood was collected from participants prior to their third vaccination on day 28, meaning there are at 14 days after a 0 and 14 day schedule[2] [Jelinek T. J Travel Med 2015; Lyons A. Vaccine 2007].

In terms of the results from the primary study supporting the accelerated schedule, 99% of subjects who received the 0 and 7 day schedule were seroprotected at 28 days after dose 2 compared with 100% who were seroprotected after 2 doses when the doses were administered 28 days apart. The geometric mean titer (GMT) in the accelerated schedule group was higher than in the conventional schedule group. At 1 year after the second JE-VC dose, 94% of subjects who received the 2 doses 7 days apart and 86% of those who received the 2 doses 28 days apart were seroprotected, and the GMT remained higher in the accelerated schedule group [[1]Jelinek T. J Travel Med 2015; [2]Cramer JP. J Travel Med 2016; [3]https://clinicaltrials.gov].



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Regarding the additional data from the Phase 2 study, 96% of subjects who received 2 JE-VC doses on days 0 and 14 were seroprotected at 14 days after the second dose and the GMT was 328, which was almost the same as the seroprotection rate and GMT in the subjects who received the 2 doses on days 0 and 28 [Lyons A. Vaccine 2007].

The dose of JE-VC varies by age group and the accelerated primary series schedule data are only approved for adults ages 18 to 65 years. For children aged 2-35 months, the dose will be two 0.25mL doses administered on days 0 and 28. For children and adolescents aged 3-17 years, two 0.5mL doses are administered on days 0 and 28. For adults aged 18-65 years, the dose remains 0.5mL, but the second primary series dose can be administered from 7-28 days after the first dose. For adults aged >65 years, two 0.5mL doses are administered on days 0 and 28.

The vote for this section was for the proposed new recommendation for an accelerated schedule in adults aged 18-65 years. The wording is as follows:

> "In adults aged 18-65 years, the primary vaccination schedule is two doses administered on days 0 and 7-28"

**JE-VC Booster Doses**

**Dr. Susan Hills, MBBS, MTH**
**Arboviral Diseases Branch**
**Division of Vector-Borne Diseases**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**
**Fort Collins, Colorado**

The final topic Dr. Hills reviewed for the vote was JE-VC booster doses. As a reminder, in September 2010, the FDA approved a JE-VC booster dose for adults aged 17 years and older. ACIP subsequently approved a booster dose recommendation for adults. In February 2016, the manufacturer presented data to ACIP for a booster dose in children. In June 2017, the manufacturer submitted to the FDA a BLA amendment for a pediatric booster dose. In April 2018, the FDA approved the pediatric booster dose. In October 2018, the WG re-presented relevant booster dose data to ACIP. The current ACIP recommendation for a JE-VC booster dose is for adults aged 17 years and older is, "If the primary series of JE-VC was administered more than 1 year previously, a booster dose may be given before potential JE virus exposure" [CDC. *MMWR* Morb Mortal Wkly Rep 2011].

The topics for consideration in regard to changes to the recommendation were to lower the recommended age for a booster dose to include children, and to strengthen the current permissive booster dose recommendation. The supporting data for each topic were presented to ACIP during previous meetings and draft recommendations were presented in October 2018. Dr. Hills provided a brief review of the supporting data for each topic . For the pediatric booster dose recommendation, the supporting data come from one open label randomized trial conducted among children aged 14 months through 17 years. The study was conducted in the Philippines, which is a JE endemic country. It included 300 children randomized to receive or not receive a booster dose of JE-VC. For the 150 randomized to receive the booster dose, it was administered at 11 months after the second dose of the 2-dose primary JE-VC series[1]. Among these children who received the booster dose, 100% were seroprotected at 28 days



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after the booster dose with a GMT over 2000. At 2 years after the booster, 100% remained seroprotected and the GMT was 350 [Kadlecek V. Pediatr Infect Dis J. 20182; Kadlecek V. Pediatr Infect Dis J. 2018]. The WG concluded that the current booster dose recommendation for adults should be modified to include children.

The second booster dose topic Dr. Hills briefly reviewed were the data supporting the strengthening of the current booster dose permissive recommendation stating, “if the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure.” In the three studies that were the basis for this recommendation, the data showed that at 12-15 months after the 2-dose primary JE-VC series, 58%-83% of subjects were seroprotected. These studies were conducted in Europe where tick-borne encephalitis (TBE) vaccine is available. TBE virus is a flavivirus related to JE virus, and there was concern that there might have been a boosting effect of TBE vaccine which could explain some of the variability in study results. As a result, the manufacturer conducted a post hoc analysis that stratified subjects by TBE vaccination status [Schuller E. Vaccine 2008; Dubischar-Kastner K. Vaccine 2010; Eder S. Vaccine 2011; Dubischar K. ACIP presentation. February 2016].

That analysis showed that if subjects had received TBE vaccine before or after JE-VC, seroprotection rates over the following 5 years ranged from 92% at 1 year to 86% at 5 years. However, if subjects had not received TBE vaccine, seroprotection rates were lower, ranging from 75% at 1 year down to 64% at 5 years. In the group who had received TBE vaccine, geometric mean titers were also higher at each time point [Dubischar K. ACIP presentation. February 2016].

The WG concluded that after a 2-dose primary series, long-term JE seroprotection rates are lower in those not administered TBE vaccine compared with those administered TBE vaccine. TBE vaccine is not available in the US, and other flavivirus vaccines such as yellow fever (YF) vaccine are not routinely administered with JE-VC. Therefore, among US travelers, duration of protection following a booster dose of JE-VC is likely to be most similar to the subjects not administered TBE vaccine who had lower seroprotection rates through 5 years. Based on these data, the WG recommended that the permissive booster dose recommendation should be strengthened from “may be given” to “should be given.”

In summary, the final vote for an updated recommendation for a JE-VC booster dose will apply to both children and adults and will read as follows:

> “A booster dose (i.e., third dose) should be given at ≥1 year after completion of the primary JE-VC series if ongoing exposure or re-exposure to JE virus is expected.”

In terms of next steps, the draft *MMWR Recommendations and Reports* on JE vaccine for US travelers was circulated to ACIP members prior to this meeting, and the WG expected to be able to finalize and move to publication of the document after this meeting. Dr. Hills concluded that with the topics addressed in the votes during this session and the publication of the *MMWR*, the objectives for the JE Vaccine WG would all have been addressed and all activities completed. Therefore, the WG expects to discontinue the JE Vaccine WG meetings.



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## Discussion Points

Dr. Bernstein inquired as to whether there are any data for multiple boosters over time.

Dr. Hills responded that in the adult data following a single booster, there are seroprotection data through 6 years which show 96% protection. There are not additional data beyond that, so there are no recommendations for additional booster doses.

Dr. Romero pointed out that one consideration for the vote would be to mention that this is for both children and adults, because the recommendations over time have changed.

Dr. Hunter said he assumed the recommendation for the booster did not decrease the amount of vaccine available in permanent residents of the high risk areas, because a small amount of vaccine would be used.

Dr. Hills responded that the vaccine licensed in the US is not used in the national immunization programs in endemic countries because there are additional vaccines. A live-attenuated vaccine is produced in China that is used most extensively in JE-endemic countries. There also is a chimeric vaccine that is not licensed in the US that is available in endemic countries. JE-VC is licensed in some of the endemic countries and might be used in the private sector, but is not used in the very large national immunization programs, so there will be no impact there.

Dr. Walter asked whether three different motions would be needed, given that there were three separate recommendations.

Dr. Cohn confirmed that three votes would be needed. She explained that the process for the vote would be for ACIP members to propose/second a motion to vote, further discussion would then be entertained, and the vote would be stayed until the afternoon following public comment. During the JE session, Dr. Romero read each of the proposed recommendations into the record. During the voting session in the afternoon, Dr. Hills re-read the proposed recommendations before the vote with the incorporation of an suggested revisions. The proposed recommendations, motions, additional discussion, and the vote are combined as follows for ease of reading:

> *#1: Proposed JE Vaccine Recommendations*
>
> "JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g., ≥1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas.
>
> JE vaccine also should be considered for shorter-term (e.g., <1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations. Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities.
>
> JE vaccine is not recommended for travelers with very low risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside of a well-defined JE virus transmission season."



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Motion/Further Discussion

Dr. Frye proposed a motion to vote on JE Vote #1 as stated, which was seconded by Dr. Atmar.

No further discussion was posed.

**Motion/Vote #1: Proposed JE Vaccine Recommendations**

Dr. Frye proposed a motion to vote on JE Vote #1 as stated, which was seconded by Dr. Atmar. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**15 Favored:** Atmar, Ault, Bernstein, Ezeanolue, Gravenstein, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
**0 Opposed:** N/A
**0 Abstained:** N/A

*#2: Proposed New Recommendation for Primary Series Schedule in Adults Aged 18-65 Years*

"In adults aged 18–65 years, the primary vaccination schedule is two doses administered on days 0 and 7–28."

Motion/Further Discussion
Dr. Walter made a motion vote on the second recommendation as stated, which was seconded by Dr. Moore.

Dr. Lee thought it would be beneficial to have additional information if possible post-recommendation on safety surveillance for the accelerated schedule, it would add to the benefit-risk balance over time.

**Motion/Vote #2: Proposed New Recommendation for Primary Series Schedule in Adults Aged 18–65 Years**

Dr. Walter made a motion to vote on the second recommendation as stated, which was seconded by Dr. Moore. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**15 Favored:** Atmar, Ault, Bernstein, Ezeanolue, Gravenstein, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
**0 Opposed:** N/A
**0 Abstained:** N/A



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*#3: Proposed New Recommendation for JE-VC Booster Dose*

"A booster dose (i.e., third dose) should be given at ≥1 year after completion of the primary JE-VC series if ongoing exposure or re-exposure to JE virus is expected."

Motion/Further Discussion
Dr. Moore made a motion to vote on the third recommendation as proposed, which was seconded by Dr. Walter.

Dr. Szilagyi suggested adding, "for children and adults" because it differs from the other recommendation.

**Motion/Vote #3: Proposed New Recommendation for JE-VC Booster Dose**

Dr. Moore made a motion to vote on the third recommendation as proposed, which was seconded by Dr. Walter. The recommendation was revised to read, "For adults and children, a booster dose (i.e., third dose) should be given at ≥1 year after completion of the primary JE-VC series if ongoing exposure or re-exposure to JE virus is expected." The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**15 Favored:** Atmar, Ault, Bernstein, Ezeanolue, Gravenstein, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
**0 Opposed:** N/A
**0 Abstained:** N/A

## Anthrax Vaccine

### Introduction

**David S. Stephens, MD, FIDSA**
**ACIP Anthrax Vaccine Work Group (WG)**

Dr. Stephens reminded everyone that the Anthrax Vaccine WG was reconvened in March 2017 to discuss new data published since the last review in 2010. The US government stockpiles medical countermeasures, including anthrax vaccine, and CDC provides guidance for vaccine use and other aspects of preparedness should there be a wide-area release of *Bacillus anthracis* (*B. anthracis*) spores. The WG considered the body of evidence since the last review in 2010 for policy changes to optimize the use of anthrax vaccine for use prior to and following a wide-spread release of *B. anthracis* spores.

The topics of focus for this session included an informational session on the use of a new anthrax vaccine (AV7909) for postexposure prophylaxis (PEP), and policy vote on a change to the pre-exposure prophylaxis (PrEP) booster dose interval for persons who are not at current high risk of exposure to anthrax. The ACIP Anthrax WG will stand down after the *MMWR* policy update is published, which is anticipated to occur within the next 3 months. It is anticipated that the WG will be reactivated in the 2021-2022 timeframe to review new data from studies on



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AV7909 currently underway or planned to start later in 2019, as well as potentially new data on booster dose interval of greater than 3 years for PrEP.

## Next Generation Anthrax Vaccine: AV7909

**William Bower, MD, FIDSA**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**

Dr. Bower indicated that the purpose of this session was to present information on the use of a new anthrax vaccine, AV7909, for PEP following exposure to aerosolized *B. anthracis* spores when anthrax vaccine adsorbed (AVA) availability is limited. Currently, AVA is the only approved vaccine with an indication for use as PEP in persons with exposure to aerosolized *B. anthracis* spores. These data compare the immunogenicity and safety of AV7909 administered as a 2-dose series 2 weeks apart compared to AVA administered as a 3-dose series 2 weeks apart. This is a unique policy issue for the ACIP Committee. AV7909 is not currently a licensed vaccine and would only be available for emergency use. The WG chose present information on this vaccine to ACIP during this meeting because they believe it is important to review the data in this open forum prior to a public health emergency. In the event of an anthrax incident, an emergency meeting of ACIP will be convened to review these data plus any new data generated since this meeting and ask ACIP's recommendation regarding the use of this vaccine under an Emergency Use Authorization (EUA).

To set the stage, Dr. Bower began by providing some background information important for understanding the use of anthrax vaccine for PEP. There are four types of anthrax categorized by the route of spore entry into the body. Spores introduced through skin lesions lead to cutaneous anthrax. It has an incubation period of between 1 and 14 days and can have a fatality rate as high as 24% if untreated. Spores that are introduced through the gastrointestinal tract lead to ingestion anthrax. It also has an incubation period of between 1 and 14 days and can have a fatality rate as high as 40% even with treatment. Spores inhaled into the lungs lead to inhalation anthrax. After gaining entry, *B. anthracis* spores are thought to either germinate locally or to be transported by phagocytic cells to regional lymph nodes, where they can germinate. Spores inhaled into the lungs may not germinate immediately and incubation periods of up to 43 days have been documented. This is why vaccine is recommended after exposure to aerosolized spores to protect against the late germination of spores after antimicrobial prophylaxis has been discontinued. Inhalation anthrax mortality rates have improved in the age of modern critical care medicine, but are still as high as 47% even with treatment. Injection anthrax is a newly described form which has only been documented in Northern Europe. It has only been seen in injection drug users who used heroin contaminated with spores.

Anthrax is usually a disease of herbivores that ingest spores while grazing. Humans are secondarily infected by handling infected carcasses or consuming contaminated meat. Historically, inhalation anthrax was seen as an occupational risk in textile mills that processed animal hides that were contaminated with spores. Today, rare cases of inhalation anthrax are seen in persons related to work or hobbies that involve animal hides, such as drum making.

However, it is known that *B. anthracis* is one of the most likely pathogens to be used as a bioweapon. *B. anthracis* spores are relatively easy to produce, can be stored for a long time, and can be dispersed in the air through a variety of means. In addition, inhalation anthrax is highly lethal and the spores may survive in the environment for greater than 40 years. A wide-area release of aerosolized spores over a densely populated area could cause widespread



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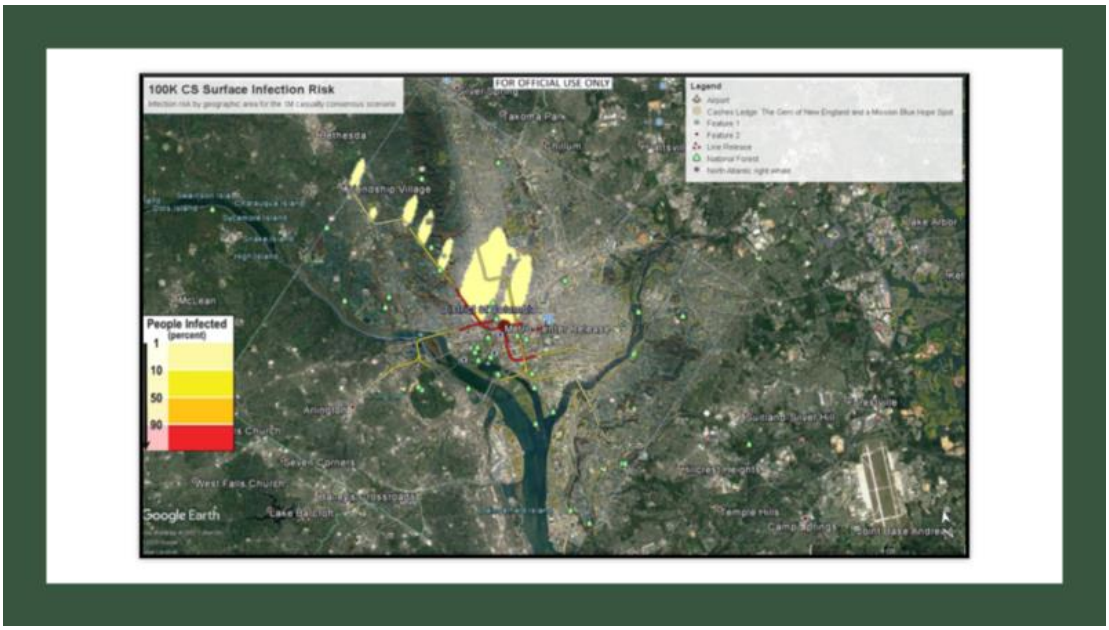
illness and death among unprotected persons. In 1979, an accidental release of anthrax spores from a Soviet bioweapons laboratory in Sverdlosk resulted in the deaths of at least 60 persons in the community that was downwind of the facility. In 2001, *B. anthracis* spores sent through the US Postal Service (USPS) resulted in at least 22 cases of anthrax and 5 deaths.

To illustrate the potential public health emergency that a release of *B. anthracis* spores could produce, the following graphic using data from US government sources shows a hypothetical release of aerosolized *B. anthracis* spores along a commuter rail line in a major metropolitan city. This model predicts that the spore plume drifting over a densely populated area could potentially expose hundreds of thousands of persons to spores who would require a combination of antimicrobials and vaccine PEP to prevent disease:




PEP for anthrax requires early use of antimicrobials to prevent disease until the vaccine has a chance to produce a protective immune response. Currently, the only licensed anthrax vaccine is AVA, which is FDA-approved for both PrEP and PEP of anthrax. Doxycycline, penicillin G, ciprofloxacin, and levofloxacin are FDA-approved for the antimicrobial component of PEP to prevent inhalation anthrax. The manufacturer of AVA is Emergent BioSolutions. AVA is a cell-free filtrate derived from avirulent *B. anthracis* growth in culture. The primary antigen is protective antigen (PA). AVA contains aluminum as an adjuvant and two preservatives. AVA primes the immune system to recognize and block PA, which is common to all anthrax strains. Vaccine efficacy against numerous anthrax strains has been demonstrated in many animal studies. For PEP, AVA is given by the subcutaneous (SC) route as a one-month primary series at 0, 2, and 4 weeks in conjunction with 60 days of antimicrobials.

AVA was last reviewed by ACIP in 2009 and recommendations were published in 2010. ACIP recommended three subcutaneous doses at 2 week intervals. At the time, AVA did not have an indication for PEP, so the vaccine would have been used under an EUA protocol. This recommendation extended to pregnant and breastfeeding women as well. The data that supported the safety for use in these populations came from the use of the vaccine for PrEP. There were no data for use in children, but the committee felt that given the high risk of mortality



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related to anthrax that the vaccine could be given to children under an Investigational New Drug (IND) protocol.

Since the last ACIP review of anthrax vaccine in 2010, there have been slight modifications to the licensed indications. In 2015, AVA was licensed for PEP in conjunction with antimicrobials in persons who have been potentially exposed to aerosolized *B. anthracis* spores. In 2018, ACIP voted to allow these policy changes. The intramuscular route of administration (IM ROA) may be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination. In immunocompetent individuals, co-administration of antibiotics may be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later. Should there be inadequate supplies of AVA available for PEP, dose-sparing regimens of either 2 full doses or 3 half doses of AVA may be used to expand vaccine coverage.

AV7909, NuThrax®, is an investigational anthrax vaccine under development by Emergent BioSolutions in pursuit of licensure with an indication for anthrax PEP. AV7909 is similar in composition and manufacturing process to AVA. It consists of the licensed AVA vaccine combined with a novel adjuvant, CPG 7909. CPG 7909 is a synthetic immunostimulent designed to induce both an enhanced antigen-specific antibody response and a natural killer T-cell immune response when used in combination with vaccines. AV7909 is anticipated to be added to the US Government's Strategic National Stockpile (SNS) starting in July 2019. It is also anticipated that AV7909 will replace currently stockpiled AVA for PEP as the stockpiled AVA expires. CDC has requested FDA's permission for emergency use of AV7909 in conjunction with appropriate antimicrobial therapy for PEP of anthrax through a Pre-EUA submission. The intended use of AV7909 under the proposed EUA is administration as a 2-dose series 14 days apart intramuscularly, in conjunction with appropriate antimicrobial therapy in adults greater than 18 years of age, including individuals greater than 65 years of age, pregnant women, and nursing mothers with suspected or known exposure to *B. anthracis*. It would be used under an IND protocol for those less than 18 years of age.

In terms of the public health importance of this vaccine, while the US government's anthrax PEP response plans for a large-scale event include both vaccine and antimicrobials, the currently stockpiled quantity of FDA-approved AVA might be insufficient for vaccine coverage in a large-scale, aerosolized anthrax attack as previously described. The availability and use of AV7909 under an EUA would increase the supply of anthrax vaccine and response capability to provide vaccine protection should a mass anthrax event occur if the available stockpiled AVA is insufficient for the necessary vaccine response. In addition to augmenting vaccine supply to enable an effective vaccine response, AV7909 may provide the following additional advantages:

- ❑ Two intramuscular doses of AV7909 administered 2 weeks apart may provide protective immunity 1 or 2 weeks sooner than the licensed 3-dose postexposure prophylaxis regimen of AVA. The 2-dose schedule of AV7909 has an operational advantage in a large-scale, mass vaccination response and potential for better patient compliance with completion of the vaccine dose series in comparison to the licensed 3-dose postexposure prophylaxis schedule of AVA.

- ❑ With fewer injection site-related adverse events (AEs) observed with the IM ROA for AVA compared with the SC route, it may be reasonable to anticipate that AV7909 administered intramuscularly may have fewer injection site-related AEs compared to AVA given by the SC ROA.



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Before presenting the non-clinical data the WG reviewed, Dr. Bower briefly described the assays used in these studies. The anti-PA immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) measures the total amount of IgG against PA in micrograms per milliliter. It is a species-specific assay, so inter-species measurements may have some systematic biases. The toxin neutralization assay (TNA) measures the ability of antibodies to neutralize the toxin. It is species-neutral, so measurements between species are comparable. TNA can be reported in raw or normalized units. The raw unit is effective dilution 50 (ED50), the dilution that neutralizes 50% of a fixed amount of toxin. The scale is from ~50 to >10,000. The normalized unit is neutralization factor 50 (NF50), which is the ED50 of the sample relative to a known reference standard. The reference standard ED50 is ~500, so the scale is smaller, from ~0.1 to >10.

Inhalation anthrax is very rare, so the effectiveness of AVA cannot be directly assessed for PEP in humans. For this situation, the FDA has recommended using the Animal Rule where data from animals and humans are bridged to determine correlates of protection that can be used to predict human survival based on antibody titers generated by the vaccine in humans. AV7909 was tested in guinea pigs and in non-human primates (NHP). In the guinea pig model, 2 doses of AV7909 at days 0 and 14 provided complete protection in all animals, with measurable TNA titers when challenged at day 28. The day 70 challenge had one animal with a measurable titer that died.

The NHP model was performed the same way. There was only one NHP at the day 28 challenge with measurable TNA titers that did not survive, and two from the Day 70 challenge set. The 70% predicted protection titers for AV7909 are significantly lower than the same protection level of 0.56 for AVA. These studies showed that AV7909 is highly protective in animal models. The 0.15 NF50 titer level has been proposed by Emergent as the target protective level for the Phase II human clinical trial at day 28. Note that the Phase I trials achieved levels almost 10-fold higher than this, suggesting that AV7909 should be highly protective in humans.

Turning to the clinical immunogenicity studies the WG reviewed, 3 clinical studies have been completed as part of the AV7909 development program in which 342 healthy subjects were enrolled, 241 of whom were exposed to the combination of AVA + CPG 7909 in various doses and immunization schedules. A total of approximately 100 subjects between the ages of 18 and 50 received one or more doses of the AV7909 formulation currently under development. Dr. Bower summarizes the important findings from these studies.

The initial Phase 1a clinical trial assessed the safety and immunogenicity of AVA mixed with CPG 7909 in 69 healthy subjects between 18 and 45 years of age. They received either AVA alone (0.5 ml), CPG 7909 alone (1 mg in 0.6 ml), or a combination of the two agents (0.6 ml). Vaccinations were administered intramuscularly on days 0, 14 ± 1 days, and 28 ± 2 days. The geometric mean peak TNA concentration for the AV7909 arm was 8.8-fold higher than that observed for the AVA-alone arm. The median time to reach geometric mean of the highest peak TNA concentrations for subjects receiving AV7909 was 21 days, a 25-day acceleration over the median 46 days it took for the AVA alone arm to reach this concentration. The TNA assay results paralleled those observed with anti-PA IgG and both were statistically significant.

The primary objective of the Phase 1b study was to evaluate the safety and tolerability, as determined by AE incidence rates, of four AV7909 formulations compared to placebo (saline) and AVA alone. Safety and immunogenicity data allowed for the selection of 0.5 ml AVA plus 0.25 mg CPG for use in Phase 2 studies.



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The primary objectives of the Phase 2 study were to assess safety and immunogenicity as measured by TNA NF50 values for each study arm at Day 63. The study was designed to access both 2 and 3 doses of AV7909 at 2-dose levels in the 5 study arms. Immunogenicity was measured on Days 0, 21, 28, 35, 42, 49, 63, 84. The study was designed to look at comparability of AV7909 and AVA at day 63, as at the time of this study, AVA was recommended in conjunction with antimicrobials for 60 days.

Analysis of the AV7909 TNA threshold of protection data revealed that addition of the CPG 7909 adjuvant to AVA improved the kinetics and magnitude of the immune response. Two-dose AV7909 was found to be comparable to three-dose AVA given IM at Day 63, but achieves peak response by day 28 versus day 45 for AVA.

Regarding the clinical safety data, the WG reviewed, during clinical testing in which a total of 241 subjects in three completed clinical trials were exposed to the combination of AVA + CPG 7909, systemic reactogenicity manifested primarily as mild to moderate fatigue, muscle ache, and headache. The most common injection site reactions were mild to moderate pain, tenderness, and arm motion limitation. These reactions often resolved within 48 hours after dosing. The most common AE reported in ≥ 20% of subjects receiving AV7909 across the three completed clinical trials were various forms of injection site reaction. AEs associated with CPG 7909, as reported in a number of reviewed infectious disease vaccine trials, are considered to be associated with activation of proinflammatory innate immune responses at the injection site. Most reactions are mild to moderate in intensity, of short duration, and remediated with over-the-counter analgesics.

In subjects who received AV7909 as well as with other CPG 7909-adjuvanted infectious disease vaccines, the vaccines were generally well-tolerated with a low rate of vaccination discontinuation because of AEs. In reviewed trials, rash, positive antinuclear antibody, generalized pruritus, urticaria, and fever have been reported as reason for study discontinuation. No vaccine-associated deaths or serious adverse events (SAEs) have been reported in AV7909 trials or other infectious disease vaccine trials that used CPG 7909. It is important to note that these safety studies were all conducted in healthy adults aged 18-50. There are no data on the use of this vaccine or other adjuvant CPG 7909 vaccines in children or other special populations, including persons greater than 65 years of age.

With regard to the timeline for the BLA submission provided by Emergent BioSolutions pertaining to the studies that are underway or planned to start in 2019, non-clinical studies will include safety studies in pregnant and juvenile rats. A Phase 2 clinical trial is being conducted to assess the safety and immunogenicity of AVA and AV7909 in adults > 65 years of age compared to adults 18–50 years of age with preliminary results anticipated in the second or third quarter of 2019. Approximately 200 adults aged ≥ 66 years and 100 aged 18 through 50 years will be enrolled in the study. The main study goal is to determine optimal dosing for AV7909 in the elderly population via the evaluation of three different postexposure vaccine schedules. A Phase 2 drug-vaccine interaction study is planned to investigate whether co-administering AV7909 with ciprofloxacin or doxycycline affects antibiotic pharmacokinetics or AV7909 immunogenicity in 210 healthy adults, with results anticipated in 2021. A Phase 3, randomized, double-blind clinical trial to evaluate the lot consistency, immunogenicity, and safety of a 2-dose AV7909 series administered intramuscularly at Day 0 and 14 in 3850 healthy adult subjects is planned to start in 2019. It is anticipated that this WG will reconvene in 2021 to review these data.



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With respect to the WG's discussions, the WG felt that the data show that AV7909 generates a similar to better immune response when compared to AVA given by the IM route of administration over the time points reviewed and would provide similar protection after exposure to aerosolized *B. anthracis* spores. The data suggest that two doses two weeks apart produce a rapid response providing the highest level of protection early, while two doses four weeks apart provide a higher sustained response. However, limited safety data are available. Therefore, until there are more data available, the WG was not in favor of a preferential use of AV7909 over AVA. Given the high mortality associated with inhalation anthrax, the WG felt that the benefits of providing prophylactic vaccine outweighed the potential risk of AV7909. The WG supported the use of AV7909 if supplies of AVA are exhausted or unavailable once the pre-EUA package has been accepted by FDA. The WG also was concerned that there are no safety data in children or other special populations. However, given the high mortality associated with anthrax, the WG felt that the benefits of the vaccine outweighs the potential AEs in these populations and would be an option for PEP if AVA supplies are exhausted or unavailable once pre-EUA package has been accepted by FDA.

The proposed wording for the *MMWR Policy Update* is:

- ❑ AV7909 is scheduled to become part of the US government's Strategic National Stockpile by July 2019 and is currently under consideration for use under an Emergency Use Authorization protocol.
- ❑ AVA is preferred for PEP for potential exposure to aerosolized *B. anthracis* spores as it is licensed for this indication. Additional safety data will be reviewed by ACIP as they become available, and recommendations on preferential use will be updated as needed.
- ❑ However, based on very limited safety and immunogenicity phase 2 data, AV7909 appears safe and elicits a robust immune response in healthy adults.
- ❑ AV7909 could be an option for PEP if AVA is not available. As with AVA, antimicrobials should be taken for up to 60 days in conjunction with the vaccine
- ❑ CDC guidance for AV7909 will include statements on dosing schedules and special populations

**Discussion Points**

Dr. Walter requested clarity regarding whether both AV7909 and AVA have the same amount of antigen and are made by the same manufacturer, as well as clarity on how the SNS works and would increase the supply.

Dr. Bower replied that AV7909 and AVA have the same amount of antigen and are made by the same manufacturer. He indicated that there is set amount of AVA in the SNS, but it is expiring and there is no plan to purchase more AVA. Therefore, AV7909 will be coming into the SNS. Over time, the balance will shift from more AVA to more AV7909. The hope is that by that time, there are more data such that ACIP can make a preferential decision on its use.

Dr. Cohn emphasized that the purpose of this presentation and the information being included in the updated recommendations was to ensure that states use this recommendation and report for their planning, so CDC wants them to have information available. However, in the event of a widespread release and a need to use this product prior to the product being licensed, an



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emergency ACIP meeting would be convened and a vote would be taken at that time for use of this vaccine.

Dr. Frey suggested that it might be helpful for the group to understand that the AVA in the SNS is an older vaccine.

Dr. Bower indicated that AVA has expiration dates and is on an expiration date extension program, but the thought is that CDC wants to move away from that. Based on the logistical advantages of AV7909, they want to move toward that because it is anticipated to provide better protection by giving the vaccine over a shorter period of time and the adjuvant boosting the response.

Dr. Walter asked whether AVA still being manufactured.

Dr. Bower responded that Emergent BioSolutions has the capacity to make AVA and it is still going to be made for PrEP.

Dr. Szilagyi requested clarification regarding the concept of the AVA stockpile being exhausted this meant in the US or if there is a worldwide distribution plan and any agreements with other nations or stockpiles.

Dr. Bower indicated that the SNS belongs to the US government, and AV7909 is not intended to be used by anybody but the US government. He was not privy to information about any agreements with other nations/stockpiles.

Dr. Lee wondered whether the WG would consider age-specific recommendations as data start emerging, and whether the recommendation would differ for pregnant women and children versus the adult population. She was thinking about understanding the risk-benefit in those populations given what is currently known, understanding that this information probably will change over time.

Dr. Atmar added that it was unclear whether data would be available in pediatric or other special populations. The Institute of Medicine (IOM) has concluded that it would be reasonable to conduct studies in pediatric patients, but he did not know whether any were planned. There are still ethical considerations that must be addressed in such discussions.

Dr. Bower thought perhaps it would be administered under an IND as is done with AVA if a situation arises in which there is a need to use AV7909.

It seemed to Dr. Lee that in a PEP setting, the benefit-risk would be highly in favor the benefit of giving it in the absence of additional data. She was thinking about the overall supply and the balance of that supply over time. If there is availability of AVA alone, that might be reasonable to consider.

Dr. Frey indicated that there might be some CPG data available in pediatric populations for different vaccines. This was a controversial adjuvant in its earlier days, but many studies since that time have shown it to be effective and thus far safe. An example of Dr. Lee’s point is that smallpox would be given to children and pregnant women if it was thought to be emergent.

Dr. Cohn added that CDC has protocols in place to perform a substantial amount of data collection on implementation among children in the event of an incident.



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To follow up on the CPG comment, Dr. Stephens said he believed this to be a new CPG that has not been used extensively in other vaccines.

Dr. Bower confirmed that there are no licensed vaccines that use this particular adjuvant. However, there have been trials in malaria vaccine and hepatitis B vaccine that use this adjuvant. The WG reviewed those studies and they did not give any signal to indicate that there was anything more than some mild to moderate AEs and no SAEs. He did not know the status of those vaccines.

Sean Bennett (Emergent BioSolutions) confirmed that CBG 7909 was evaluated in previous investigational vaccine trials. As far as he knew, none of those have continued development. There are some limited pediatric safety data from HEPLISAV-B® that uses the 1018 immunostimulatory sequences (1018-ISS), which is a similar mechanism of action.

## Next Generation Anthrax Vaccine: AV7909

**William Bower, MD, FIDSA**
**National Center for Emerging and Zoonotic Infectious Diseases**
**Centers for Disease Control and Prevention**

Dr. Bower next presented on the WG's AVA PrEP booster dose interval discussions, indicating that it was important to note for this discussion that AVA is approved for PrEP in persons at high risk of exposure to *B. anthracis*, such laboratory workers handling *B. anthracis* or veterinarians working with potentially infected animals. The policy question ACIP was asking during this session was related to persons not at high risk, but who may in the future be at high risk of exposure. Thus the policy question is, "Can persons who are not at current high risk of exposure to *B. anthracis* spores maintain adequate immunity by being boosted with AVA every three years after immunological priming, with the caveat that if they were required to enter a high-risk area, they would receive a booster with or without antimicrobials, depending on the timing of their last booster dose?" The population of interest is persons aged 18 years or older with potential future, but not current, exposure to aerosolized *B. anthracis* spores. The intervention is a 6-month priming schedule at 0, 1, and 6 months followed by a booster every three years with AVA and compared to the currently licensed AVA PrEP vaccine schedule. The outcome of interest is protection. Before presenting the data to support the policy change for this vaccine, Dr. Bower provided some background information important for understanding the PrEP anthrax vaccine recommendations. He emphasized that while he already provided a description of AVA (BioThrax®), this presentation would focus on the vaccine schedule for PrEP rather than PEP as in the last presentation.

AVA is licensed for PrEP of anthrax in persons 18 to 65 years of age at high risk of exposure and is given by the IM route as a 6-month priming series at 0, 1, and 6 months, with booster doses given at 12 and 18 months and annually thereafter. This vaccine is quite old, with a long history. In the 1950s, the vaccine was made at Ft. Detrick from a cell culture filtrate and precipitated with alum. This is the "Wright" or "Ft. Detrick" formulation which was studied extensively by Dr. Phil Brachman for prevention of anthrax in textile mill workers exposed to animal hides contaminated with *B. anthracis* spores. In the 1960s, the manufacturing process was improved, resulting in increased PA concentration, purity, and potency. This new formulation was referred to as the "Lansing" formulation and was produced by the Michigan Department of Health and Human Services (MDHHS) in Lansing, Michigan. In the 1970s, the "Lansing" formulation was licensed using data from the Brachman studies. In 2008, the two-



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week priming dose was dropped and the ROA was changed from SC to IM for PrEP. In 2012 and subsequent to the last ACIP review, the priming series was changed from 5 doses to 3 doses at 0, 1, and 6 months with the last 2 priming doses changed to booster doses at 12 and 18 months and an annual booster thereafter. This enabled laboratory work or deployment to high risk areas to occur after 6 months rather than 18 months under the old priming schedule. AVA was last reviewed by ACIP in 2009 and recommendations were published in 2010. ACIP did not recommend that emergency responders routinely receive anthrax PrEP, but did suggest that emergency responders on a voluntary basis could opt-in to receiving PrEP. They also noted that the data suggested an increased booster interval does not decrease the ultimate immune response.

As discussed previously, *B. anthracis* is considered one of the most likely pathogens to be used as a bioweapon. As illustrated earlier with the image of a hypothetical wide area outdoor release, modeling scenarios show how a large release of *B. anthracis* spores from a commuter train traveling through a densely populated area could theoretically expose tens to hundreds of thousands of persons to anthrax resulting in a public health emergency. If this type of event were to occur, having a group of emergency responders with a primed immune response and only requiring a booster dose to begin work in the affected area would greatly improve the surge capacity for the public health response.

In terms of the public health importance of this policy question, AVA for PrEP is only indicated for persons currently at high risk of exposure to anthrax. However, there are groups of persons, such as the military, who may need to enter an area of high risk, then leave, and may not return for several years. There also are persons, such as emergency responders, who are not at current risk, but might be required to enter an area of high risk on short notice. New data on immunogenicity following extended booster intervals suggest that in these situations, persons can have a booster interval of greater than one year and maintain a robust amnestic response to a booster dose. This potentially would reduce the number of AEs by decreasing the number of vaccinations and decrease logistic issues related to deploying emergency responders should a mass anthrax event occur. If approved, an updated policy statement will be published that will combine information from the previous 2010 *MMWR* document with updated indications and dosing schedules for AVA.

With regard to the studies that provide the basis for an extended booster dose interval, the main concern with extending the booster interval is the level of protection at the pre-boost time points when antibody levels are at their lowest. The correlates of protection approach was designed to evaluate protection at those time points, which should be the minimum protective levels for each schedule. Since inhalation anthrax is very rare in humans, the effectiveness of AVA cannot be directly assessed for PrEP. Instead, the correlates of protection model must be used to estimate human survival at vaccine-generated anti-PA IgG concentrations compared to NHP anti-PA IgG concentrations and survival data.

The animal antibody concentration and survival data came from the 2012 Quinn study in which NHP were given AVA at full strength or at various dilutions at 0, 1, and 6 months to generate a range of anti-PA IgG concentrations. The animals were then challenged with 200-400 $LD_{50}$ *B. anthracis* spore concentrations at 12, 30, and 52 months. The antibody concentrations and survival data were placed in a logistic regression model to generate a survival curve. This study showed that three IM priming doses elicited sustained production of functional PA-specific interferon gamma- and interleukin-4-secreting T-cells, lymphocyte proliferation responses, and memory B-cells for the study duration. In 2014, Chen et al. performed a comprehensive analysis of 21 humoral and cell-mediated NHP immune-response variables at multiple time points. The



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anti-PA IgG level at the last available time point before challenge and lymphocyte stimulation index at study months 2 and 6 were identified consistently as COP. Anti-PA IgG levels and anthrax lethal toxin neutralization activity at both the time of exposure and month 7 were practicable and accurate metrics for correlating vaccine-induced immunity with protection against inhalation anthrax. The model indicated that even very low levels of circulating antibody at the time of challenge correlated with significant levels of protection.

All vaccinated NHP had measurable antibodies at month 7. By time of challenge, some of the 1:10 and lower dilution groups no longer had measurable serum anti-PA IgG levels and some of the animals with undetectable antibody levels still survived. Fisher's exact test was used to compare the overall survival rates between all pairs of challenge times for the vaccinated NHP. There was a statistically significant difference between the survival of animals challenged at 12 months and that of animals challenged at 30 months; however, no statistical differences were evident between animals challenged at 12 months and 52 months or between animals challenged at 30 months and 52 months. The Quinn study showed that the 3-dose priming series at 0, 1, and 6 months with a human dose and dilutions of up to 1:10 of AVA provided levels of protection from 60% to 100% against inhalation anthrax for up to 4 years in NHP. In general, serum anti-PA IgG and TNA responses remained significantly above control levels through 50 months, which was the last time point measured. It also showed that protection was achieved even when using diluted vaccine doses.

The human data come from one main source. The 2014 Wright paper looked at the licensed priming series and increasing booster dose intervals that provided the immunogenicity data for the correlates of protection model. Data from the 2013 and 2014 Pittman papers support the robust amnestic immune response seen in the Wright study. This table shows the different arms and number of arm participants used to assess the booster dose intervals in the Wright study:

Vaccine Schedule for the Wright Study

| Study Group (N) | Month 0 | Month 0.5 | Month 1 | Month 6 | Month 12 | Month 18 | Month 30 | Month 42 |
|---|---|---|---|---|---|---|---|---|
| 8-SC (260) | AVA | AVA | AVA | AVA | AVA | AVA | AVA | AVA |
| 8-IM (262) | AVA | AVA | AVA | AVA | AVA | AVA | AVA | AVA |
| 7-IM (256) | AVA | S | AVA | AVA | AVA | AVA | AVA | AVA |
| 5-IM (258) | AVA | S | AVA | AVA | S | AVA | S | AVA |
| 4-IM (268) | AVA | S | AVA | AVA | S | S | S | AVA |
| Placebo (260) | S | S | S | S | S | S | S | S |

AVA – Anthrax Vaccine Absorbed
S – Saline
IM – Intramuscular route
SC – Subcutaneous route

Wright JG, et al. Vaccine 2014: 32;1019-28.

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The 7-IM arm represents the current licensed PrEP schedule as the 2-week dose was dropped from the schedule in 2008. The 4-IM arm represents the proposed PrEP schedule with an up to 3-year booster interval.



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In the Wright study, all groups produced high immune responses by month 7 and there were no statistically significant differences between groups at that time point. Only 2 out of 1303 vaccinated participants did not produce detectable antibody at month 7. Both individuals dropped out of the study before receiving another dose, so there are no data on follow-up. All groups and all remaining participants responded to boost. The 5-IM and 4-IM groups showed gradually receding levels of antibody in the periods between boosts relative to the 7-IM schedule. Geometric mean antibody levels remain well above background through month 42 in all groups. At month 42, all of the 7-IM cohort had detectable antibodies, 97.9% of the 5-IM group had detectable antibodies, and 80.2% of the 4-IM group had detectable antibodies significantly higher than controls. Response to the month 42 boost in the 4-IM group was nearly double that of the 7-IM group and statistically significantly superior. The 5-IM group was also higher than the 7-IM group, but not statistically significant.

The aim of the 2014 Pittman study was to compare the level of persistence of the anti-PA IgG concentrations and toxin neutralization response in persons who had a delay of up to 7 years in receipt of the 6-month dose compared to those who received the dose on schedule. The delayed cohort in the Pittman study was non-inferior to the on-schedule cohort for both anti-PA IgG and TNA ED50 at day 28 and 180 post-vaccination. In fact, the delayed cohort was superior to the on-schedule cohort on days 28 and 180 for both mean anti-PA IgG concentration and mean TNA ED50 titer. Furthermore, antibody levels receded significantly faster in the on-schedule cohort than in the delayed group, thus demonstrating a reason to delay the booster dose.

In summary, the data presented confirm that a 3-dose IM priming series administered at 0, 1, and 6 months followed by boosters at 18 and 42 months or a single booster at month 42 established robust immunological priming and sustained immunological memory. The correlates of protection model predicts high survival estimates with even the most reduced boosting schedule. As expected, an increasing period between booster doses resulted in lower levels of anti-PA IgG just prior to vaccination. However, the persistence of quantifiable anti-PA IgG and the exceptional recall responses to a booster dose administered at either month 18 or 42 were noteworthy. The greater interval between boosters generated a significantly higher response, which if assuming a similar decay curve, should provide higher protection between booster doses. Increasing the intervals between booster doses should decrease the frequency of vaccine related AEs and decrease the operational cost of administering the vaccine. These data, together with duration of protection studies in NHP, suggest that AVA established long-term antibody secreting plasma cell populations and robust immunological memory manifested by rapid and high anamnestic responses.

With respect to the WG discussions, the WG discussed a 3-year booster interval for persons at current high risk of exposure to *B. anthracis*. The WG felt for persons at continuous high risk of exposure that the higher titers just prior to boosting were the most important factor when deciding the booster interval. This is provided by an annual booster and thus the WG was not in favor of extending the booster interval to greater than one year for individuals at current high risk of exposure. However, in persons not currently at high risk of exposure, but who may in the future be at high risk of exposure, the WG felt the data showed that a booster interval of up to 3 years provides a robust amnestic immune response. There are also limited data suggesting the booster interval could be up to 5 to 7 years, but more data are required to make a recommendation for greater than 3 years at this time.



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The work group also felt a gap in recommendations should be addressed for persons who are in the process of receiving the 6-month priming series and are required to enter a high-risk area prior to completing the priming series. These recommendations came from review of the data on immune response to the AVA PrEP priming series that show 3 doses provide priming for an amnestic immune response and from the AVA PrEP data that show 3 doses given 2 weeks apart provides high levels of protection. There are no data on the effect on the immune response for starting PrEP by the IM route and switching to the SC route to join the PrEP schedule; however, there is no reason to believe that the immune response would be adversely affected by mixing the route of administration. While in the high-risk area, the licensed booster schedule for high risk exposure would apply.

In terms of the recommendation, AVA is licensed for prevention of anthrax in persons at high risk of exposure to *Bacillus anthracis*. There are no proposed changes to this indication. The WG is proposing a booster interval for AVA that is longer than the licensed booster schedule for persons who are not currently at high risk of exposure, but who may need to deploy to a high-risk area quickly. While in the high-risk area, the licensed booster schedule for high risk exposure would apply. The proposed wording for the *MMWR Policy Update* for recommendations on priming persons not currently at high risk of exposure to anthrax is:

- For persons who lack current, but may have future, high risk of exposure to *B. anthracis*, AVA may be given as an intramuscular 3-dose priming series at 0, 1, and 6 months, followed by an intramuscular booster every 3 years.

- After receiving the 3-dose priming series, persons who have not received a booster dose in the last 6 months but need to enter an area where *B. anthracis* is suspected to be in use would be given an IM booster dose and either:

  - Wait 2 weeks to enter the high risk area

    OR

  - If required to enter immediately, take antimicrobial PrEP for 2 weeks

Persons who have not completed the priming series for PrEP with AVA who are exposed to aerosolized *B. anthracis* spores should join the PEP schedule. This table provides information on additional AVA doses needed based on the number of PrEP doses already received and recommended antimicrobial coverage:

Table: Transition from PrEP to PEP schedule for persons who have not completed priming series who need to immediately enter an area with high risk of anthrax exposure

| PrEP Doses | Interval Since Last Dose | AVA PEP | Duration of Antimicrobial PEP |
|---|---|---|---|
| 0 | | Dose 1 (day 0)<br>Dose 2 (day 14)<br>Dose 3 (day 28) | 42 days after first dose of AVA or 14 days after last dose, whichever is later |
| 1 | | Dose 2 (day 0)<br>Dose 3 (day 14) | 28 days after first dose of AVA or 14 days after the last dose, whichever is later |
| 2 | | Dose 3 (day 0) | 14 days |
| ≥ 3 | > 6 months | Booster dose | 14 days |
| ≥ 3 | ≤ 6 months | No booster | No antimicrobials needed |



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Dr. Bower presented for discussion and a motion the following policy change that ACIP would be asked to vote on later in the day:

> "To maintain memory response, a booster dose of AVA should be given every 3 years to persons who received an AVA priming series if they lack current high-risk exposure to *B. anthracis*."

**Discussion Points**

Dr. Atmar said that to be clear, already there is a recommendation for off-label use of the vaccine for groups who are worried about potential future exposure, such as emergency responders. This is providing clarification of how often one can boost those individuals to try to maintain some immune memory. Thus, it is an off-label recommendation for an already off-label use of the vaccine.

Dr. Cohn added that this is a group that is not recommended to receive the vaccine, but there is permissible language with regard to using the vaccine.

Dr. Bower indicated that the 2010 recommendation said they could voluntarily receive the vaccine, but they want to provide some guidance about how to go about it. The WG thinks that this would be a better use than trying to get the vaccine annually.

Dr. Moore acknowledged that there are not sufficient data available currently on the sustaining of titers following booster doses and the opportunity to space boosters out for those at ongoing high risk, but wondered if the WG would consider this should additional data become available to reassure them that an interval greater than one year would be appropriate for these individuals.

Dr. Bower responded that the FDA has seen the data and did not want to extend the booster dose for people at current high risk. The Department of Defense (DoD) will have some opportunities to assess that question, so if promising data come up, the WG will certainly present it.

Dr. Atmar pointed out that the Wright study looked at intervals of 2 and 3 years and suggested that an interval longer than 1 year led to a proportion of persons on the longer interval being potentially susceptible. That was considered to be an undue risk for individuals who have continued exposure, so it is unlikely based on the Wright data with AVA that such data would come forward in the future. Certainly, if they were generated the WG would likely reconsider it, but there already are some pretty good data suggesting that is not likely to be the case.

Dr. Moore said that she was thinking about it looking like there was a really nice response after that first annual booster dose and a slower degradation. While she understood that it was not an issue for discussion currently, she wondered what it would take to get there.

Dr. Lee observed that it seemed that moving away from a more permission recommendation to a routine recommendation would be helpful because it would result in better workforce readiness to respond to events, and wondered whether that was part of the intent with this revised recommendation.



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Dr. Bower replied that first responders in high target areas probably would take advantage of this, and spreading out the booster dose interval would make it more appealing to them. As AVA expires and leaves the stockpile, there has been some consideration of making it available to first responders so that they could be prepared for an event. This is why they are seeking some guidance on how that might occur.

Dr. Atmar added that the recommendation is still permissive. The booster dose is permissive for off-label use of the vaccine, but the way it is stated it says for those who want "to maintain immune memory." This would give access to the vaccine for groups like emergency responders who want to take advantage of access to the expiring vaccine.

Dr. O'Neal Eckert (ACOG) wondered whether any pregnant or post-partum breastfeeding women would be in the booster studies after the priming.

Dr. Bower indicated that currently, consideration is being given to collaboration with the DoD which does have women who are inadvertently vaccinated during pregnancy.

Dr. Cohn clarified that the permission language regarding people who are not at increased risk is for persons 18 years of age and older.

Dr. Baker (IDSA) observed that "should be given" did not sound very permissive in these presumable low-risk individuals.

Dr. Atmar replied that the qualifier "to maintain memory response" it should be given. It is not saying that the booster has to be given.

Dr. Cohn clarified that when this language is published in the full recommendation and report, it would be language below the language around use of this vaccine in persons not at high-risk, which is permissive language.

Dr. Stephens emphasized that these individuals already have been vaccinated, so there must have been some anticipation about risk. This is simply extending the booster to a longer interval. He was concerned about the word "maintain" when it is actually about eliciting a memory response, not necessarily maintaining it. The memory response is already there. He recommended that the word be changed from "maintain" to "elicit." Dr. Gravenstein suggested stating, "To boost memory response."

Dr. Hunter shared Dr. Baker's concern about "should." He had a feeling that this could be excerpted and people could leave out part of this when they copy it to their friends and colleagues. Therefore, he suggested replacing "should" with "may."

Dr. Stephens moved to accept the recommendation as stated. Dr. Lee seconded the motion.

Dr. Cohn stressed that minor language modifications could be made at the time of the vote that do not change the intent of the motion, but are helpful for clarification purposes.

Dr. Romero indicated that the language would be modified before being presented for the vote later in the afternoon.



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In the afternoon following the public comment period, the discussion and vote on the anthrax policy change continued. Dr. Bower read the following slightly edited language into the record for final discussion and the vote:

> "Among persons not currently at high risk of exposure to *B. anthracis* who have been previously primed with AVA and wish to maintain protection, a booster dose of AVA should be given every 3 years."

Dr. Atmar recalled the desire in the earlier discussion to change "should" to "may."

Dr. Szilagyi clarified that the WG added the clause at the beginning "among persons not currently at high risk of exposure and who wish to maintain protection" and thought it actually would be more precise to say "should." It does not imply that all people "should." This is just among the subgroup.

Dr. Hunter reiterated his concern that the statement could be excerpted and should, therefore, be "may."

Dr. Atmar agreed that "should" could be misinterpreted by some end-users, while "may" offers the same idea without the push.

Dr. Bernstein suggested keeping "should" and changing "given" to "considered."

Dr. Lee asked whether, if they used "may" and then someone went 6 years whether they would have to restart their primary series. Her concern was that if the interval was too long, they would lose the benefit of having the primary series and the booster would not be sufficient.

Dr. Bower indicated that they would never have to restart the primary series.

Dr. Atmar recalled that one of the points made during presentation was there are some data that suggest the interval can be even longer. Those data will be further developed and probably will be reconsidered in a few years when they are available. The 3-year interval is what there are data for currently as an acceptable minimum interval for those not at continuous risk. The "should" has been suggested to be used where there is the thought that the person should be getting it and not as a permissive suggestion. That said, Dr. Szilagyi agreed that it would be fine to use "may."

Dr. Frey recalled that in the earlier discussion, it was suggested that language stating "to maintain or boost memory response" needed the word "should" because that is what there are data for.

Dr. Bernstein suggested, "A booster dose of AVA should be given every 3 years to maintain protection."

Atmar suggested, "A booster of AVA may be given every 3 years among persons not currently at high risk of exposure to B. anthracis who previously have been primed with AVA and wish to maintain protection." By flipping the statement Dr. Bower just read, the idea would be captured and it would be made clear that it is still permissive as opposed to mandated.



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For the sake of accuracy, Dr. Baker (IDSA) suggested that the desired words be displayed before the vote.

Dr. Atmar suggested the following revised proposed recommendation language into the record, which was displayed for the vote:

> "A booster dose of AVA may be given every 3 years to persons not currently at high risk of exposure to B. anthracis who have been previously primed with AVA and wish to maintain protection."

Dr. Cohn clarified that they must first motion/second to vote on the revised language, and then motion/vote on approving the recommendation as revised.

Dr. Atmar made a motion to approve the recommendation as proposed, which Dr. Gravenstein seconded.

**Motion/Vote #1: To Accept the Revised Language for the Vote on Anthrax Vaccine Use for PrEP in Persons NOT at Current High Risk of Exposure to Anthrax**

Dr. Atmar made a motion to approve for a vote the revised the recommendation language as last proposed reading, "A booster dose of AVA may be given every 3 years to persons not currently at high risk of exposure to B. anthracis who have been previously primed with AVA and wish to maintain protection." Dr. Gravenstein seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**15 Favored:** Atmar, Ault, Bernstein, Ezeanolue, Gravenstein, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
**0 Opposed:** N/A
**0 Abstained:** N/A

**Motion/Vote #2: Anthrax Vaccine Use for PrEP in Persons NOT at Current High Risk of Exposure to Anthrax**

Dr. Atmar made a motion to approve the revised policy change recommendation reading, "A booster dose of AVA may be given every 3 years to persons not currently at high risk of exposure to B. anthracis who have been previously primed with AVA and wish to maintain protection." Dr. Gravenstein seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**15 Favored:** Atmar, Ault, Bernstein, Ezeanolue, Gravenstein, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
**0 Opposed:** N/A
**0 Abstained:** N/A



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# Influenza

## Introduction

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

Dr. Walter reminded everyone that during the October 2019, there were presentations on: 1) the Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) study of effectiveness of influenza vaccine in preventing hospitalization among pregnant women; and 2) a study of Fluzone® Quadrivalent at a 0.5mL dose for children aged 6 through 35 months, which was approved by the FDA in January 2019.

Since the October 2018 ACIP meeting, the WG has engaged in several meetings and calls during which members heard presentations on: 1) 2018-2019 season US influenza activity; 2) interim 2018-2019 season vaccine effectiveness (VE) estimates from the US Flu VE Network; and 3) results of the third Vaccine Safety Datalink (VSD) study of inactivated influenza vaccines (IIVs) and spontaneous abortion (SAB) among pregnant women. The third VSD study was a follow-up to an earlier study presented to ACIP in October 2017, which detected an association between receipt of IIV and SAB in first 28 days post-vaccination when an H1N1pdm09-containing vaccine had also been received during the previous season.

The agenda for this session included the following topics:

- ❑ 2018-2019 US Surveillance Update
- ❑ Interim Estimates of 2018-2019 Seasonal Influenza VE: US Flu VE Network
- ❑ Phase III Randomized Observer-Blind Comparator-Controlled Study of Afluria® Quadrivalent (Afluria® QIV) for Children 6 through 59 Months
- ❑ Case-Control Study of IIV and SAB in the VSD 2012-2013, 2013-2014, and 2014-2015
- ❑ Summary and WG Considerations

## Influenza Surveillance Update

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

Dr. Brammer presented an update on the US influenza activity for the current season, provided preliminary in-season burden estimates for influenza, additional information on virus characteristics for the currently circulating viruses, and an update on vaccine virus component selection for the 2019-2020 influenza season.

In terms of the week ending February 16, 2019, *MMWR* Week 7, based on information reported to CDC by US clinical laboratories, 27% of tests were positive. This has been a very strongly predominant influenza A season. Based on data from public health laboratories across the country, the predominant influenza A virus was A(H1N1)PDM09. Those represented approximately 75% of the influenza A viruses for the season overall. However, in recent weeks, influenza A(H3N2) viruses have increased and for the most recent week represented 47% of the



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influenza viruses detected. There has been very little influenza B activity. One of the unusual aspects of this seasons is that while there has been H1 predominance nationally, there have been regional differences. H3N2 has been the predominant virus in the Southeast for the entire season. In the most recent 3 weeks in 3 other regions, the number of H3 viruses have been either equal to or greater than the number of H1 viruses.

The percent of outpatient visits for influenza-like illness (ILI) also continues to increase. In the most recent week, 5.1% of visits to outpatient clinics were for ILI. This is higher than in several recent seasons, but is still well below what was observed last year. For the most recent week, New York City (NYC) and 30 states had high levels of ILI. An additional 11 states and the District of Columbia (DC) had moderate activity.

While the overall rate of laboratory-confirmed influenza-associated hospitalizations was 27.4/100,000 population, the highest rate is among those 65 years of age and older, followed by children 0 through 4 years of age. At this time, this season is fairly average and is well below what was observed last year.

The percent of influenza and pneumonia deaths reported to the National Center for Health Statistics (NCHS) has exceeded the epidemic threshold for only two weeks thus far. The highest level was 7.4%, which is well below what was seen last year at peak of 10.8%. Even though pneumonia and influenza mortality has been relatively low this season, there have been 41 influenza-associated pediatric deaths. Among those 41 deaths, all but 2 were influenza A viruses. The majority of the influenza A viruses from those children that have been subtyped have been H1N1 as would be expected.

This year for the 2018-2019 season, CDC published preliminary in-season burden estimates for the first time. These estimates show that for this season so far, there have been up to 20.4 million influenza illnesses, up to 9.6 million medical visits, up to 256,000 influenza-associated hospitalizations, and up to 22,300 influenza-associated deaths. To put that into context, since the influenza pandemic in 2009, the range of deaths was 12,000 to 79,000 last year. Granted these are in-season deaths, the estimate is preliminary, and the season is not over yet. It can basically be said that the estimate is now higher than what was seen in the very low 2011-2012 season, but still well below what was seen last year [www.cdc.gov/flu].

In terms of the characteristics of currently circulating influenza A (H1N1)pdm09 viruses collected from September 30, 2018 to present, all 626 influenza A (H1N1)pdm09 viruses from the US tested so far belong to the single genetic group 6B.1. However, a considerable amount of genetic diversity has emerged within clade 6B.1. Of the 263 (H1N1)pdm09 viruses that have been antigenically characterized using a hemagglutination inhibition (HI) assay with ferret antisera, 259 (98.5%) were similar to both the egg and cell culture-propagated A/Michigan/45/2015 reference virus. However, testing with human sera recently has shown reduction in some of the titers against some recent influenza A (H1N1)pdm09 viruses compared to titers against A/Michigan/45/2015.

Phylogenetic analysis of the HA genes of recent H3N2 viruses show extensive genetic diversity in multiple genetic clades and subclades co-circulating. The 3 predominant clades or subclades are the 3C.2a1, which is the clade to which the current vaccine strain belongs, 3C.2a, and 3C.3a. The proportion and geographic spread of viruses belonging to clade 3C.3a clade has increased in recent weeks. The most recent figure was that for the season, they represent 52% of the H3N2 viruses circulating. Of the 194 A(H3N2) viruses antigenically characterized by focus reduction assay (FRA), 128 (66%) were well-inhibited by ferret antisera raised against the



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A/Singapore/INFIMH-16-0019/2016 (3C.2a1) cell-propagated reference virus. Among the 66 viruses that reacted poorly against the A/Singapore, 65 (98.5%) belonged to clade 3C.3a.

There are currently 3 genetic groups of B/Victoria lineage viruses co-circulating. The V1A group was the older Brisbane-like vaccine strain clade. The V1A.1 clade is the clade to which the current B/Colorado virus belongs and was referred to last year as V1A-2DEL because it has a 2-amino acid deletion in the hemagglutinin. The V1A-3DEL subclade has 3 amino acid deletions in the hemagglutinin. Of the 40 B/Victoria lineage viruses antigenically characterized, 33 (82.5%) were similar to the cell-propagated B/Colorado/06/2017-like V1A.1 reference virus that is in the vaccine. All 7 viruses that reacted poorly to A/Colorado belonged to the V1A group, which is the older group similar to the old B/Brisbane vaccine strain.

All of the B/Yamagata lineage viruses tested belong to a single genetic group, Y3. All influenza B/Yamagata-lineage viruses antigenically characterized are similar to cell-propagated B/Phuket/3073/2013 (Y3), the reference vaccine virus representing the influenza B/Yamagata-lineage component of the 2018-2019 Northern Hemisphere quadrivalent vaccines.

WHO held its Consultation on the Composition of Influenza Virus Vaccines for Use in the 2019-2020 Northern Hemisphere Influenza Season on February 18-21, 2019. Their recommendation was to maintain both of the influenza B components, B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage), which will be only in quadrivalent formulations. They recommended updating the (H1N1)pdm09 component to an A/Brisbane/02/2018 (H1N1)pdm09-like virus. WHO elected to delay the decision on the A(H3N2) virus component until March 21, 2019 to allow time for collection of more data and to allow for completion of testing on potential vaccine candidate viruses. FDA's VRBPAC will meet on March 6, 2019 and is also expected to delay this decision.

In summary, influenza activity remains elevated. Influenza A(H1N1)pdm09 viruses have predominated overall, but H3N2 viruses were detected more commonly than H1N1 viruses in the Southeast and have increased in other regions in recent weeks. An increasing proportion of the H3N2 viruses belong to the 3C.3a genetic group, which is antigenically distinct from the 3C.2a genetic group. WHO's recommendation for the H3N2 component for the 2019-2020 Northern Hemisphere vaccine has been delayed until March 21, 2019 to allow for the collection of more data and to allow for completion of testing of potential candidate vaccine viruses.

## Interim Estimates of 2018–19 Seasonal Influenza Vaccine Effectiveness Against Medically Attended Influenza from the US Flu VE Network

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

Dr. Flannery presented data from the US Flu VE Network. Participating since the 2012 influenza season, the 5 sites and their Principal Investigators (PIs) are:

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



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As a reminder, the US Flu VE Network enrollees include outpatients aged >6 months with acute respiratory illness with cough ≤7 days duration. For this enrollment period, sites began enrollment once there was influenza activity at their sites. The period of influenza positivity ranged from November 23, 2018–February 2, 2019. A test-negative design was utilized for this analysis, which compares the vaccination odds among influenza reverse transcriptase polymerase chain reaction (RT-PCR) positive cases and RT-PCR negative controls. The vaccination status for these interim analyses was receipt of at least one dose of any 2018-2019 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. One site uses medical records and immunization registries only, and four sites also use self-reports for interim estimates. Adjustments in this analysis included study site, age, self-rated general health status, race/Hispanic ethnicity, interval from onset to enrollment, and calendar time. The interim estimates that were published on February 15, 2019 in the *MMWR* included 3254 subjects enrolled from November 23, 2018-February 2, 2019 at the 5 sites. Of these, 465 (14%) were influenza RT-PCR positive and 2789 (86%) tested influenza RT-PCR negative. Among the influenza positives, 63% were H1N1, 22% were H3N2, 13% were unsubtyped A, 1% were B/Yamagata, and 1% were B/Victoria [Doyle et al, *MMWR* 2019].

At the time of the interim report, approximately 20% of enrollees were testing positive. Considering any influenza A or B virus for all age groups, 43% of influenza positives were vaccinated and 57% of influenza negatives were vaccinated, for an adjusted VE of 47% (CI: 34, 57). By age group, VE was 61% (CI: 44, 73) for children 6 months through 17 years of age, 37% (CI: 9, 56) for adults 18 through 49 years of age, and 24% for adults ≥50 years of age. The confidence interval for the ≥50 years of age group was not statistically significant (CI: -15, 51). Overall VE for Influenza A/H1N1pdm09 was 46% (CI: 30, 58). By age group, VE was 62% (CI: 40, 75) for children 6 months through 17 years of age, 45% (CI: 14, 64) for adults 18 through 49 years of age, and 8% (CI: -59, 46) for adults ≥50 years of age. Again, the confidence interval for the ≥50 years of age group was not statistically significant. The age groups depend upon whether there are enough samples to be able to divide into age groups and have confidence in the estimates. This was possible for these interim estimates for A/H1N1, but not for A/H3N2. Overall VE for all ages for A/H3N2 was 44% (CI: 13, 64).

In Summary, interim results for 2018-2019 season through February 2, 2019 indicate protection against influenza at 47% (CI: 35, 57) VE overall against any influenza virus, 46% (CI: 30, 58) against H1N1pdm09, and 44% (CI: 13, 64) against H3N2. Effectiveness estimates among children aged 6 months through 17 years was 61% (CI: 44, 73) against any influenza, and 62% (CI: 40, 75) against H1N1pdm09. Effectiveness estimates ranged from 37% to 45% among adults aged 18 through 49 years. Effectiveness estimates were not statistically significant among those ≥50 years. The US Flu VE study will continue enrolling through the end of the season. To put these in context, there are some recently published estimates of 2018-2019 VE from several networks shown here:

- Canada, Skowronski et al, Eurosurveillance 2019
  - VE 68% (CI: 55, 77) against any influenza, 72% against H1N1pdm09
- Europe, Kissling et al, Eurosurveillance 2019
  - VE 32% – 43% against influenza A, 45% – 71% against H1N1pdm09
  - UK, LAIV: VE 87% (CI: 4, 100) against H1N1pdm09
- Hong Kong, Chiu et al, Eurosurveillance 2019
  - Inpatient VE 92% (CI: 82, 96) against H1N1pdm09, 6m-17 years
- Australia (2018), Australian Government website
  - VE 78% (CI: 51, 91) against H1N1pdm09, all ages



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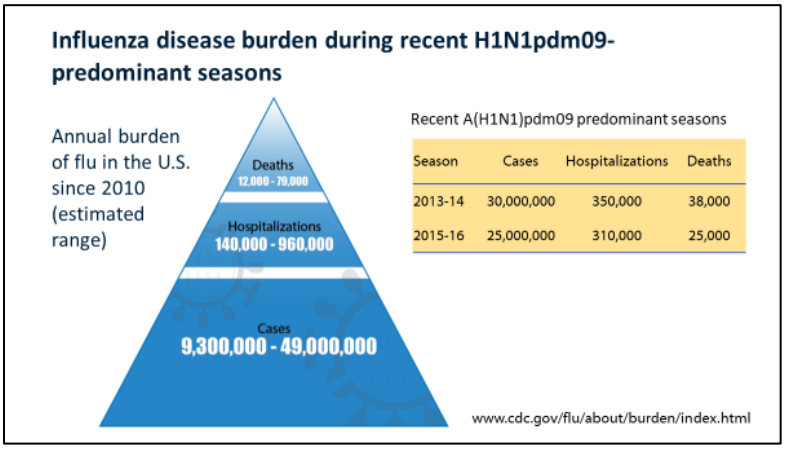
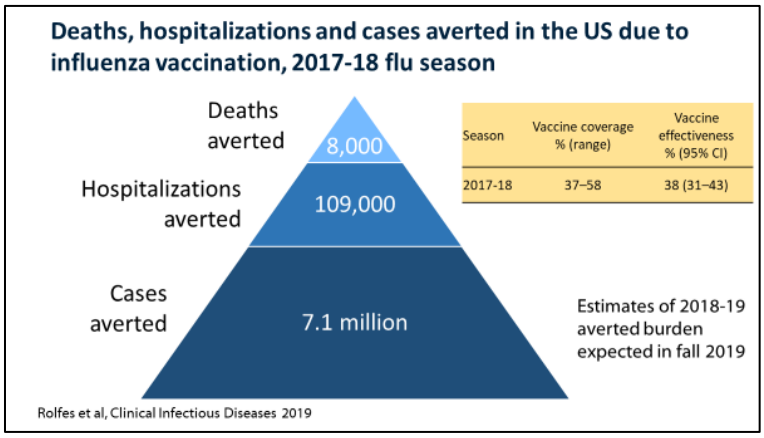
To put US estimates in context, CDC has begun posting estimates of disease burden on the CDC website. These pyramids are shown on the website:




In the first graphic above, the box on the right shows the recent A(H1N1)pdm09 predominant seasons, 2013-2014 and 2015-2016. For comparison, the numbers for A(H1N1)pdm09 predominant seasons fall somewhere in the middle of this range that has been seen since 2010. The second graphic combines end-of-season VE estimates together with burden averted. These results were published in January 2019 in *Clinical Infectious Diseases*. This same approach will be taken for end-of-season VE and disease burden as soon as those data are available later this fall. The substantial numbers of disease burden averted last season were based on a vaccine coverage that is within the range seen for this season and a VE of about 38%—again, the range seen for the interim estimates.

## Discussion Points

Dr. Romero asked whether there are any data on live attenuated influenza vaccine (LAIV) VE in the US, whether there is enough use of LAIV such that there will be some reasonable and trustworthy VE data at the end of the season, and whether there are any variations in susceptibility to antivirals given in terms of the A(H3N2) viruses and the intra-clade variation.

Dr. Flannery replied that there is not very much LAIV use in the US Flu VE Network sites. It is questionable whether there will be enough at the end of the season to be able to provide LAIV-specific estimates. For the interim estimates, only a handful of children have received LAIV.



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Regarding susceptibility of the A(H3N2) viruses to antivirals, Dr. Brammer indicated that all viruses tested so far this year have been susceptible to all antivirals.

Dr. Szilagyi asked whether in addition to the United Kingdom (UK) there is much LAIV use in other countries.

Dr. Flannery replied that the information he has is that there are several countries that have used LAIV in the past that continue to use LAIV, and that there may be some estimates from Finland and others. LAIV use in Canada has reportedly been very low.

Dr. Allyn Bandell (Senior Director, Medical Affairs, AstraZeneca) indicated that VE estimates for LAIV are anticipated from Finland, the UK, possibly Hong Kong, and Canada. Some of those data are expected to be presented during the European Society for Paediatric Infectious Diseases (ESPID) meeting in the European Union (EU) in May.

Dr. Quach (NACI) reported that Canada has not stopped using LAIV, but there is not much use. If they do have an estimate, it is not anticipated to be statistically significant in any way.

Dr. Walter asked whether there were any thoughts regarding the potential downstream effects of the delay in strain selection in terms of manufacturing and availability of vaccine.

Dr. Fink (FDA) indicated that as mentioned, VRBPAC would be meeting the next week and likely would not be able to make a recommendation on the H3N2 selection. Beyond that, he could not comment further on the potential downstream implications.

Dr. Bernstein observed that VE for LAIV in the UK was encouraging and wondered how that population compares to the US population in terms of use and ages, and whether it is administered to school-aged children only.

Dr. Flannery indicated that there was a recent paper from Huong Q. McLean et al at Marshfield Clinic that examines prior season vaccination, which does not seem to indicate that prior season vaccination was one of the major contributors to what was observed in the US with low VE. There was some speculation at the time about the UK population being less vaccinated than the US population, but the children in the LAIV group in the UK have received vaccine over several seasons with predominantly LAIV. The program rollout in the UK is now in its 6$^{th}$ year, with a large population vaccinated. The population is slightly different in terms of repeat vaccination with LAIV, but is similar in that the population has now been vaccinated several different seasons. The UK program is widely school-based, but there is a program for children from the age of 2 years.

Dr. Stephens was curious about the WHO recommendation for change in the H1N1 component, given the HI data of very good protection in the US. He wondered whether there were data outside of the US pertaining to H1N1.

Dr. Brammer said she thought the decision was made based primarily on the fact that even though it is known that there are genetic changes occurring within the H1N1 viruses and the data look good with ferret antisera, reduced titers were seen with human sera.



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Dr. Jackie Katz (CDC, Influenza Division) added that the recommendation was based on the fact that over the last 18 months or so, there has been an accumulation of genetic changes—one change in each of 3 antigenic groups. In the last 6 months or so, there has been an additional change that appears to be sweeping through the H1N1pdm09 virus population as have the other 3. Collectively, it seems that there is a selection for these particular substitutions. As noted, antigenic changes were not observed using ferret antisera. As a reminder, there was a similar situation when the change was made to A/Michigan/45/2015 a couple of years ago. They also assessed panels of pre- and post-vaccination serum from individuals of various age groups who have received the current 2018-2019 season's vaccine and noted that the post-vaccination GMTs in multiple populations were substantially reduced against the recent viruses that have 183P in addition to the other changes. That substantial reduction was seen in some individual pediatric sera as well. This was thought to be an indication that the virus was on the move and that an updated recommendation should be made.

Dr. Frey observed that the estimates Dr. Flannery shared from other countries seemed to be higher than US estimates, LAIV aside, and wondered what would explain this difference (e.g., strain change, vaccine type, use of adjuvant, low numbers, et cetera).

Dr. Flannery indicated that the one caveat for all of these estimates was that they were interim and the confidence intervals were wide. While the interim numbers from Canada were perhaps encouraging in that they were high overall and also by age group, the numbers were small. The US did not feel confident breaking out the estimates for adults ≥65 years, which is why it was presented as ≥50 years. For the European estimates just published, the overall estimates from 4 different studies were within the range that are seen in the US. There was some heterogeneity in the age-specific group, again with small numbers. While a caveat is that the US does not have a lot of cases in the ≥50 years of age population at this point in the season, there may be a change in those estimates as the seasons goes on.

Dr. Szilagyi appreciated seeing the slide on deaths, hospitalizations, and cases averted. Data are often presented on the burden of disease, but are presented infrequently on diseases that are actually averted by vaccinations. If they could acquire New Vaccine Surveillance Network (NVSN) data, he suggested adding emergency department (ED) visits averted as well as direct and indirect costs averted by the vaccination program. He emphasized that while he raised this specifically regarding influenza, he thought this would be useful for other vaccines as well.

Dr. Bernstein asked whether the percent of vaccine receipt was known for those who had died.

Dr. Brammer replied that while they do not have this information for the general population, the proportion of children fully vaccinated among influenza-associated pediatric deaths is very similar to what is typically observed annually at about 20%.

Dr. Kimberlin (AAP) inquired as to whether anyone could comment on the Baloxavir experience in Japan and the rapid emergence of resistance, and whether that is being monitored in the US and the amount of Baloxavir use in the US. He emphasized the need to follow this carefully.

Dr. Jackie Katz (CDC, Influenza Division) indicated that the likelihood of resistance in the US is being monitored, and there has been one example in a treated case. However, she said she could not speak to the amount of use in the US.

Dr. Foster (APhA) asked whether any changes had been observed in the uptake of vaccine this year, particularly given that last year was such a bad season.



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Dr. Flannery indicated that there are some early estimates of vaccine uptake on the CDC website, which suggest that there was an uptick. A caveat with that is that there have been some changes in how immunization coverage is being monitored and estimated. He invited additional information from the Immunization Services Division (ISD).

Dr. Wharton (Division Director, ISD) indicated that the National Immunization Survey (NIS) data have shown an increase in pediatric influenza vaccination coverage.

Dr. Lee asked whether there would be any estimates on the burden of disease in pregnant women.

Dr. Alicia Fry (SME) reported that a special study is being conducted for last season, which hopefully will be published before this season's estimate is available. CDC is working on this.

**Afluria® Quadrivalent Influenza Vaccine (QIV) Phase III, Randomized, Observer-Blind Comparator-Controlled Study Among Children 6-59 Months**

**Gregg C. Sylvester, MD, MPH**
**Medical Affairs**
**Seqirus™**

Dr. Sylvester presented the results from Seqirus's™ Phase III trial for its QIV inactivated split virion influenza vaccine, Afluria® QIV, among children 6 through 59 months of age. The Seqirus™ trivalent influenza vaccine (TIV) formulation used in the Southern Hemisphere during the 2010 influenza season was associated with increased reports of fevers and febrile seizures in children, especially those less than 5 years of age. As a result, Afluria® TIV was not recommended for continued use in this age group. Investigations by Seqirus™ identified residual lipid under the previous manufacturing conditions as a likely cause of the fevers. In vitro studies showed that increasing the concentration of the splitting agent reduced the lipid content and pyrogenicity of the vaccine.

Accordingly, the concentration of the splitting agent used in the manufacturing process for Afluria® QIV was increased. Seqirus™ took a stepwise approach to license Afluria® QIV. For 2014-2015, an Afluria® QIV Phase III randomized controlled trial (RCT) in adults ≥ 18 years of age was approved by the FDA in August 2016. For 2015-2016, an Afluria® QIV Phase III RCT in children 5 to <18 years of age was approved by the FDA in August 2017. For 2016-2017, Afluria® QIV Phase III RCT in children 6 months to <5 years of age was approved by the FDA in October 2018.

In the study among children 6 months to <5 years of age, Seqirus™ evaluated the immunogenicity and safety of Afluria® QIV compared to a US licensed influenza vaccine, both containing the 4 influenza strains recommended that season. The study was conducted at 39 US sites between September 2016 and August 2017. The protocol was approved by the Institutional Review Boards (IRBs). Randomization was characterized by a younger cohort ages 6 to 35 months (n=935) and an older cohort ages 36 to 59 months of age (n=1312). Participants were randomized 3:1 to receive Afluria® QIV or the comparator influenza vaccine. Participants received 1 or 2 doses based upon their influenza history. The younger cohort received a 0.25 mL dose of vaccine and the older cohort received a 0.5 mL dose of vaccine.
The primary immunogenicity objective was to demonstrate that vaccination with Afluria® QIV elicits an immune response that is non-inferior compared to a US-licensed influenza vaccine.



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The primary safety objective was to describe the tolerability of Afluria® QIV compared to the comparator vaccines, especially noting fever rates.

Healthy children in the specified age group were enrolled in the study. Children were excluded if they were febrile, acutely ill, immunocompromised, or allergic to any component of either vaccine. Children also were excluded if they had a history of SAEs to any influenza vaccine; history of seizure, with the exception of simple febrile seizures; or had received any vaccine within 21 days. This study was not designed to assess co-administration with other childhood vaccines. Seqirus™ wanted to study the safety profile of Afluria® QIV alone. The demographics and baseline characteristics are well-balanced within the two groups and within the two age cohorts. The mean age is slightly over 3 years. There are slightly more boys in the study than girls. African Americans are well-represented, but Asians are under-represented. The pre-vaccine temperature median was all within the normal range. Approximately 40% of all participants were indicated for 2 doses, which was higher in the younger age group and lower in the older age group.

A non-inferiority immunogenicity study design was used, with 8 co-primary endpoints to gain licensure in the US. GMTs and seroconversion rates (SCR) were analyzed for the 4 viral strains. These endpoints were defined in accordance with the FDA guidance for non-inferiority studies, and are commonly used in the evaluation of efficacy of influenza vaccines. For GMTs, the upper bound of the 2-sided 95% CI of the GMT ratios should not exceed 1.5. For SCR, the upper bound of the 2-sided 95% CI of the SCR differences should be ≤10%. If all 8 co-primary endpoints meet the prespecified FDA criteria, then non-inferiority for Afluria® QIV compared to the US comparator influenza vaccine can be concluded.

In terms of the results, the GMT ratios were similar between vaccines. The upper bound of the 95% CI did not exceed the prespecified margin of 1.5. The SCR were similar, and the difference of ≤10% between vaccines met the prespecified criteria. Immune responses were similar across the two age groups and within the two vaccine groups. The primary co-endpoints, measured by GMTs and SCRs, for each of the viral strains were met.

Solicited AEs are collected for 7 days post-vaccination by e-diaries, telephone calls, and clinic or ED visits. The categories for local AEs are Mild/Grade 1 AEs that do not interfere with daily activity, Moderate/Grade 2 that involves pain resulting in crying upon touch, and Severe/Grade 3 that involves crying when the limb is moved. In the younger cohort, local reactions were similar between both vaccine groups and most reactions were mild or moderate. In the older cohort, the same 3 symptoms were assessed, the reactions were similar between both vaccine groups, and most reactions were mild or moderate. In the younger and older cohorts, the vast majority of local reactions resolved within 2 days of vaccination.

The AEs for solicited systemic AEs are irritability, diarrhea, loss of appetite, and nausea/vomiting. The pain categories are Mild for AEs that are easily tolerated, minimal discomfort, and does not interfere with any daily activity; Moderate for AEs that are sufficiently discomforting and can interfere with daily activity; and Severe for AEs that are severe and prevent daily activity or requires significant medical intervention. Like the local reactions, the systemic events in the younger cohort were similar between both vaccine groups, most were mild or moderate, and there were very few severe events. In the older cohort, solicited systemic AEs were seen in 5% or more of the older cohort. Once again, the events were similar between the groups and were mild or moderate in intensity.



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The categories for fever events were Mild (99.5 °F to <100.4 °F), Moderate (≥ 100.4 °F to 101.3 °F), and Severe (≥ 101.3°F). The overall fever rate for Afluria® QIV was 7.2% versus 11.9% for the comparator. Severe related fevers were similar between the two vaccine groups. When the Mild, Moderate, and Severe categories are combined for the overall related fever group, only 4% of the subjects given Afluria® QIV had a fever related to the vaccine versus 7.9% of the subjects given the comparator. In the older cohort, the Afluria® QIV overall for any fever rate was 4.8% versus the comparator of 6.0%. Severe related fevers were similar between the two vaccine groups, with an overall related fever rate of 3.1% for Afluria® QIV versus 4.7% in the comparator. In both age groups, most fevers had onset within Day 1 to Day 3 following vaccination.

There were 11 SAEs by the end of the study in the younger cohort for Afluria® QIV. These 11 events were all determined to be unrelated to the vaccine by the study investigators and by an independent Data and Safety Monitoring Board (DSMB). There were 2 Adverse Events of Special Interest (AESIs). Both children were classified as having a simple febrile seizure, one of which occurred at Day 43 and the other of which occurred at Day 103 of the study. Neither child was febrile during the 7 days post-vaccination, which is considered the risk window for febrile seizures related to influenza vaccination. These 2 AESIs also were determined to be unrelated to Afluria® QIV.

In this study of children 6 months through 59 months of age, similar immune responses were demonstrated for Afluria® QIV and the US licensed influenza comparator vaccine for all 4 strains as assessed by GMTs and SCRs. The safety and tolerability of Afluria® QIV is similar to the comparator vaccine in children <5 years of age. The overall any fever ( ≥ 99.5 °F) rate for Afluria® QIV was 7.2% and 11.9% for the comparator. There were no febrile seizures during the first 7 days, and severe related fever are similar between the two groups in both age groups. The FDA criteria for non-inferiority was met for all 8 co-primary endpoints and thus, Seqirus's™ received approval for licensure on October 31, 2018 for the new age group of 6 month through 59 months.

**Discussion Points**

Dr. Bernstein inquired as to how much Afluria® QIV is used in the US in the younger age group.

Dr. Sylvester indicated that no Afluria® QIV is used in the younger age group, because it was just licensed. Prior to that, it had not been recommended. It was this clinical trial that demonstrates that it is safe and effective in this age group. The plan is to use Afluria® QIV in the upcoming influenza season.

Dr. Moore pointed out that it is always great to have additional products becoming available for younger age groups, and wondered whether there are future phased studies that will assess the 0.5 mL dosing in the 6 month to 35 month group. While the dose was 0.25 mL at the time this study was designed, other manufacturers with similar products have now moved up to the 0.5 mL dose, which is very popular programmatically because it simplifies inventory management and dosing and prevents administration errors.

Dr. Sylvester indicated that they wanted to assess the 0.25 mL dose because of the issue of fever in 2010. They are discussing internally whether there are opportunities to study Afluria® QIV in the 6 month to 35 month group at a higher dose.

Dr. O'Leary (PIDS) requested further information about the SAEs at Day 28.



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Dr. Sylvester indicated that of the 11 SAEs among Afluria® QIV recipients, there were the 2 febrile seizures mentioned earlier, 3 respiratory syncytial virus (RSV) infections, 2 croup infections, 1 dysphasia, 1 dehydration, 1 foreign body aspiration, and 1 animal bite. Among the 3 that occurred in the comparator group, 1 was a broken arm, 1 was bronchiolitis, and 1 was impaired gastric emptying.

## Case-Control Study of Inactivated Influenza Vaccine and Spontaneous Abortion in the Vaccine Safety Datalink, 2012-13, 2013-14, and 2014-15

**Jim Donahue, PhD, DVM**
**Marshfield Clinic Research Institute**

Dr. Donahue reported on a recently completed case-control study of IIV and SAB in the VSD, which covered 3 seasons: 2012-2013, 2013-2014, and 2014-2015. This is the third case-control study. Matched case-control studies were conducted in women who were pregnant in 2005-2006 and 2006-2007 in the VSD, which did not find an association between SAB and IIV receipt in a 28-day risk window. The odds ratio was 1.2 and the 95% CI included 1.0 [Irving, Obst Gyn 2013].

After the 2009 pandemic, CDC funded another matched case-control study in the VSD to examine the association between SAB and influenza vaccination during the 2010-2011 season, the first full season after the 2009 pandemic, and the 2011-2012 season. The design was similar, with individual matching by VSD site, maternal age group, date of last menstrual period (LMP). Chart reviews were done for all cases and controls. Vaccine association with SAB was assessed in 3 risk windows: before SAB: 1-28 days (primary), 29-56 days, and >56 days. In that study, the results were somewhat different. SAB was associated with IIV receipt in the 28 day risk window (odds ratio=2.0, 95% CI 1.1-3.6). No other associations were found in any other risk windows. IIV-SAB association was statistically significant in 2010-2011 but not in 2011-2012. In both seasons, statistically significant associations were found only in women who had received influenza vaccine in the prior influenza season. This is suggestive of an effect modification, but this was only in the 1-28 day window. A number of additional analyses were performed to try to figure out whether there was some bias or confounding, but nothing could be clearly attributed to bias or confounding.

For the current study, they wanted to focus on the effect modification question regarding whether being vaccinated in the previous season was somehow influencing the relationship between current season vaccination and SAB. The two main objectives were to: 1) evaluate the IIV-SAB association in the 28 days before SAB among women who received influenza vaccine during the prior season; and 2) evaluate the IIV-SAB association in the 28 days before the SAB among women who did not receive the vaccine during the prior season. The secondary objectives were to: 1) evaluate the IIV-SAB association for vaccine receipt relative to conception; and 2) evaluate the association in each of the three seasons.

They were fortunate to have input from two scientific advisory groups for this study. The first one, comprised of VSD and CDC scientists, met in late 2015 primarily to advise on study design. The second was a subgroup of the Influenza WG of the ACIP, the Maternal Influenza Vaccination Safety Sub-WG. This group was comprised of epidemiologists, biostatisticians, and clinicians. The mission was to provide advice on the analytic plan and recommendations to enhance the interpretability of the results. The 6 VSD sites that participated in this study included: Kaiser Colorado, Kaiser Northern California, Kaiser Northwest, Kaiser Southern



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California, Kaiser Washington, and Marshfield Clinic. These are the same sites as in the previous study.

The study design, a matched case-control, was similar to the previous two studies. The subjects were matched on age group (18-24, 25-34, 35-44), site, LMP, and influenza vaccination status in the previous season (which differed from the last study). Also different in this study was that 50% of the cases in each season were vaccinated in the previous influenza season. Eligibility criteria were close to the same as before and included adults 18 to 44 years of age as of LMP, individuals who were enrolled in VSD site ≥ 20 months prior to LMP (which differed from the last study, which was 12 months), LMP has to be documented in the record, and SAB (cases) or live birth (controls) had to be confirmed.

Potential cases were identified using International Classification of Diseases (ICD)-9 codes assigned during influenza season. Medical record review and adjudication were done for all potential cases. For the primary analysis in this study, SAB was defined as occurring between 6 to <20 weeks gestational age. A secondary analysis was performed in which the date of SAB was increased between 5 to <20 weeks gestational age. The date of SAB was considered to be the reference date for each case-control pair. Controls were identified in a similar way using a VSD pregnancy database or ICD-9/ICD-10 codes for live births. Vaccine exposures were documented from the medical record. The primary risk window was the 28 days before the reference date. Other risk windows included 29-56 and >56 days. The secondary analysis windows were relative to conception, with 4 windows: >42 days before, 0-42 days before, 1-28 days after (and before the reference date), and >28 days after (and before the reference date).

Extensive review was done to try to determine the data of SAB and gestational age. All cases were adjudicated to confirm SAB and estimate gestational age and date of SAB, and were blinded to vaccination status. The adjudication process was under the direction of the obstetrician co-investigator and followed the established adjudication algorithm that was used in the previous study, though it was somewhat more polished in this study. In addition to the algorithm, the estimate incorporates information from medical records: U/S data, clinical events (e.g., hemorrhaging), LMP, ICD coding, et cetera.

Because this was a matched case-control study, conditional logistic regression was done. The referent group for all of the estimates were women not vaccinated as of the reference date. Separate models were done for women with and without prior season vaccination, and all women combined. Confounding was assessed separately for each model. Five variables were included in all 3 of those models: maternal age, body mass index (BMI), and health care utilization represented as natural cubic splines, race, and ethnicity. The other covariates differ for different models depending upon the bivariate analysis that was done. When planning for this study, it was important to determine the ability to detect an odd ratio in the stratum-specific and season-specific estimates. If there were 250 matched pairs in each stratum and season, there would be 82% power to detect an odd ratio of 3.5. If some of the strata could be combined for 500 matched pairs in each season, there would be 82% power to detect an odds ratio of 2.3. If strata and season could all be combined, 1500 matched pairs would provide 83% power for an odds ratio of 1.6. They identified a little less than 1400 pairs.



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Matched pairs and controls were identified beginning with 1908 presumptive cases of SAB. After eliminating 166 who had outcomes other than SAB, there were 1634 confirmed SABs. The adjudication process eliminated another 224 of those, leaving 1410. It was not possible to match 29 of those, which left 1381 cases between 5 and <20 weeks. The <6 weeks gestational age cases were eliminated leaving 1236 matched pairs, which was the primary group analyzed for the study.

Regarding descriptive characteristics among vaccinated and non-vaccinated cases in the previous season, cases were slightly older than controls. That was particularly true in the 40 to 44 age group. Cases also had a somewhat higher BMI than controls in both strata. Cases were more likely to be African American and Hispanic and less likely to be Asian. At least in women who were vaccinated in the previous season, cases were more likely to have diabetes and asthma. Within the two strata, cases and controls had pretty similar proportions in terms of having had 1 or 2 previous SABs.

In terms of the frequency of vaccination exposures for cases and controls, if there had been an association between vaccine and SAB, the numbers in the risk window of 1-28 days, a greater number of cases would have been expected to have been vaccinated proportionately than controls. However, this was not the case in any of the 3 seasons. For the 1-28 day window among those who were vaccinated in the previous season in 2012-2013, the odds ratio was 0.5 (0.2, 1.1), in 2013-2014 the odds ratio was 1.1 (0.6, 2.3), and in 2014-2015 it was 1.7 (0.7, 4.0). In the other two risk windows of 29-56 and >56 among those vaccinated in the previous season, all of the odds ratios were less than or close to 1. For those who were not vaccinated in the previous season in the 1-28 day risk window, all of the odds ratios were pretty close to or less than 1. In 2012-2013, the odds ratio was 0.7 (0.3, 1.6), in 2013-2014 it was 0.6 (0.2, 1.4), and in 2014-2015 it was 0.7 (0.3, 1.8). In the 2014-2015 season, there were slightly elevated odds ratios in the group vaccinated in the previous season of 1.7 (0.7, 4.0) in the 1-28 day risk window. There also were slightly elevated odds in the 2012-2013 season in the not vaccinated group of 1.8 (0.2, 14.9) in the 29-56 risk window, with very wide confidence intervals and small discordant pairs of 2/2.

Because there did not appear to be any season-specific differences, all 3 seasons were combined for odds ratios less than 1.0 in both the vaccinated in the previous season and unvaccinated in the previous season groups. Because there did not appear to be an effective modification by prior vaccination, the two strata were combined. This resulted in odds ratios of less than or close to 1.0 and in all cases, and confidence intervals that include 1.0 in all cases for each of the 3 seasons. Combining all seasons and both strata, the adjusted odds ratios were all less than 1.0. Those were all exposures in the 3 risk windows that were before the reference data.

The secondary analysis examined exposures relative to conception. This time the risk window strata for days between vaccination and conception were: >42 before, 0-42 before, 1-28 after, >28 after. For the most part, the adjusted odds ratios were less than and close to 1.0. To highlight a couple that were somewhat higher, in the 2014-2015 season among those vaccinated in the previous season, the odds ratio was 2.1 (0.8, 5.2) in the 1-28 days after conception risk window. In the 2012-2013 season among those not vaccinated in the previous season, the odds ratio was 3.2 (0.9, 11.9) in the 1-28 days after risk window. Combining the seasons, the adjusted odds ratios ranged from 0.5 to 1.1 in both strata.



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Additional secondary analyses were done because the definition for SAB in the previous study was a gestational age between 5 and <20 weeks in the previous study. The results were essentially the same when gestational age range expanded to include 5 to <20 weeks, and when another analysis was performed that excluded women with history of ≥2 SABs.

Comparing the third IIV-SAB study with the previous 2 IIV-SAB studies, and few differences were found between the 3 populations. Some differences that stand out are that the IIV-SAB-3 2012-15 study included women who were about 2 years older than women in the previous 2 studies, and there were fewer smokers among the women in the third study. The median gestational age at the time of the SAB was almost identical in all 3 studies. Most of the other characteristics were fairly similar. The gestational age at the time of SAB in the third study was compared to the IIV-SAB-2 2010-2012 study, and the overall distribution was similar. However, the prior study had more women in the 6-week gestational age range and the third study had more in the 7-8 week range. Both studies had a median gestational age of 7 weeks (IQR 6, 9).

There were some differences in terms of the results. There were methodologic differences between the current and prior VSD study, including different seasons (2012-2013, 2013-2014, and 2014-2015), the current study was matched on previous season influenza vaccination status, the current study was matched on 3 age groups (18-24, 25-34, and 35-44 years) rather than 2 age groups, and the study population was approximately 3 times larger compared to the prior study (2762 vs. 970).

The major findings of the third study were that there was no significant association between influenza vaccine receipt and SAB, regardless of prior season vaccination status. Odds ratios were less than or close to 1.0 in all risk windows. For the odds ratios that were greater than 1.0, the 95% confidence intervals included 1.0 in each case. There were no significant associations in the season-specific analyses. These findings support the current recommendation for vaccination of pregnant women in any stage of pregnancy.

**Discussion Points**

Dr. Szilagyi observed that this was a very elegant presentation of a complex study. He asked whether Dr. Donahue had any additional thoughts about the prior study, recalling that he had mentioned when the second study was presented to ACIP that it was not an optimally designed study and there were some potential problems. Having now studied this matching for prior vaccination and a much larger sample size provides a lot of comfort, but having rethought the prior study, he wondered if there were any additional explanations.

Dr. Donahue indicated that the design changes they made for this study were important and allowed them to focus on the effect modification issue. He did not think it would have changed anything had they done this in the previous study. They cannot really explain why those results were different. Perhaps it is random variation, different time periods, further removed from the 2009 pandemic, a 3 times larger study population to allow for examination of the effect modification, and/or relevance to women who are pregnant now. The design of the third study was not intended to either confirm or refute the results of the previous study.



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## Summary and Work Group Considerations

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

In addition to the WG members, Dr. Grohskopf recognized and appreciated the various CDC staff who make a regular and important contribution to the discussion. She then briefly summarized some of the WG discussions and described plans for the next few months.

Regarding influenza vaccines for young children, primarily 6 months through 35 months of age, there have been a number of recent licensure changes. During this session, they heard the presentation on Afluria®. In October 2018, FDA licensed both Afluria® TIV and Afluria® QIV for children ≥6 months of age, which was a change from the ≥5 years of age. The dose for children 6 through 35 months of age is smaller at 0.25mL versus 0.5mL for those aged ≥3 years. There was also discussion during the October 2018 ACIP meeting on Fluzone® Quadrivalent data. This has been licensed for children 6 through 35 months for some time. For a number of seasons until relatively recently, this was the only influenza vaccine licensed for this age group. It was originally licensed at 0.25mL/dose. As of January 2019, FDA licensed 0.5mL/dose for all ages based on the results of a randomized non-inferiority trial of immunogenicity and safety of 0.25mL vs. 0.5mL in children aged 6 through 35 months presented to ACIP in October 2018. Per the labeling for this vaccine, either 0.25mL or 0.5mL is acceptable for children 6 through 35 months of age.

One of the questions asked when this age groups is discussed regards what the experience is with concomitant vaccination. Younger children are more likely to have febrile reactions to vaccines. With the newer age indications, expansions of age indications, and dose changes there is overall less cumulative experience with this in terms of this age group. Conversely, the clinical data and clinical study data that have been accumulated thus far is reassuring. Another point that was discussed is that there are now five licensed IIV vaccines that are licensed for 6 through 35 months of age, but the dose volumes differ as shown in the table below:

| Vaccine | Dose Volume |
|---|---|
| Fluarix® Quadrivalent (IIV4, GSK) | 0.5mL |
| FluLaval® Quadrivalent (IIV4, ID Biomedical Corp/GSK) | 0.5mL |
| Fluzone® Quadrivalent (IIV4, Sanofi Pasteur) | 0.25 mL or 0.5 mL |
| Afluria® (IIV3, Seqirus) | 0.25 mL |
| Afluria® Quadrivalent (IIV4, Seqirus) | 0.25 mL |

Fluarix® Quadrivalent and FluLaval® Quadrivalent were initially licensed for ≥3 years. and FluLaval® Quadrivalent had an age expansion to ≥6 months in November 2016 and Fluarix® Quadrivalent in January 2019 at the 0.5mL, which is the same dose as persons aged ≥3 years. It will be important to focus on this moving forward, depending upon the vaccines expected to be available next season, in terms of providing guidance to ensure avoiding the potential for confusion.



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With regard to the VSD study, the WG discussed the differences between the current and the previous IIV and SAB studies in terms of methodology, matching, study size and statistical power, and available vaccines during the different periods. Overall, the results were felt to be reassuring.

Between now and the June 2019 meeting, the development of the 2019-2020 ACIP Influenza Statement will be ongoing. There will probably be some further discussion during the June 2019 ACIP meeting. Based on what is known currently, no substantial changes are anticipated, and the anticipated publication date is August 2019. The WG continues the discussion of 2018-2019 influenza VE data. As mentioned earlier, no estimates of LAIV effectiveness are anticipated this season from the US Flu VE Network as there may not be sufficient utilization of LAIV in the US to be able to do that. The WG will continue to follow what is occurring in other countries that use LAIV. As is typically done during the June ACIP meetings, a general influenza vaccine safety update is anticipated to be presented during the June 2019 meeting.

**Discussion Points**

Dr. Maldonado (AAP) expressed AAP's concern with providers asking about a preference because there are 2 different doses of Fluzone® Quadrivalent (IIV4, Sanofi Pasteur) of 0.25 mL or 0.5 mL, and she wondered whether there were plans to phase out the lower dose or if both would continue to be on the market.

Dr. Grohskopf indicated that as the WG understands it, the study submitted to FDA for licensure for the 0.5 mL was a non-inferiority study. Therefore, it might be difficult to have a discussion about a preference for one or the other dose. The question regarding whether the lower dose would continue to be on the market would be best directed to the manufacturer.

Julian Ritchey (Sanofi Pasteur) indicated that they plan to manufacture the 0.25 mL dose as long as there is sufficient demand, which is part of the overall calculation for influenza in the pre-booking process. They will anticipate it being available as long as physicians would like it, because they view it both as a convenience and a practice opportunity.

Ms. Hayes (ACNM) asked whether new data on pregnant women were provided to the FDA in the recent approval on Fluzone® Quadrivalent being safe in pregnancy.

Dr. Grohskopf said she was not aware of any changes, but that perhaps the FDA representative could respond.

Dr. Fink (FDA) indicated that there have been no changes to any FDA licensure of the vaccine with respect to pregnancy. It is not contraindicated in pregnancy, but it is not indicated specifically for use in pregnancy.

Dr. Ezeanolue inquired as to whether a Sanofi Pasteur representative could further address the question regarding the 0.25 mL or 0.5 mL doses in terms of whether there is an advantage of one over the other.

Julian Ritchey (Sanofi Pasteur) indicated that he did not have any additional information, given that it was a non-inferiority study. It does not really provide a conclusion about the ability to make a recommendation of one over the other. This was done as a response to the physician and office preference. While they would be happy to further discuss it, the data are limited at this point in the ability to make a conclusion.



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# Human Papillomavirus (HPV) Vaccines

## Introduction

**Peter Szilagyi, MD, MPH**
**Chair, ACIP HPV Vaccines WG**

Dr. Szilagyi indicated that the human papillomavirus (HPV) vaccination policy issue being addressed by the WG is, "Should HPV vaccination be recommended for persons aged 27 through 45 years who were not previously vaccinated?" There is an expanded age indication for 9-valent HPV (9vHPV) vaccine. The manufacturer filed a Supplemental Biologics License Application (sBLA) in April 2018 to expand the age indication for 9vHPV vaccine from age 9-26 years to age 9-45 years. This was approved by FDA in October 2018. As a reminder, the 9vHPV vaccine is the only HPV vaccine currently available in the US.

To recap the past two ACIP HPV sessions, there have been some significant policy discussions about HPV. In June, there was an overview and presentation on the history of the application for licensure in mid-adults; a review of HPV epidemiology, natural history, and burden of disease; and a presentation on the clinical trial data that was included in the sBLA. In October 2018, presentations included a review of the regulatory basis for licensure and several aspects of the US HPV vaccination program, including vaccine coverage and the impact on infection and disease. There were reviews of HPV epidemiology and sexual behavior, post-licensure effectiveness studies, and global HPV vaccination and vaccine supply. GRADE also was reviewed for efficacy, immunogenicity, and safety of mid-adult vaccination. There also was a review of preliminary health economic analyses, and discussion of some policy considerations.

Since October, the HPV Vaccine WG has been very active. Topics reviewed that relate to mid-adult vaccination since October 2018 include impact modeling and health economic analyses, HPV epidemiology and natural history, values and acceptability to stakeholders, and recommendation options for consideration. In terms of the modeling and health economic analyses for mid-adult HPV vaccination, 3 models were initially providing evidence for this policy question. All were going through CDC/ACIP economic review at the time of the October meeting, and the economic review is still ongoing. There are differences in results across models, with preliminary data presented at the October 2018 ACIP meeting. Several WG calls have been devoted to reviewing the results of these models.

Dr. Szilagyi indicated that this session would include presentations on the following topics:

- ❑ Overview and Background
- ❑ Impact and Cost Effectiveness, Mid-Adult HPV Vaccination
- ❑ Overview of Health Economic Results from 4 Modeling Groups
- ❑ Mid-Adult HPV Vaccination: Patient Values and Acceptability
- ❑ Program and Vaccine Provider Surveys
- ❑ WG Considerations



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## Overview and Background Expanded Age Indication for 9vHPV Vaccine

**Lauri Markowitz, MD**
**Division of Viral Diseases**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Markowitz indicated that the purpose of this presentation was to provide some background for the subsequent two modeling presentations, and describe some of the uncertainties regarding HPV epidemiology and natural history that impact considerations for mid-adult HPV vaccination.

As a reminder, the current recommendations for HPV vaccination in the US are routine vaccination at age 11 or 12 years; catch-up vaccination for females through age 26 years and males through age 21 years, as well as certain populations (e.g., MSM, transgender persons, and persons with certain immunocompromising conditions) through age 26 years; and males aged 22 through 26 years may be vaccinated [*MMWR* 2014;63 (RR05), *MMWR* 2015;64:300-4, *MMWR* 2016; 65:2105-8].

From WG discussions of mid-adult vaccination, Dr. Markowitz highlighted that the WG affirms the importance of adolescent HPV vaccination and the primary focus of the immunization program on this age group. Regarding vaccination for mid-adults, vaccination is safe and effective among mid-adults, if they are exposed and susceptible to infection. However, the question being addressed is the additional health benefit and incremental cost-effectiveness of extending the HPV vaccine program through age 45 years or through another age between 27 and 45 years.

Preliminary results from 3 health economic models were presented to ACIP during the October 2018 meeting. These models were the US HPV-Agent-based Dynamic model for Vaccination and Screening Evaluation (HPV-ADVISE) model, developed at Laval University working with CDC; the Simplified Model developed at CDC; and the Merck model. There were large differences in cost-effectiveness for mid-adult vaccination across models. After October, CDC requested input from another modeling group, the Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET is a modeling network funded by the US National Cancer Institute (NCI).

Modelers and ACIP/CDC economic reviewers have been working to understand reasons for the differences across models. As part of this effort, reviewers asked all modelers to include a set of results when using a set of standardized health economic parameters to facilitate comparisons. Exploration of reasons for the large differences across the models have focused not only on health economic parameters, but also on other issues such as vaccination coverage. The model structures also have been reviewed. HPV epidemiology and natural history parameters could have a large impact on the models, so some aspects of these that might be contributing to differences in the model results were re-reviewed. Most HPV attributable cancers occur in mid-adults or older persons. The main question for current policy discussions and one of the issues that will impact the results from the modeling is, “How much disease is due to incident HPV infections that occur in mid-adults?”

Dr. Markowitz reviewed selected issues regarding natural history that would impact considerations in mid-adults. Understanding the burden of disease due to incident HPV infection in mid-adults requires consideration of many aspects of natural history, many of which were



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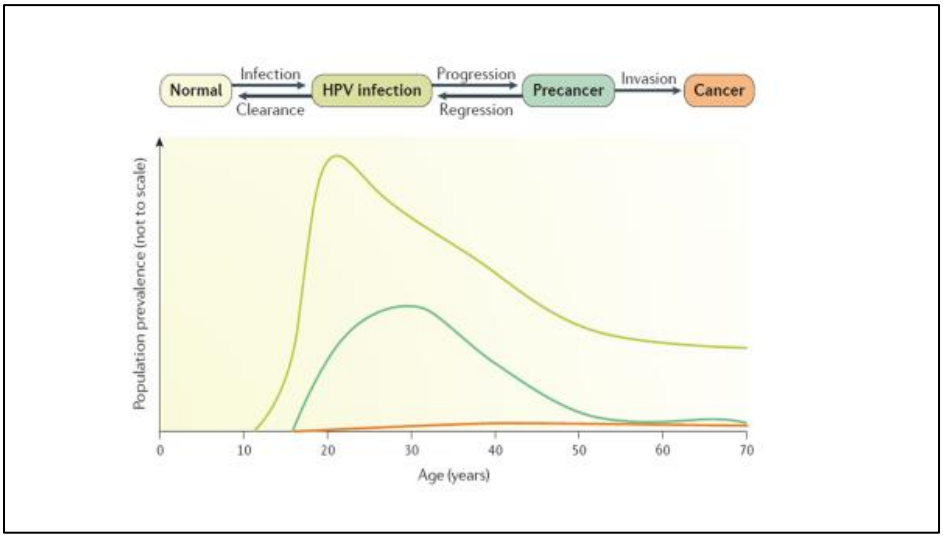
discussed in June and October 2018. As a brief summary, incidence is highest in the late teens and early twenties. Over 90% of infections clear or become undetectable. New HPV infections do occur in mid-adults, with a new partner being the main risk factor. Epidemiology of HPV infection differs for males and females. There is some uncertainty about immunity after clearance of natural infection. This is thought to be generally low, but higher for females than males. Progression to cancer occurs over years to decades. Among HPV types that are oncogenic, some types are more oncogenic than others, particularly HPV 16. Less is known about the natural history of HPV and progression to cancer in males than in females [Rodriquez et al. *JNCI* 2010; Winer et al. *CEBP* 2011; Winer *JID* 2016; Beachler et al. *JID* 2016; Kahn et al. *JNCI* 2005; Giuliano et al. *Int J Cancer* 2015].

To review, the median age at diagnosis of 6 HPV-associated cancers in the US from 2011-2015 was shown. Among women, the median age at diagnosis of cervical cancer was age 49 years and for the other cancers, in the 60s. For men, the median age at diagnosis for all cancers was in late 50s and 60s. Again, the main question for the current policy discussion is, “How much of the disease is due to new HPV infections in mid-adults between the ages of 27 and 45 years old (versus how much is due to HPV acquired at younger ages)?” [https://www.cdc.gov/cancer/hpv/statistics/age.htm].

Results have been shown to ACIP at past meetings from one of the CISNET modeling groups attempting to answer the question, “What proportion of cervical cancers is caused by HPV infections acquired at different ages?” The model estimate was that of women with cervical cancer, 50% acquired their causal infection by age 21 years and 75% by age 31. Other modeling teams are also working to estimate causal age at infection. Age at infection predicted by the model could account for some of the differences in cost-effectiveness across models. Similar estimates have not been done for the other HPV-associated cancers.

The remainder of Dr. Markowitz’s talk focused on HPV infection and natural history in females at the cervical site, as much more is known about this natural history. She briefly reviewed infection, time from infection to cervical precancer, and from precancer to cervical cancer. This is a schematic showing the conceptual model of HPV infection leading to cervical cancer. This graphic is not to scale but shows approximately when these events occur:




Schiffman et al, Nature Reviews 2016



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Again, infection is highest in late teens and early 20s and then declines. Cervical precancers, shown in green, are detected during and after the peak of infection, but the timing of precancer detection depends on cervical cancer screening because these lesions are asymptomatic. Most infections clear or become undetectable within 1-2 years. Many precancers also clear (30%-40%). Precancer can progress to cancer after many years to decades.

Data have been presented to ACIP before from a variety of studies showing the decrease in prevalent and incident HPV infection with older age in females. Data from a study in Kaiser Permanente Northern California (KPNC) of the proportion of women with prevalent infection at enrollment and newly detected HPV infections at a follow-up among those who were negative at their first visit, show that both of these were significantly lower among older age groups.

Seroprevalence data also can provide information of incidence of infection, although seroprevalence is an imperfect measure of cumulative infection for HPV as not all individuals develop antibody after infection. Data from the National Health and Nutrition Examination Survey (NHANES) in the pre-vaccine era include any high risk 9vHPV type seroprevalence and any high risk 9vHPV type DNA prevalence by age group among females. In these data, DNA is highest at age 20-24 years and lower in older age groups. Seroprevalence increased from 11% in 14-19 year olds to 34% in 20–24 years, and is highest in the 30s. Seroprevalence did not change between early and late 30s. Seroprevalence was lower in older age groups as antibody from natural infection wanes and there is less new infection. Between the late teens and early 20s, there was a 23 percentage point increase in seroprevalence and between late 20s and early 30s there was an 8 percentage point increase. These are cross-sectional data and age specific findings could be due to cohort effects. They do suggest new infection after the 20s but less than between the teens and 20s [National Health and Nutrition Examination Survey; CDC, unpublished data].

Breaking down the age groups into smaller categories (14-16, 17-19, 20-21 and 22-24 years), it is possible to see more clearly the rapid increase in high risk 9vHPV type seroprevalence in the late teens through early 20s from 8% in 14-16 year olds to 30% at age 20-21. These data also can be used to estimate cumulative infection. By age 21 years, an estimated 50% of females already had evidence of infection with at least one high-risk 9vHPV type. This calculation was based on the assumption that 60% of females develop antibody after infection, as has been shown in prospective studies. This estimate showing a large percent of females infected by the early 20s is consistent with the estimated age for causal infection from the model shown earlier in the presentation [National Health and Nutrition Examination Survey; CDC, unpublished data].

To understand the burden of disease due to incident infection in mid-adults, it also would be helpful to know time for progression of incident infection to precancer and cancer. This might allow determination of age at which an infection occurred that caused that outcome. Time from infection to precancer has been estimated from the placebo arms of HPV vaccine clinical trials and from cohort studies. However, precancers are detected through screening, so duration of follow-up and intensity and methods of screening in these studies will impact findings. Time from precancer to cancer is more difficult to study as it is unethical to follow women prospectively with untreated high grade precancers, CIN3; however, it is likely to be decades based on the peak age of infection and cancer diagnosis. This also has been assessed in models. *An estimate from a statistical model also suggests a median of 23.5 years from precancer to screening-detected invasive cancer, with only 1.6% progressing within 10 years [*Vink et al. AJE 2013].



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Dr. Markowitz showed data from three studies which looked at time from infection to CIN2+ detection. These studies had intensive screening ranging from every 4 months to every 6 months. The median time from incident infection to precancer detection was 1-2 years[1,2,3]. In the Winer 2005 study, a simulation exercise was done to look at the impact of screening frequency on incidence, because cervical abnormities clear and would not be detected with less frequent screening. In terms of cumulative incidence under the assumption of different screening intervals after 48 months of follow-up, every 4-month screening yielded cumulative incidence of low grade cervical abnormalities of 29%, while with every 24-month screening the cumulative incidence was more than 2-fold lower 11.7% The simulation looked at low grade lesions, and a smaller impact of frequency would be expected for higher grade lesions but the direction of the effect would be similar[1] [[1]Winer et al. JID 2005; [2]Insinga et al. CEPB 2011; [3]Skinner et al. Int J Cancer 2016].

As just reviewed, time from incident infection to CIN2+ diagnosis estimated from studies can be short, but is impacted by duration of follow-up and screening. Age at CIN2+ diagnosis depends on age at clinical screening initiation, frequency, and methods. Importantly, a CIN2+ lesion can be present for years before it is detected because the time between CIN2+ and cancer is long. Because of this, it is difficult to use age at CIN2+ diagnosis to estimate when infection occurred, particularly with the type of opportunistic screening available in most of the US.

Regarding the age distribution of cervical precancers in the US, data from CDC's 5-site population-based surveillance, HPV Vaccine Impact Monitoring Project (HPV-IMPACT) from 2008 were shown. These data were from before the impact of vaccination on precancers and before some of the recent changes in screening recommendations. CDC used these data to make projections for the US, and estimated that the annual number of CIN2+ cases in the US in 2008 was 215,700 and the median age at diagnosis was 28 years [CDC, unpublished data; based on Gargano et al. CID 2018].

To illustrate the challenges of estimating age at infection from epidemiologic studies and surveillance data, Dr. Markowitz compared data from two different sources, the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions (ASC-US/LSIL) Triage Study (ALTS) and the 5-Site HPV-IMPACT project. In the ALTS trial, which was a screening trial conducted among US women aged 18 years or older with every 6 month screening, the median age of CIN3 detection was 23 years. In contrast, in the 5-site HPV-IMPACT surveillance project in which there is opportunistic "real life" screening, the median age at CIN3 detection was 30 years. Age at acquisition was likely similar, but the age at detection of precancer differed due to screening practices. This illustrates that it is difficult to use age at precancer detection to estimate age at causal infection.

Dr. Markowitz noted that while she did not provide an answer to the question about the amount of disease due to incident infections in mid-adults, she highlighted several issues related to the challenges in determining this. There is rapid acquisition of HPV in late teens and early twenties, and progression from incident infection to precancer can be within a few years. Over 90% of infections clear and many of the precancers clear. Time from progression of precancer to cervical cancer is >20 years. Age at cervical precancer detection depends on screening age and frequency. Again, it is difficult to estimate age at causal infection from epidemiologic and surveillance data. Finally, less is known about the natural history of HPV at non-cervical sites and about progression from infection to cancer in males.



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There are challenges in estimating the burden of disease due to incident infections in mid-adults from empiric data. As mentioned at the beginning of this talk, health economic models have estimated this burden. However, exact model-based estimates of the burden of disease due to incident infection in mid-adults is also challenging. This is because model-based estimates depend on a variety of assumptions that are included in the models. This includes probability of infection, immunity after clearance of natural infection, sexual behavior and partner mixing, and progression and regression of precancer lesions. There will be further information about this in the health economic analyses in the next two presentations.

In closing, Dr. Markowitz briefly mentioned two other issues as an introduction to presentations later in this session: mid-adult vaccination recommendations and harmonization of HPV vaccination catch-up recommendations. Individual clinical decision-making for HPV vaccination in mid-adults is one of the options being considered by WG. This was presented to ACIP in October 2018. Acceptability and values about individual decision-making in mid-adults have been explored with some key stakeholders, which will be presented later in this session. In February 2018, before awareness of the application to FDA for the expanded age range, the ACIP WG was considering harmonization of the catch-up recommendations across genders. The WG has continued to focus on harmonization while considering mid-adult vaccination and members of the WG support harmonization. Results from surveys on harmonization conducted prior to consideration of mid-adult vaccination also will be presented later in this session.

## HPV-ADVISE: Cost-Effectiveness of Extending HPV Vaccination Above Age 26 years in the US

**Marc Brisson, PhD**
**Professor, Université Laval**

Dr. Brisson indicated that the study question they were given was, “From the health care sector perspective, what is the additional impact and cost-effectiveness of extending the established HPV vaccine program in the US to females aged 27-45 years and males aged 22-45 years? The scientific objective was to evaluate the additional population-level effectiveness and incremental cost-effectiveness of vaccinating females and males up to 45 years of age in the US against HPV versus the current recommendation.

In order to do this, they used their model known as HPV-ADVISE. This model originally was developed to help inform HPV vaccination policy decisions in Canada, but has since been used and adapted for policy decisions in the US and more recently for global decisions in collaboration with the WHO. This is an individual-based transmission-dynamic model, so it is important to note that it includes herd immunity effects from vaccination. This model has 6 integrated components: demographic, sexual behavior and HPV transmission, natural history of disease, vaccination, screening and treatment, and economics. The population is open and stable, and it includes individual women and men 10 to 100 years of age. HPV-ADVISE models 18 genotypes individually, including the 9 types in the 9vHPV vaccine (6/11/16/18/31/33/45/52/58). The diseases modeled are anogenital warts (AGW), cervical cancers and cancers of the anus, oropharynx, penis, vagina, and vulva.

A very important element when developing a model is not only the programming, but also to confirm the model so that it reproduces actual epidemiological and behavioral data. The fitting process is very important. This is done through three steps. The first step was to find a minimum and maximum value for each of the parameters in the model, which are derived from the literature. The second step was to sample different combinations of these parameter values.



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The third step was to identify multiple parameter sets that fit the US data. The US data that were fit include sexual and screening behavior that were stratified by gender and age; HPV prevalence stratified by HPV type, gender, age and sexual activity; incidence of anogenital warts, cervical lesions, cervical cancer and other HPV-related cancers stratified by HPV type, gender, and age. A total of 776 data points were fitted. There were 200,000 different combinations of parameters sampled from the prior parameter distributions. These were run through the model and 50 parameter sets were found that produced an acceptable fit to the 776 pre-specified data target points. These sets were run through the model again with vaccination data to get effectiveness. Given that model fit is important, Dr. Brisson shared examples to illustrate model fit. For sexual behavior for women in the past 12 months aged 20-29 and 30-34, HPV prevalence in women for HPV-16/18 prevalence by age, AGW amongst females and males over age groups, and incidence of squamous cell carcinoma (SCC). The data also were fit to other HPV-associated cancers. Once the 50 data parameter sets are identified, the model is validated to real-world data (e.g., what is occurring in the US post-vaccination). The data were found to fit quite well, and will continue to be validated.

Once the model is validated, model predictions are done. For this question, the modelers wanted to focus on the experience in the US as much as possible. The changes in vaccination policies in the US were reproduced. In 2007, the policy was 3 doses of 4vHPV amongst females 9 through 26 years of age. In 2011, the policy changed to gender-neutral vaccination with the addition of 4vHPV for men from 9 through 21 years of age. In 2015, there was a switch to 9vHPV with 3 doses. In 2016, there was a switch for 9vHPV to a 2-dose strategy in girls and boys <15 years of age. In 2019, there is a new decision either to stick with the current recommendations or to extend HPV vaccination to mid-adults.

Historical vaccine coverage for the US also is reproduced in the model. For this, data were used from the National Immunization Survey-Teen (NIS-Teen) for individuals 13 through 17 years of age. Included in the model were the observed uptake rates and changes in uptake rates from 2007 to 2016. There were no data for 18 year-olds, so the same uptake rates as 17 year-olds were assumed for 18 year-olds. From 2017 onward, uptake rates were assumed to be constant in the US at 2016 levels. For uptake rates amongst women and men above 18 years of age, uptake rates were provided by CDC HPV modelers. Coverage was validated to be reproduced extremely well.

There are 4 mid-adult vaccination scenarios for males and females. The first scenario is a harmonization scenario in which men up to 26 years of age are vaccinated. The other 3 scenarios are vaccinating females and males up to 30 years of age, up to 40 years of age, and up to 45 years of age. Under these base case scenarios, vaccination uptake among adults not previously vaccinated is assumed to be 2.6% per year for women and 1.9% per year for men.

In terms of the economic analysis, it is conducted from the health care sector perspective. All direct medical costs are included. The outcome measure is cost per quality-adjusted life-year (QALY) gained. The future costs and benefits are discounted at 3% annually. The time horizon is 100 years beginning in 2007, the first full year of HPV vaccination in the US. The 9vHPV vaccination cost per dose was provided by CDC HPV modelers and for individuals ≤18 years is $205 (range $176-$235) and for those ≥19 years is $225 ($176-$235). Economic costs are included in the model for genital warts diagnosis and treatment, cervical cancer screening and treatment, and treatment of HPV-associated cancers. Costs found in the literature were included in the base case, but a sensitivity analysis also was performed using the maximum costs found in the literature and standardized costs provided by CDC were included as well in order to enable the comparison of all results to other modeling results.



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In terms of the results for effectiveness of HPV vaccination, the model predicts that over 100 years with the current recommendation the US will prevent 13 million cases of CIN2/3; 32 million cases of AGW; 653,000 cases of cervical cancer; and 269,000 cases of non-cervical HPV-associated cancers. With the current recommendation plus mid-adult vaccination up to 45 years of age in females and males, there is very little difference. The model is predicting that there would be very small additional benefits of 56,000 additional cases of CIN2/3 prevented; 124,000 additional cases of AGW prevented; 3000 additional cases of cervical cancer prevented; and 4000 additional cases of non-cervical HPV-associated cancers prevented.

Regarding why mid-adult vaccination is predicted to produce small additional reductions in burden compared to the current situation, the first reason pertains to the number of people vaccinated. The number of additional people vaccinated by extending vaccination to mid-adults is small compared to the enormous number of people who are vaccinated under the current program. The second reason is herd effects. The current vaccination program is predicted to provide substantial herd effects among unvaccinated adults older than 26 years. The incidence of infection and cancer among unvaccinated adults 26-45 years old will decline substantially due to herd effects. The third reason is the age of causal infection. In this model, a large proportion of cervical cancers are predicted to be caused by an HPV infection acquired before 26 years of age.

In a situation of no vaccination or screening, the model predicts that 50% of the cancers are caused by an infection occurring before the age of 20. This is very much in line with the results that Dr. Markowitz presented earlier from the Harvard group. In addition, about 80% of all of the cancers are due to infections that were acquired before 25-26 years of age. Thus, there is limited potential for additional gain by vaccinating mid-adults.

With respect to how this translates into cost-effectiveness, the first comparison to assess is the current recommendation compared to no vaccination. This model suggests that the current strategy is highly cost-saving. Various mid-adult scenarios were then compared to the current recommendations. The first scenario assessed was harmonization in which females and males are vaccinated up to 26 years of age. It was not possible to calculate a case-effectiveness ratio in this case, because it was not possible to identify significance gains in this scenario. For mid-adult vaccination up to 30 years of age, the medium cost-effectiveness ratio was $830,000. For the scenario in which females and males are vaccinated up to 45 years of age, the cost-effectiveness ratio jumped up to $1.5 million. It is also important to note that the results are quite variable, so there is a lot of uncertainty around the estimates. The ranges shown reflect the 90% uncertainty interval. This is the 5$^{th}$ and 95$^{th}$ percentile of predictions generated by the 50 best-fitting parameter sets. This could be the analogue to a confidence interval, and they are quite wide.

It was identified that the driver for the results being so variable was likely to be the variability in natural immunity parameters. Two families of parameter sets were found: the 22 parameter sets that had faster progression from infection to lesions and lower natural immunity, and the 28 parameter sets that had slower progression and higher natural immunity. In the “faster progression” parameter sets, the average time from an infection to a lesion was about 2 years. In terms of lower natural immunity, these scenarios were predicting that natural immunity following clearance in females was 35%, so the probability of developing natural immunity was less than 35%. Conversely, in the “slower progression” parameter sets, the average time from infection to lesions was 30 months and the probability of developing natural immunity after clearance was 35%. This stratification of parameter sets by natural history parameters did make



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a big difference. For example, the cost-effectiveness for vaccinating females and males up to 30 years of age, the median result for the 50 parameter sets was $830,000. However, when using the family of parameter sets with faster progression, the cost-effectiveness ratio was then $404,000; whereas, for the slower progressors, the cost-effectiveness ratio was $2.3 million.

In the sensitivity analyses for vaccination parameters, two parameters stood out more than others. In the scenario of vaccinating females and males up to 30 years of age, the first parameter that had a major impact on the results was historical vaccination coverage. With lower historical vaccination coverage, the cost-effectiveness ratios were much lower. Just assuming lower historical vaccination coverage reduced the median cost-effectiveness ratio from $830,000/QALY gained to $336,000/QALY gained. The other parameter that had a big influence on the model was vaccine efficacy (VE). If low VE was assumed, cost-effectiveness was better. Both scenarios of low historical vaccination coverage or low VE make it such that the current program has lower herd effects, which results in less reduction in HPV in the men and women who are 26 years of age and older. The absolute potential reduction in HPV in these mid-adults will be bigger. That is, there will be bigger potential for reductions in HPV in mid-adults if there are lower herd effects of the historical vaccination program. Sensitivity analyses also were performed to assess whether varying the economic parameters would have an impact on the predictions, and they did not significant impact the model predictions.

In terms of the strengths of the analyses, HPV-ADVISE is calibrated to highly stratified US data. The model is validated with post-vaccination US data. The predictions are consistent with age-specific post-vaccination HPV infection and AGW diagnosis data from the US.[1] HPV-ADVISE has also been validated to post-vaccination data in Australia.[2] Predictions are made using 50 parameter sets, which captures uncertainty in the natural history of HPV infection and related diseases, and variability in sexual behavior data. This results in wide uncertainty intervals, reflecting that results are highly sensitive to natural history assumptions and lack of data among mid-adults. Sensitivity analyses were performed on key parameters [[1]Drolet IPVC 2018; [2]Drolet JID 2018].

Regarding the limitations of examining mid-adult vaccination, long-term herd effects of vaccinating younger age cohorts on mid-adult women and men remains uncertain. If HPV-ADVISE overestimates herd effects of the current program, the results may overestimate the cost-effectiveness ratios of vaccinating mid-adult men and women. However, the model's consistency with post-vaccination data suggests that the model reproduces short-term post-vaccination herd effects. Time to lesions and level of natural immunity after infection remain uncertain. Model predictions are very sensitive to these natural history parameters. The relative progression of a re-infection or new infection in mid-adults versus younger adults is unknown. HPV-ADVISE assumes that progression is independent of age. However, it has been suggested that a proportion of re-detection is due to deposition[1], and that new infections later in life have a smaller risk of progressing to cervical cancer.[2,3] If this is the case, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios. Screening recommendations are changing in the US. If changes to screening result in more effective cervical cancer prevention, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios [[1]Malagon *JID 2017*; [2]Plummer *Int J Cancer* 2012; [3]Rodrigez *JNCI* 2010].

In summary, the current HPV vaccination program is predicted to reduce the burden of HPV-related disease substantially (e.g., 82% reduction in anogenital wart diagnoses and 59% of cervical cancer cases over 100 years), and is likely cost-saving versus no vaccination. Extending vaccination to 45-year-old females and males is predicted to produce small additional reductions in HPV burden of disease (e.g., additional 0.2-0.4 percentage point reduction in



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anogenital warts diagnoses and cervical cancer cases). This results in cost-effectiveness ratios of ≥$360,000 per QALY-gained in 95% of model simulations under the base case assumptions, with a median of $1.5 million. Finally, the cost-effectiveness of mid-adult vaccination is highly sensitive to natural history assumptions and historical vaccination coverage.

## Impact and Economic Analyses

**Harrell Chesson, PhD**
**Health Economist**
**Centers for Disease Control and Prevention**

Dr. Chesson provided an overview of all of the modeling results, including those just presented by Dr. Brisson. The ACIP review process is ongoing for four of the five health economics models presented during this session. The ACIP review is completed for the HPV-ADVISE model, but the results presented from the other models should be considered preliminary. During the October 2018 ACIP meeting, the 3 health economics models available of 9vHPV vaccination were reviewed (HPV-ADVISE, Simplified, Merck). It was shown that there were notable differences in the cost-effectiveness estimates across the models.

Since then, some progress has been made in examining these issues. The HPV-ADVISE estimates have been finalized. The Simplified model has been adjusted to better approximate scenarios in which there is re-infection. The Merck model has been recalibrated to fit pre-vaccine era HPV prevalence data and now uses NIS-Teen data for historical vaccine coverage assumptions, as in the other models. As Dr. Markowitz mentioned, results from two CISNET models are now available and there is a better understanding of some of the reasons for differences across models.

The 5 9vHPV models now available include:

- HPV-ADVISE model (Laval University/CDC)
- Simplified model (CDC)
- Merck Model
- Two CISNET models: 1) Harvard; 2) Policy1-Cervix (Cancer Council New South Wales, CCNSW)

All 5 of these models are dynamic; that is, they include herd effects. They also include a wide range of health outcomes that can be prevented through vaccination, such as cervical precancers and cancer, other HPV-associated cancers (e.g., anal, vaginal, vulvar, penile, oropharyngeal), and genital warts. All of the models apply recently published estimates of the medical costs for HPV-associated cancers. The models all exclude productivity costs and examine a relatively long time horizon of 100 years or more to capture all of the benefits of HPV vaccination.

In terms of selected model attributes, 3 of the 5 models (HPV-ADVISE, CISNET Harvard, CISNET Policy1-Cervix) are individual-based, which means the models keep track of individuals in the population. The other 2 models (Simplified, Merck) are compartmental, which means that they keep track of groups of people in the population. All of the models, except the Simplified model, include historical vaccination coverage. In terms of model calibration, HPV-ADVISE uses the 50 best-fitting parameter sets for analyses. The Merck model and the 2 CISNET models use a single best-fitting parameter set.



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All of the models except the Simplified model assume that the vaccine will protect against reinfection for those who are vaccinated after clearance. Regarding cervical cancer screening assumptions, HPV-ADVISE and the Merck model approximate real-world cervical cancer screening. The CISNET models in the base case assume perfect compliance to cervical cancer screening guidelines, but also examine the impact of applying real-world screening scenarios in the sensitivity analyses. The vaccine uptake among mid-adults is similar for all of the models. The only difference really is that Merck allows for the possibility of incomplete vaccination series, given that some adults might receive 1 or 2 doses rather than all 3 doses. As described in the previous presentation, the models were calibrated to fit the data. One of the parameter values that is fit during the calibration process has to do with natural immunity. In all but the Simplified model, there are assumptions regarding natural immunity.

Moving on to some of the results across the models, the median age of first acquisition with at least one high risk 9vHPV type (16/18/31/33/45/52/58) is closer to 20 to 21 years in the HPV-ADVISE and Simplified model, and in the Merck model is around 25-26 years of age. Based on the NHANES seroprevalence data presented earlier in the session by Dr. Markowitz, by age 20-21 years an estimated >50% of females already had evidence of infection with >1 high risk 9vHPV type assuming that 60% of females develop antibody after infection. As far as the cost-effectiveness of the current HPV vaccination strategy, in the HPV-ADVISE model the current program is estimated to be cost-saving. This is a very consistent result with the other models, which find a very low cost per QALY for the current vaccine program versus no vaccination.

Before showing the cost-effectiveness results for mid-adult vaccination, Dr. Chesson indicated that he would be presenting 2 main measures. The first is the cost-effectiveness of adding mid-adult vaccination through age 30 years versus the current program, and the second is for extending mid-adult vaccination through age 45 years versus the current program. Though he did not present it during this session, Dr. Chesson indicated that modelers have examined a wide range of other strategies, such as vaccination to age 35 years or 40 years. They also have examined the incremental cost-effectiveness ratios, such as the cost-effectiveness of a mid-adult vaccination program through age 35 years versus age 30 years.

In terms of the base case results from the models of mid-adult vaccination through 30 years of age, the median from the 50 parameter sets in the HPV-ADVISE model was about $830,000. The estimates in the other models ranged from about $100,000 in the Merck model to over $600,000 in CISNET Harvard model. For vaccination through 45 years of age, the median in the HPV-ADVISE model was about $1.5 million. The estimates in the other models ranged from about $150,000 in the Merck model to about $400,000 in the Simplified and CISNET Harvard model.

A distinctive feature of the CISNET results is that the cost per QALY is lower for mid-adults through age 45 than it is for mid-adults through age 30. This was a somewhat unexpected result because typically, the cost per QALY gained by HPV vaccination is estimated to increase when the age at vaccination is increased. The main reason for the CISNET result is thought to be that vaccinating younger people is having herd effects on unvaccinated mid-adults. Thinking of herd effects as a wave moving from the young people to the mid-adults, that wave will hit the younger mid-adults before it hits the older mid-adults. Therefore, there is more room for the vaccine to have an effect on the older mid-adults up to age 45 rather than the younger mid-adults under age 30.



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Several factors have been assessed to try to determine what could account for the differences across the models. In terms of health economic parameters, issues such as vaccination costs, medical treatment costs, and QALY assumptions could have an impact. ACIP reviewers asked the modelers to include a set of results when using a standardized list of health economic parameters. It is known that historical and future vaccination coverage assumptions can affect these estimates. Model structure and assumptions regarding sexual behavior and HPV transmission dynamics; natural history of HPV infection; and cervical cancer screening, diagnosis, and treatment also can affect the estimates.

It is not clear yet whether the differences in results can be explained by differences in health economic assumptions (e.g., vaccination costs, medical treatment costs, QALY impacts), given that these analyses are not yet complete. The results are anticipated to be available before the next ACIP meeting. Regarding whether historical vaccination coverage assumptions matter, all of the models include historical vaccination coverage, except the Simplified model. Instead of examining whether mid-adult vaccination should be added to an ongoing program that has been in existence for over a decade, the Simplified model asked what the cost-effectiveness would be if HPV vaccination was started today that included mid-adult vaccination in the program. Accounting for the historical vaccine coverage does matter. When lower historical coverage or no historical coverage is assumed, the cost per QALY gained by mid-adult vaccination is much lower. With lower historical vaccination coverage, there are less herd effects of the current vaccination program on mid-adults, and thus more potential benefits of mid-adult vaccination. In a sensitivity analysis, the HPV-ADVISE and Merck models eliminated the historic vaccination program to make them compatible with the Simplified model assumptions. In doing so, the Simplified model result and the HPV-ADVISE result are much closer together than they were before.

With respect to what can be learned by exploring multiple parameter sets, the HPV-ADVISE examines the 50 best-fitting parameter sets and the Merck and CISNET models use a single best-fitting parameter set. Using multiple parameter sets helps to understand how sensitive the results are to key assumptions regarding natural history of HPV infection, HPV transmission dynamics (sexual behavior, transmission, et cetera), and so forth. As Dr. Markowitz pointed out in her presentation, these assumptions are subject to considerable uncertainty. Across the 50 parameter sets, the cost per QALY by mid-adult vaccination through age 45 years ranged from a median of about $1.4 billion to a low of about $360,000 to undefined.

Regarding the effect of assuming perfect screening compliance, the CISNET models assume perfect cervical cancer screening compliance in their base case analysis and real-world screening in a sensitivity analysis. The HPV-ADVISE and Merck models simulate real-world screening. The CISNET estimates of the cost per QALY gained by mid-adult vaccination are much lower when assuming real-world screening versus perfect screening. That is because there is more potential benefit in these scenarios for the vaccine to prevent cervical cancer. The estimates for the CISNET models when assuming real-world screening rather than their base case assumption of perfect screening are $363,800 (Harvard) and $199,300 (Policy1-Cervix).

The following tables summarize what the studies show about the general range of cost per QALY estimates for mid-adult vaccination through age 30 years and through age 45 years in terms of whether the estimated cost per QALY gained is below the following values: $100K, $150K, $200K, $300K, $400K and $500K:



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## Cost-effectiveness of mid-adult vaccination through age 30 years

**Is the estimated cost per QALY below the following values: $100K, $150K, $200K, $300K, $400K and $500K?**

| Cost per QALY<br>Under base case assumptions | Model | | | | | |
|---|---|---|---|---|---|---|
| | HPV-ADVISE: Median | HPV-ADVISE: Lower bound (90% UI) | Simplified | Merck | CISNET (Harvard) | CISNET (Policy1-Cervix) |
| < $100,000 | No | No | No | No | No | No |
| < $150,000 | No | Yes | No | Yes | No | No |
| < $200,000 | No | Yes | No | Yes | No | No |
| < $300,000 | No | Yes | Yes | Yes | No | No |
| < $400,000 | No | Yes | Yes | Yes | No | Yes |
| < $500,000 | No | Yes | Yes | Yes | No | Yes |

UI: Uncertainty interval (based on results across 50 parameter sets)
QALY: quality-adjusted life year
Cost per QALY gained by mid-adult vaccination through age 30 years compared to current program

## Cost-effectiveness of mid-adult vaccination through age 45 years

**Is the estimated cost per QALY below the following values: $100K, $150K, $200K, $300K, $400K and $500K?**

| Cost per QALY<br>Under base case assumptions | Model | | | | | |
|---|---|---|---|---|---|---|
| | HPV-ADVISE: Median | HPV-ADVISE: Lower bound (90% UI) | Simplified | Merck | CISNET (Harvard) | CISNET (Policy1-Cervix) |
| < $100,000 | No | No | No | No | No | No |
| <$150,000 | No | No | No | Yes | No | No |
| < $200,000 | No | No | No | Yes | No | No |
| < $300,000 | No | No | No | Yes | No | No |
| < $400,000 | No | Yes | No | Yes | No | Yes |
| < $500,000 | No | Yes | Yes | Yes | Yes | Yes |

UI: Uncertainty interval (based on results across 50 parameter sets)
QALY: quality-adjusted life year
Cost per QALY gained by mid-adult vaccination through age 45 years compared to current program.

There is still agreement across most of the models that the cost per QALY gained through mid-adult vaccination through age 45 years is not less than $300,000.



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To summarize the cost-effectiveness estimates from the models, the current US HPV vaccination program has a very favorable cost-effectiveness profile. The program is likely cost-saving or at least a very low cost of <$10,000 per QALY gained. All models find that mid-adult vaccination is relatively less cost-effective than the current program. However, because of the uncertainties in the natural history of HPV, transmission dynamics, and other factors it is not possible to provide a single precise estimate of the cost-effectiveness of mid-adult vaccination. It is only possible to show the ranges across the models. For mid-adult vaccination through age 30 years, the cost per QALY gained exceeds $200,000 in 3 of the 5 available models; $300,000 in 3 of 4 of the models that take into account historical vaccination coverage; and $800,000 in the median of the HPV-ADVISE model. Similarly, for mid-adult vaccination through age 45 years, the cost per QALY gained exceeds $300,000 in 4 of the 5 available models; $400,000 in 3 of the 5 available models; and $1.4 million in the median of the HPV-ADVISE model.

The next steps are to complete the ACIP reviews that are ongoing for 4 of the 5 models. Collaboration will continue with the modelers to understand the important differences in model structures and assumptions that drive the results, including completing a “standardized health economic assumptions” scenario; finalizing the ACIP economics review process; and providing more details to the HPV WG. Preparations will be made for the June 2019 ACIP meeting and to address any issues raised during this session.

**Discussion Points**

Dr. Elbasha (Health Economist, Merck) indicated that he has led the development of the Merck HPV model over the last 16 years or so, and expressed appreciation for the opportunity to share Merck’s perspective on the public health impact on the cost-effectiveness of expanding vaccination to 45 years of age. According to analyses from the Merck model, expanding vaccination avoids significant disease and deaths of approximately 26,400 cancer cases, 8800 cancer deaths, and 1.6 million cases of AGW and cervical lesions at an incremental cost-effectiveness ratio (ICER) of less than $150,000 per QALY. Several other policy options for expanding the program were not highlighted, but have lower ICERs. These include limiting the duration of the program to 10 years, expanding only to women, or expanding the program to only age 35 for both men and women. The findings of the results from all of these models is not aligned and requires further investigation, as mentioned by Dr. Chesson. In the younger cohort in the current recommendation, these models have aligned. It is unusual for models to have wide variation in the results like this. Merck thinks it is important for all modeling groups to work together to fully understand what might be driving the results and the differences in the results. This would include sharing equations, inputs, and other technical details of the models. Merck would welcome further review by the CDC team, any advice from the ACIP WG and ACIP, and any opportunities to work with other modeling groups, including participating in a face-to-face meeting. This would greatly help decision-makers to accurately assess the public health impact and the true economic value of expanding HPV vaccination to 45 years of age.

Dr. Talbot observed that this would be a permissive recommendation for someone who is newly at risk or who has a changed risk. None of these models evaluated by risk, but she wondered whether that would be feasible to do. While she could not imagine that a 35-year old in a committed relationship suddenly being at risk, but a 35-year old who is divorced and out exploring would be at a completely different risk and would have a different cost per QALY gained.



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Dr. Markowitz indicated that consistent with Dr. Talbot's observation, the WG is considering the option of individual decision-making. They have been spending a lot of time looking at the modeling and hope to be able to address the issue of who would benefit—low risk people who are just entering or re-entering sexual activity, or high risk people who are continuing high risk sexual activity. While this is another full project for the modelers, it is a very good question.

Dr. Ezeanolue observed that herd effects seemed to be an important factor in all of the modeling shown. Based on the 10-year history of vaccine uptake, he wondered whether vaccine uptake is anticipated to increase, decrease, or stay the same. He also wondered what the thoughts were on making a recommendation for 10 years and then stopping. This is an important option that should be considered, because the goal is catch-up such that by the end of the 10 years a lot of the people who have received vaccination will have aged into this age group. He liked the suggestion for all of the modelers to get together, and thought it would be beneficial for ACIP to have more information before making a decision, including modeling projected outcomes from a 10-year catch-up strategy.

Dr. Markowitz responded that even if current uptake remains consistent, eventually coverage will increase as vaccinated people age into the older age groups. The models do take that into account. With higher coverage, there will be higher herd immunity. The models are assuming current coverage based on NIS-Teen, which levels off at a certain point.

Dr. Brisson added that their assumption is that at some point, an equilibrium will be reached in vaccination coverage of just under 80%. With this level of vaccine coverage, substantial herd effects would be expected. Data from other countries, that have reached very high coverage of approximately 80%, indicate important herd effects occur in the older age groups. There is good literature based on real-world data showing that herd effects are occurring in men and older women who are not vaccinated. They have performed some additional analyses on the wave of herd effects, and found that a short-term catch-up strategy among mid-adults would be more cost-effective than a permanent catch-up strategy, because the main gains predicted by the model are in the first cohorts vaccinated before all of the herd effects are realized. It is a very good idea to consider whether a short-term mid-adult vaccination strategy would be worthwhile, cost-effective, and beneficial. As Dr. Elbasha mentioned, another strategy would be to vaccinate only mid-adult females. Though not presented during this session, modelers at Laval have analyzed this strategy and found it to be more cost-effective. He thought it would be interesting to examine the potential outcomes of a 10-year catch-up strategy. Dr. Brisson is involved with WHO in writing a paper regarding how to do comparative modeling. There is a systematic approach that can be taken that it is better than sitting in a room debating who is right and who is wrong, which is not going to change things. A systematic approach to comparing the models is a better way forward.

Dr. Lee said the strategy suggested was a precision public health approach, which is to optimize the health benefits for the population but target the recommendations accordingly. The challenge is with implementation and de-implementation of programs, which is part of the EtR Framework. The same challenges are arising with the pneumococcal recommendations.



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## HPV Vaccination in Mid-Adults: Patient Values and Acceptability

**Nancy McClung, PhD, RN**
**Epidemic Intelligence Service Officer**
**Division of Viral Disease**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. McClung reminded everyone that patient values and acceptability are part of the EtR used by ACIP, and that the objective of this presentation was to review what is known about patient values and acceptability for HPV vaccine in mid-adults 27-45 years of age among women, men, and MSM. In terms of methods, a literature search was conducted using PubMed for "HPV vaccine acceptability." The search included US studies with information reported in mid-adult women or men and if greater than 50% of the sample was age 26 years or older. After reviewing 336 results, 10 papers were selected for inclusion. Of these, 6 papers were in women, 2 in men, and 2 in MSM. The studies were ordered by the year data were collected, which is shown in parenthesis after each study.

Regarding values and acceptability in mid-adult women, the most recent study by Dempsey (2014) assessed wanting to receive the HPV vaccine if a provider had it available and recommended it. Of the women, 50% reported definitely or probably wanting it. The Liau (2009) study assessed, on a scale of 0 to 100, willingness to be vaccinated if the vaccine was free. The mean score was 64. The Weiss study (2008) assessed relevance of the HPV vaccine. Of the respondents, 67% reported that the HPV vaccine was relevant to them. Of those, 71% reported likely to get the vaccine if available. The Fazekas study (2006) found that 66% of respondents were likely to get the vaccine if it was free. The Hopenhayen study (2005) and Slomovitz study (2004) assessed values and acceptability prior to routine recommendation in the US. In the first, 85% reported that if an HPV vaccine was approved to prevent cervical cancer, they would want to get vaccinated. The second found that 77% would accept the HPV vaccine if it worked at any age. Common reasons mid-adult women reported not valuing or intending to receive the HPV vaccine include being married, being in a monogamous relationship, perceived low risk for HPV infection, lack of sexual activity, and unknown adverse side effects.

In terms of values and acceptability in mid-adult men, all of the studies in mid-adult men were conducted prior to a routine vaccine recommendation for men. The most recent study by Daley (2007-2009) included men in a longitudinal HPV study and reported, by race/ethnicity, likelihood to get the vaccine if safe and effective for males. Of the men, 74% to 94% reported being likely or very likely to be vaccinated. The study by Reiter (2009) assessed willingness to get the vaccine if it was approved for males, with 37% of men reporting that they would receive the vaccine. The study by Sanchez (2008) among MSM assessed willingness to receive the vaccine, with 86% of MSM reporting that they would receive the vaccine. The study by Reiter (2009) among MSM assessed willingness to receive the vaccine if it was approved for males; 74% reported that they would receive the vaccine. Common reasons mid-adult men reported not valuing or intending to receive the HPV vaccine for heterosexual men included being married or living with a partner or having less than 5 lifetime sex partners. The reason mid-adult gay or bisexual men reported not valuing or intending to receive the HPV vaccine gay or bisexual men was having less than 5 lifetime partners.



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There are a few limitations to the studies in this review. First, it is important to note that all studies were conducted prior to licensure through age 45 years. Thus, the values and acceptability reported in these studies do not directly relate to the expanded age licensure, but rather are based on a hypothetical situation. In women, the most recent data were collected more than 5 years ago. In men, all of the studies occurred before a routine HPV vaccine recommendation was made for men.

In conclusion, overall value and acceptability of HPV vaccination was moderate. Valuing or intending to receive the HPV vaccine was reported by at least 50% of the sample in all studies but one. Willingness to receive the vaccine was high in both studies among MSM. However, HPV vaccination was not valued by all respondents. The most common reason the vaccine was not valued was low perceived risk for HPV; that is, being married, in a monogamous relationship, or having few sex partners.

## Program and Vaccine Provider Surveys

**Elissa Meites, MD, MPH**
**Medical Epidemiologist, Division of Viral Diseases**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Meites presented the results of program and vaccine provider surveys regarding mid-adult HPV vaccination. The EtR Framework includes consideration of acceptability of mid-adult HPV vaccination to key stakeholders. In addition to patients, discussed in the previous presentation by Dr. McClung, key stakeholders also include immunization programs and vaccine providers such as physicians. This presentation summarizes data from 4 different surveys on 2 issues related to adult HPV vaccination: 1) harmonization of upper age catch-up recommendations across genders, including surveys of programs and primary care physicians; and 2) individual decision-making, including surveys of programs related to mid-adult HPV vaccination, and primary care physicians on category B recommendations.

The first survey is a harmonization survey of immunization programs, conducted in January and February 2018 by the Association of Immunization Managers (AIM). Among 64 immunization programs, the response rate was 80%. Almost three-quarters of these programs purchased adult HPV vaccine through the CDC contract and also provided adult HPV vaccine to any health department clinic. This survey found that 96% of programs were aware that catch-up recommendations currently differ between males and females, and 59% stated that the current recommendations cause challenges or confusion. Almost all, 98% of programs, were in favor of harmonizing the recommended age for catch-up vaccination to include everyone through age 26 years. Reasons why 50 of 51 programs were in favor of harmonization were as follows:

- ❑ Easier to implement (46, 90.2%)
- ❑ Easier to explain to patients (44, 86.3%)
- ❑ Would simplify health department recommendations and guidelines (42, 82.4%)
- ❑ Easier to explain to providers (42, 82.4%)
- ❑ Facilitate reaching high-risk populations (42, 82.4%)
- ❑ Create equity between genders (39, 76.5%)
- ❑ Reduce burden on health care providers (38, 74.5%)

[Unpublished data, Association of Immunization Managers (AIM), January–February 2018].



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A second harmonization survey of primary care physicians was conducted in January and February 2018 by the University of Colorado. Among 1,383 physicians, including about equal numbers of pediatricians, family physicians, and internal medicine physicians, the response rate was 59%. Here, only about 58% said they were aware of the difference in catch-up recommendations for males and females, and about a quarter (27%) said the current recommendations have caused challenges or confusion in their practices. But again, most (93%) were in favor of harmonization across genders.

Reasons why 713 physicians favored harmonization were:

- Simplify the vaccination schedule (693, 99.3%)
- Easier to implement (668, 97.0%)
- Easier to explain to patients (664, 96.1%)
- Facilitate reaching high-risk populations (605, 87.9%)
- Reduce burden on health care providers (544, 80.1%)
- Create equity between genders (412, 60.7%)

Reasons why 53 physicians did not favor harmonization were:

- I don't have a problem with the current recommendation (44, 91.7%)
- Vaccination is less cost-effective in older age groups (24, 53.3%)
- I don't think HPV vaccine should be administered to all males in this age group (23, 52.3%)

[Unpublished data, Children's Outcomes Research, University of Colorado, 2018]

Regarding the topic of individual decision-making for mid-adult HPV vaccination, the third survey of immunization programs also was conducted by AIM in January and February 2019. Of 64 immunization programs, the response rate was 64%. The first question was, "If there is a recommendation for *individual decision making* for vaccination of mid-adults, how challenging would it be for your immunization program to communicate the recommendation to vaccine providers in your jurisdiction?" Of responding programs, 5 (11%) responded that it would be very challenging, 22 (49%) said somewhat challenging, and 16 (36%) said not challenging. The second question was, "If there is a recommendation for individual decision-making for vaccination of mid-adults, in your opinion and/or experience, how easy would it be for vaccine providers to determine patients in this age group who might benefit from vaccination?" Of responding programs, 5 (11%) responded that it would be easy, 14 (31%) said somewhat easy, and 19 (42%) said not easy. The third question was, "Do you anticipate any challenges to implementing such a recommendation?" Of responding programs, 31 (69%) said yes, and 14 (31%) said no.

Some of the stated reasons why programs said individual decision making could be implemented were:

- FDA already announced licensure of HPV vaccine through age 45 years
- Some immunization programs (not all) already have mechanisms in place to communicate new recommendations to adult immunization providers in their jurisdiction
- Easy to identify patients in the mid-adult age range using electronic health records (EHRs)
- Identifying patients most likely to benefit might be easier for certain provider types, for example, clinicians who are already regularly vaccinating adults and assessing sexual history



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Some of the stated reasons why programs said individual decision making could be challenging were:

- ❑ Primary focus of the HPV program is to vaccinate children and adolescents; expanding the age range could distract from this main goal
- ❑ HPV vaccine messaging should remain focused on disease prevention (cancer), not transmission (sex); individual decision making could undermine communication of disease prevention messages for adolescents by reinforcing transmission messages for adults
- ❑ Immunization Information Systems (IIS) are unable to forecast for individual decision making, and would have to prompt all or none in the mid-adult age group to have a conversation
- ❑ Not all vaccine providers assess sexual history and not all patients disclose
- ❑ Might be too complex, confusing, or time-consuming for vaccine providers
- ❑ Little funding for adult vaccine programs; 317 funds are already spread thin

[Unpublished data, Association of Immunization Managers (AIM), January–February 2019].

Although a provider survey on individual decision-making has not been conducted for HPV vaccination, the WG did review results of a 2016 survey about what was then called “Category B” recommendations for meningitis B vaccine (MenB), conducted by the University of Colorado. Among 916 primary care physicians, the response rate was 72%, including 374 pediatricians and 286 family physicians. Overall, 589 (89%) needed additional guidance on how to tell patients what a Category B recommendation is; 458 (69%) felt that vaccines with a Category B recommendation require more discussion with patients than “Category A” routine recommendations, and 299 (45%) did not know that private insurance companies routinely cover Category B vaccination recommendations. The WG noted that current terminology, using “individual decision making” instead of “Category B,” might reduce some of this confusion, and acknowledges the importance of clear guidance with this type of recommendation [Kempe et al, Knowledge and Attitudes Regarding Category B ACIP Recommendations, Acad Pediatr. 2018;18: 763-768].

In summary, harmonization of upper age for HPV vaccine catch-up recommendations across genders would likely be acceptable to key stakeholders, including 98% of immunization programs, and 93% of primary care physicians. As a reminder, these surveys were conducted before HPV vaccine was licensed above age 26, but interest in harmonization across genders likely still applies. Also, individual decision-making for persons older than the routine catch-up age group through age 45 years might be acceptable to key stakeholders. The majority of immunization programs anticipated challenges communicating such a recommendation. Almost half thought it would be easy or somewhat easy for providers to determine who might benefit from vaccination. About a third anticipated no challenges with implementation. These data will be incorporated into the EtR Framework on acceptability of mid-adult HPV vaccination to key stakeholders.



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## Recommendation Options

**Lauri Markowitz, MD**
**Division of Viral Diseases**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

To end this session, Dr. Markowitz briefly reviewed the WG's considerations for mid-adult HPV vaccination. As a reminder, the current recommendations for HPV vaccination in the US are as follows: routine vaccination at age 11 or 12 years; catch-up vaccination for females through age 26 years and males through age 21 years, as well as certain populations (e.g., MSM, transgender persons, and persons with certain immunocompromising conditions) through age 26 years; and males aged 22 through 26 years may be vaccinated [*MMWR* 2014;63 (RR05), *MMWR* 2015;64:300-4, *MMWR* 2016; 65:2105-8].

The WG is still reviewing results from health economic analyses as well as other data related to this policy question. Several policy options have been discussed, which Dr. Markowitz summarized in terms of a majority and minority opinion. The majority opinion, which is favored by a large majority of the WG members is for harmonization of the upper age for catch-up across genders. This could be at the current age or another age (e.g., 26 or 30 years). For those older than the catch-up age, individual clinical decision-making through age 45 years was favored. The minority opinion was the same in terms of catch-up vaccination; however, there would be no recommendation for vaccination of those older than the harmonized catch-up age.

Concerns among WG members favoring no recommendation above a harmonized catch-up age are that there are few benefits for vaccination in the older age group. It would be a diversion of focus from the adolescent vaccination program. A few members thought there would be potential harms to the HPV vaccination program due to temporally associated AEs in this age group. The WG also discussed the current global HPV vaccine supply situation, which was discussed with ACIP in October 2018. This was important for a few WG members.

Of note, no WG members are in favor of a catch-up recommendation through 45 years of age. If individual clinical decision-making is recommended in some age groups, the WG did understand that there would be challenges about what guidance to provide, how to communicate who might benefit, and how to communicate the lower effectiveness in this age group. All of these would have to be addressed, which the WG acknowledges.

The next steps are for the WG to continue to review results from health economic modeling and other related data, complete the EtR Framework, and prepare for a vote in June 2019.

## Discussion Points

Dr. Hunter observed that the ability to implement a cohort-based/age-based recommendation that would be not individually decision-making but would be a routine recommendation, could be conceived of as cohort-based by year of birth similar to how HepC testing is done. Everybody is tested for HepC for a birth cohort from 1945-1965. If catch-up was recommended through age 35 for a current cohort, those years of birth would be used on top of a general individual decision-making recommendation that would persist ongoing. Once individuals aged out of that cohort, then people would get the previous age-based recommendation. While he was not saying this should be done or was the right thing to do, it could be done. Further cost analyses could help determine whether that would make sense to do.



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Dr. Ezeanolue pointed out that individual decision-making is automatic, even now. If someone wants a vaccine, they can pay for it and get it. He requested clarity about how what they were discussing differed from what exists now.

Dr. Cohn indicated that if ACIP recommends a vaccine for individual clinical decision-making, that means that the vaccine goes on the immunization schedule for that age group in a different color than the color for routine vaccination. That cues providers to thinking about considering it for their patients, and provides coverage through the ACA. Payment is one of the key differences, and providers use the schedule and programs consider it as part of their decision-making when it is included on the schedule versus when it is not included.

Dr. Szilagyi clarified that if ACIP makes an individual clinical decision-making recommendation, they are recommending that clinics go through the process of making individual decision-making and guidance would follow. Making no recommendation means ACIP is silent on it. It is a different level of thought process. It was the WG's understanding that if ACIP does not make a recommendation, insurance will not cover it.

Dr. Ault pointed out that in women's health, there are a fair number of examples of individual clinical decision making (e.g., breast cancer screening, contraception, screening aneuploidy during pregnancy, et cetera).

Dr. Moore thought one analogy to use to help people think about individual decision-making with HPV vaccine in this age group is as more like a travel vaccine. The importance of having at least an individual decision-making vaccine pertains to coverage and access, and that the conversation should be held. There are men and women for whom this vaccine is beneficial and they would be put in an out-of-pocket situation to have to pay hundreds of dollars for this kind of protection that is safe and effective. That decision should be left between them and their doctor, and they should have access to coverage.

Dr. Rockwell (AAFP) requested clarity with regard to whether "individual decision-making" was intended to be synonymous with a "Category B" recommendation.

Dr. Cohn indicated that in February 2018 when the EtR Framework was adopted, the 3 types of recommendations became no recommendation, individual clinical decision-making, or routine.

In the context of the majority of the WG favoring an individual clinical decision-making recommendation and a minority wants to make no recommendation, Dr. Baker (IDSA) inquired as to whether further data would be presented during the June 2019 meeting that would influence this decision. She also requested information about the current uptake for HPV vaccine and what the slope is likely to be in the next couple of years.

Dr. Markowitz indicated that the coverage data were presented during the October 2018 meeting;1-dose coverage was about 68% in females and 63% in males. This has been increasing gradually every year in 13-17 year olds. That age group is aging into their 20s, so coverage is gradually increasing. In terms of additional data, health economic results shown during this session are in the process of being finalized. The WG needs to review them again along with the AIM survey results and feedback from ACIP.

Dr. Lee clarified that there is a difference between ACIP specifically not recommending and simply being silent.



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Dr. Markowitz stressed that they would not be recommending against. There would just be no recommendation.

Dr. Ezeanolue asked what the options would be for a vote in June.

Dr. Markowitz indicated some of the issues discussed by the WG around harmonization of the catch-up age. For example, for 26 versus 30, some WG members felt that vaccine providers are used to 26 already and it should be kept at that age. If the upper age for catch-up is changed to age 30 years, for example, other issues would have to be addressed such as changes to EMRs, IIS, and other systems. Others considered harmonization at age 30 to acknowledge the extended age recommendation; however, consideration of age 26 or 30 would be further assessed based on the health economic modeling.

Regarding “no recommendation” which does not mean “not recommended,” Dr. Fryhofer (AMA) wondered if that would be similar to what ACIP did when making the transition from 4vHPV to 9vHPV vaccination for the revaccination of adolescents and young people who received the 4vHPV series. As she recalled, the guidance included explaining the incremental benefits for males and females.

Dr. Markowitz indicated that the transition from 4vHPV to 9vHPV vaccine was somewhat different because that decision was not brought to ACIP. That was strictly CDC guidance. In this case, the WG would be bringing this before ACIP.

## Combination Vaccines

### Introduction

**Kelly Moore, MD, MPH**
**Chair, Combination Vaccines WG**
**Vanderbilt University School of Medicine**

Dr. Moore reported that the Combination WG has been focusing on a pediatric hexavalent vaccine over the last couple of months. This vaccine is a joint venture with Merck and Sanofi Pasteur that contains the following antigens:

- Diphtheria, tetanus, pertussis (DTaP5)
- Polio (IPV)
- *Haemophilus influenzae* type b (Hib; PRP-OMP)
- Hepatitis B (Hep B)

This vaccine is intended to be given in a 3-dose series at 2, 4, and 6 months. The BLA was accepted by FDA for review in October 2015, and was approved and licensed by the FDA on December 21, 2018.

In terms of the policy topics under consideration by the WG, the first is to consider whether the new pediatric hexavalent vaccine should be included as an option in the Vaccines for Children (VFC) Program for the infant series at 2, 4, and 6 months of age. This is primarily a VFC



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question, because all of the individual components are currently licensed and recommended. The WG also is considering whether the new pediatric hexavalent vaccine should be preferentially recommended for the American Indian/Alaskan Native (AI/AN) population. A preferential recommendation would require an ACIP vote. The goals of the WG are to: 1) review published and unpublished data related to the safety and immunogenicity of the investigational hexavalent pediatric vaccine that is now licensed; and 2) apply the EtR framework.

The Combination Vaccine WG formed and reviewed data early and delivered a presentation during the October 2015 ACIP meeting in anticipation of FDA approval at that time. However, FDA approval was delayed due to requests for additional information by the FDA. Therefore, the Combination Vaccine WG took a hiatus pending FDA approval. The group re-formed in December 2018 upon notification of impending licensure. The WG has had three calls since December 2018, one in January and two in February 2019. During these calls, the WG reviewed the safety and immunogenicity data, reviewed Hib epidemiology and Hib vaccines among the AI/AN population, and discussed policy options.

Coming up, the WG will be applying the EtR framework, with a VFC vote tentatively scheduled during the June 2019 ACIP meeting and publication of the *MMWR* in Fall 2019. It is important to note that the manufacturer has stated that although licensure by the FDA has already occurred, supply will not available in the US until at least 2020.

The agenda for this meeting included presentations on the following:

- ❑ Immunogenicity and Safety of Pediatric Hexavalent Vaccine
- ❑ Hib Epidemiology and Vaccines in American Indian/Alaskan Native Population
- ❑ Summary, Review of Work Group Considerations

## Immunogenicity and Safety of DTaP5-IPV-HepB-Hib (VAXELIS™): A Pediatric Hexavalent Combination Vaccine

**Andrew Lee, MD**
**Executive Director, Vaccines Clinical Research**
**Merck & Co., Inc.**

Dr. Lee presented on the immunogenicity and safety of VAXELIS™, a pediatric hexavalent combination vaccine. The benefits of combination vaccines are well-known. They are comprised of licensed component vaccines with demonstrated safety profiles. Implementation has helped to reduce the number of injections and has simplified the childhood vaccination schedule [1,2,3]. They also have been shown to improve vaccination compliance and timeliness [1,2,3]. Combination vaccines also have improved the office visit experience. There are less visits needed and less vaccine preparation time and time spent on administrative tasks. [6,7] This allows for more time to be spent on patient care[6] [[1]Kalies H et al. *Pediatr Infect Dis J* 2006;25(6):507-512; [2]Marshall GS et al. *Pediatr Infect Dis J* 2007; 26(6):496-500; [3]Happe LE et al. *Am J Manag Care* 2007; 13(9):506-512; [4]Glanz JM et al. *JAMA Pediatr*. 2013;167(11):1060-1064; [5]Omer SB et al. *N Engl J Med* 2009;360(19): 1981-1988; [6]Pellissier JM et al. *Am J Manag Care* 2000;6(9):1038-1044; [7]Goldfarb NI et al. *Managed Care* 2005; 14(6 Suppl):3-12].

To address the challenges of hexavalent vaccine manufacture and development, Merck and Sanofi Pasteur formed a joint venture called MCM Vaccine Company in 1991. Merck contributes the Hib and HepB, while Sanofi contributes the DTaP5 and IPV and is responsible for final formulation and release of the vaccine. The development work has been split with Merck taking



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the clinical lead and Sanofi the regulatory lead. Both companies will promote the vaccine and Merck holds the global safety database and leads pharmacovigilance.

In terms of the composition of VAXELIS™, Merck makes the Hib or the polyribosyl ribitol phosphate (PRP) antigen. It is conjugated to the outer membrane protein complex (OMPC) carrier protein. This is the same as in PEDVAX HIB® vaccine, except the amount of Hib vaccine is less at 3 µg instead of 7.5 µg. This was the dose that resulted in optimal immunogenicity and safety in the Phase II study. The HepB antigen is the same as in RECOMBIVAX HB®, except in this case the dose has been increased from 5 µg to 10 µg to overcome potential immune interference with other vaccine components. Sanofi contributes the 5 antigens contained in the pertussis part of the vaccine. That, with diphtheria and tetanus toxoid, are equal to the PENTACEL® vaccine. The inactivated poliovirus (IPV) is the same as in IPOL®. The polio antigen numbers may look different from recent IPOL® labels, which is because of an update to the quantification method not to a change in the antigen amount. VAXELIS™ has 0.319 mg of aluminium adjuvant and a fully liquid formulation that does not require reconstitution, which simplifies administration.

These are the indications and schedule from the VAXELIS™ US Product Information (USPI).

1. INDICATIONS AND USAGE

   VAXELIS is a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* (*H. influenzae*) type b. VAXELIS is approved for use as a 3-dose series in children 6 weeks through 4 years of age (prior to the 5th birthday).

2.1 VACCINATION SCHEDULE

   VAXELIS is to be administered as a 3-dose series at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age. Three doses of VAXELIS constitute a primary immunization course against diphtheria, tetanus, *H. influenzae* type b invasive disease and poliomyelitis.

   VAXELIS may be used to complete the hepatitis B immunization series.
   A 3-dose series of VAXELIS does not constitute a primary immunization series against pertussis; an additional dose of pertussis-containing vaccine is needed to complete the primary series.

In terms of Hib immunogenicity data from a Phase II study of a hexavalent vaccine with different Hib formulations and doses, PRP-OMPC-containing formulations of the hexavalent had acceptable Hib responses; whereas, PRP-T formulation did not. A high percentage of subjects had Hib responses ≥1.0 µg/mL and high GMCs as well. The hexavalent PRP-OMPC 3 µg and 6 µg formulations had similarly high Hib responses. The 6 µg formulation was associated with slightly higher rates of injection-site and systemic AEs. Therefore, the hexavalent PRP-OMPC 3 µg dose was chosen for further development [Diaz-Mitoma et al. *Vaccine* 29 (2011) 1324–1331].



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The following is a chart comparing the number of injections needed for combination vaccine schedules in the US, with the main point being that the VAXELIS™ regimen saves 2 to 4 injections over the PEDIARIX® regimens and 1 to 2 injections over the PENTACEL® regimen:

**Comparison of US Combination Vaccine Schedules**

| Vaccines | 2 months | 4 months | 6 months | 15-18 months | Total Shots |
|---|---|---|---|---|---|
| Pediarix®* | X | X | X | Infanrix®† | 7 or 8 |
| Hib | X | X | (X) | X | |
| Pentacel®‡ | X | X | X | X | 6 |
| HepB | X | | X | | |
| Vaxelis | X | X | X | | 4 or 5 |
| Pentacel®‡ | | | | X | |
| Daptacel®§ + Hib | | | | X + X | |

* DTaP-HepB-IPV (GlaxoSmithKline) ‡ DTaP-IPV/Hib (Sanofi Pasteur) X denotes an injection
† DTaP (GlaxoSmithKline)

For the Global Phase IIb/III studies with final formulations of VAXELIS™, Dr. Lee shared detailed results for studies 005 and 006, which are the US studies and the basis of licensure in the US. In addition, he shared Hib immunogenicity results from study 008. Several European studies also were conducted in this program to cover the variety of immunization schedules that are present in the EU. Across Phase IIb, it was shown that VAXELIS™ could be given with commonly used pediatric vaccines, and a robust safety database was provided with over 5500 VAXELIS™ recipients.

Study 005 is the pivotal non-inferiority study in the US in which VAXELIS™ was compared to PENTACEL® and separate monovalent HepB and the immunogenicity of concomitant RotaTeq® vaccine was evaluated. In terms of the antibody response rates, the confidence intervals were largely overlapping showing similar immunogenicity between VAXELIS™ recipients and controls. The exceptions are for the Hib responses at two different thresholds, which were higher for VAXELIS™ recipients and compared to controls. This is an expected result for these types of Hib vaccines. In fact, all non-inferiority criteria were satisfied for antigen response rates after the third dose. VAXELIS™ did not meet non-inferiority criteria for the GMC measure of the FHA pertussis antigen. However, the vaccine response rates for filamentous hemagglutinin FHA were satisfied. Therefore, this non-inferiority result was not felt to be clinically significant. Regarding the pertussis antigen response rates after the toddler dose (e.g., the fourth dose of the pertussis-containing vaccine), the confidence intervals overlap and non-inferiority criteria were met for all pertussis endpoints. Rotavirus immunogenicity was non-inferior when given with VAXELIS™ as compared to when it was given with control vaccine.

Study 006 looked at the immune responses to 3 consecutive lots of VAXELIS™ and a control arm also was included. Consistent immune responses were demonstrated to all antigens across the 3 lots in this study. Immunogenicity of concomitant PCV13 also was evaluated. In terms of the responses for the 13 serotypes contained in PCV13, non-inferiority criteria were satisfied for 12 out of the 13 types. Only serotype 6B did not meet the study non-inferiority criteria, which is that the lower bound of the GMC ratio should exceed 0.67. However, it is worth pointing out that the data would satisfy the non-inferiority criteria typically employed in the pneumococcal vaccine



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field, which is that the GMC ratio should be > 0.5. Again, this result was not felt to be clinically significant. Study 006 was the largest study in the US, so it included sites with AI/AN population ethnicity. Before vaccination, there was low and similar baseline immunity against Hib for both the AI/AN subset and the study as a whole. After the third dose, there were robust immune responses to VAXELIS™ and the non-inferiority criteria were met for the study overall. For the VAXELIS™ arm, the post-toddler dose means 3 doses of a PRP-OMPC containing vaccine followed by a booster dose of PRP-T that came from the PENTACEL® booster dose. That is compared to the control arm, which had 4 doses of PRP-T all the way through. Both regimens had 100% of subjects >1.0, so robust immune responses. However, the GMC were much higher in the group who received the mixed regimen. This is consistent with the Hib monovalent literature showing that the combination of OMPC first and then PRP-T results in the highest Hib responses [Block et al. *Ped Inf Dis J*. (2017) 36:202–208].

Study 008 was conducted in Italy, Sweden, and Finland where the comparator was INFANRIX® hexa, the licensed hexavalent vaccine in Europe. This study is representative of the 2+1 schedule in which there are 2 infant doses and then a booster dose, in this case given between 11 and 12 months. This study provided the opportunity to examine post-dose 2 Hib responses. By all measures after the second dose, the responses were higher in the VAXELIS™ group as compared to the control. Most dramatically, the percent of subjects ≥ 1.0 was 73% in the VAXELIS™ group compared to 27% in the control group, which clearly satisfied superiority criteria. Again, the combination vaccine results were consistent with the Hib monovalent literature that shows that there is more rapid development of immune responses with the PRP-OMPC type of vaccine as compared to the PRP-T. In terms of all Hib responses in the study, another highlight is that before the toddler dose was given, a substantially higher proportion of subjects retained protective immune responses ≥ 0.15 in the VAXELIS™ group as compared to the control. In fact, the only time that responses were higher for the control vaccine were the GMCs post-toddler. This is also consistent with the Hib monovalent literature [Silfverdal et al, *Vaccine* (2016) 3810–3816].

Moving on to safety, the following are the safety measurements for the Phase III studies:

- Daily temperature measurements for 5 days after each vaccination, with day of vaccination counted as Day 1:

| | |
|---|---|
| 38.0 ≤ Mild ≤ 38.4°C | 100.4 ≤ Mild ≤ 101.1°F |
| 38.5 ≤ Moderate ≤ 39.4°C | 101.3 ≤ Moderate ≤ 102.9°F |
| Severe ≥ 39.5°C | Severe ≥ 103.1°F |

- Solicited AEs for 5 days after each vaccination:
  - Solicited systemic AEs: fever, vomiting, abnormal crying, drowsiness, appetite loss, irritability
  - Solicited injection-site AEs: redness, swelling, and pain/tenderness
- Unsolicited AEs for 15 days after each vaccination
- All serious AEs from start to ~180 days (~6 months) after infant vaccination series in US and for 15 days after each vaccination in EU
- Deaths and vaccine-related SAEs at any time during the study for all studies in the program

The incidence of solicited systemic reactions on Days 1-5 following any dose for all studies with safety data in the Phase III program (004, 005, 006, 007, 008, 011) in general was similar. There was a slightly higher rate of pyrexia or fever, otherwise the incidences were similar. The analyses were then narrowed to just the European studies with a hexavalent vaccine versus a hexavalent vaccine, and the fever rates were similar for the VAXELIS™ group compared to the



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control. Conversely, if the analyses was limited to the US studies with a hexavalent vaccine versus a pentavalent, there was a signal for a higher rate of fever.

Taking a closer look at fever in the US studies, combining Studies 005 and 006, there was approximately a 13% rate of all fever in the US studies for VAXELIS™ as compared to control. This was driven primarily by mild and moderate fever. There was no statistically significant difference in severe fever rates, and the vast majority of temperature elevations in these studies were 2 days or less as would be expected for a component vaccine like VAXELIS™. There was a slight difference in fever rates after the first dose, which became wider by the second dose, and plateaued by the third dose. Fever-related medical events were carefully monitored in these studies for pyrexia, febrile convulsion, convulsion following any infant dose of vaccination in the US studies. As a reminder, there are approximately 4 times the recipients of VAXELIS™ as compared to control vaccine in the US studies. There was low and similar incidence of pyrexia SAEs for VAXELIS™ as compared to controls. There were no febrile seizures within 15 days of any infant dose of vaccination. When the period is extended to 6 months after any dose, there was a low and similar incidence of these events. These data support that although there is an increase self-limited mild to moderate fever associated with VAXELIS™, this higher rate of fever was not associated with medical events. The data also showed a low incidence of vaccine-related SAEs and study discontinuations due to AEs in both vaccine groups, with no statistically significant difference. The investigators determined that none of the deaths in these studies were vaccine-related.

To summarize the clinical data, VAXELIS™ was rigorously evaluated in 6 Phase III clinical studies, in which a total of over 5000 infants 6 to 12 weeks of age at enrollment received at least 1 dose of VAXELIS™. Two of these, 005 and 006, were controlled clinical studies conducted in the US, in which a total of 3380 infants 6 to 12 weeks of age at enrollment received at least 1 dose of VAXELIS™. These studies show that VAXELIS™ demonstrated robust immunogenicity and had an acceptable safety profile that is consistent with its component vaccines.

Combination vaccines improve vaccination compliance and timeliness. Hexavalent vaccines are not new. They have been used outside of the US for many years. VAXELIS™ has been available in the EU since May 2017 in 4 EU countries. Over 1.5 million doses have been distributed to hundreds of thousands of children, with no unexpected safety signals. VAXELIS™ was recently approved by the US FDA on December 21, 2018. The Merck-Sanofi Pasteur Joint Venture is building up supply for a US launch. In summary, VAXELIS™ will provide a new option for meeting the recommended US vaccination schedule with fewer injections.

**Discussion Points**

Dr. Stephens observed that a significant aspect of the effectiveness of Hib vaccines was herd immunity. Given the lower dose, he wondered if Dr. Lee could comment on herd protection with VAXELIS™.

Dr. Lee indicated that based on the strong immunogenicity results for Hib, they would not expect any difference in herd immunity due to the lower dose. They are being data-driven by the results seen in the formulation studies. The robust immunogenicity for Hib would predict equal herd immunity to what has occurred with the monovalent Hib vaccine.

Dr. Walter asked for clarification regarding whether the rates of fever increased with subsequent doses, and whether any of the children who were 6 months of age receive influenza vaccine in any of the studies.



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Dr. Lee indicated that fever rates were slightly higher for the second dose as compared to the first dose, but then the difference was similar between the second and third doses and then plateaus. In terms of the receipt of influenza vaccines, other vaccines were excluded in these studies that were not the study-designated vaccines within 14 days. All of the recipients for these studies would have received concomitant PCV13 and rotavirus vaccine.

Dr. Quach (NACI) wondered whether there was any difference in terms of formulations within this hexavalent vaccine and the other hexavalent vaccine used in Canada.

Dr. Lee indicated that the main difference is the Hib component. They have the PRP-T and the US has the PRP-OMPC. Other than that, the diphtheria, tetanus toxoid, and acellular pertussis (DTaP) is from a different manufacturer. This DTaP is from the Sanofi lineage. However, he could not comment on whether there are additional differences related to that.

Dr. Wharton (Division Director, ISD) requested further comment on the causes of death for the 6 children who died in the vaccine group, and Dr. Romero requested additional information on the sepsis death.

Dr. Lee indicated that the causes of death in the VAXELIS™ group were hydrocephalus, sepsis, 2 cases of Sudden Infant Death Syndrome (SIDS), asphyxia, and unknown cause. The unknown cause occurred 44 days after vaccination. It was reported that the subject's father fell asleep with the baby and thought that the baby had been suffocated. Details from the ED report revealed that the subject was found at home not breathing. The final autopsy report showed that the cause and manner of death were un-determinable, and the toxicology report was negative. The sepsis was caused by group A *streptococcus*, which was confirmed by autopsy.

## ***Haemophilus Influenzae* Type B in Native American Children**

**Laura Hammitt, MD**
**Associate Professor, Johns Hopkins School of Public Health**
**Director, Infectious Disease Prevention Program, Center for American Indian Health**

Dr. Hammitt presented on Hib disease epidemiology in Native American children, the rationale for preferential recommendation of PRP-OMP Hib vaccine for Native American children, and considerations pertaining to Hexavalent use.

During the pre-vaccine era from 1965-1990, Native American children experienced a rate of disease that was between 2 and 10 times higher compared to the other populations around the world. Looking specifically at Hib meningitis in the general US population, Alaska Native children experienced a much higher burden of disease compared to general US children during the pre-vaccine era. In addition, the incidence of disease in Native children peaks at a younger age of 4-5 months compared to the general US at 6-9 months. Obviously, there is a substantial disparity in these populations. Among Native American children from the Southwest US and Alaskan Natives <1 year of age in the pre-vaccine era, a significant percent had Hib disease during the first 6 months of life at 36% for American Indians and 38% percent for Alaska Natives. In Non-Alaskan Natives, the percent was 29%.



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Four conjugate vaccines were developed for prevention of Hib disease in infants shown below, two of which are available in the US, PRP-T and PRP-OMP:

- PRP-D: PRP-diphtheria toxoid (ProHIBiT®)
- HbOC: Hib oligosaccharide-$CRM_{197}$ (HibTITER®)
- PRP-T: PRP-tetanus toxoid (ActHIB®; Hiberix)
- PRP-OMP: PRP *N. meningitidis* outer membrane protein (OMP) (PedvaxHIB®)

The correlate of protection that is generally used for Hib conjugate vaccine is based on the anti-PRP antibody GMC concentration. A GMC of ≥0.15 µg/mL predicts short-term protection against invasive disease, while a GMC of ≥1.0 µg/mL predicts long-term protection against invasive disease. All four of the vaccines that were being developed for use in the US were studied in Alaska Native infants to assess the immunogenicity of these vaccines. PRP-OMP was administered as a 2-dose primary series at 2 and 4 months, which produced good immunogenicity. At the time of the 4-month vaccination, or 2 months following the first dose, 91% of children had protective titers. This compares to only 11% for PRP-D, 24% for HbOC, and about 30% for PRP-T. Therefore, a good level of protection was achieved following one dose of PRP-OMP [Bulkow et al., *Pediatr Infect Dis J* 1993;12:484-9].

The PRP-OMP vaccine was evaluated in Phase III clinical trials on Navajo Nation in which children were randomized to the PRP-OMP Hib vaccine or a placebo. Again, protective antibody levels after the first dose were achieved in approximately 90% of children who received PRP-OMP vaccine. Looking at the efficacy analysis in the intention-to-treat (ITT) cohort from the same trial, efficacy was 100% against disease after the first dose and before the second dose had been given. So, there was high immunogenetic and high efficacy following 1 dose of PRP-OMP [Santosham et al., *N Engl J Med* 1991; 324:1767-1772].

The PRP-OMP vaccine was preferred by the Indian Health Service (IHS) given those immune parameters and the documentation within the Native population of demonstrated efficacy, and the vaccine was introduced into the general US immunization schedule in 1991. It achieved substantial reductions in the burden of disease. Most of this disease is Hib meningitis, which has a 2% to 5% case fatality rate. Of survivors, 15% to 30% have hearing loss or neurologic sequelae. This is a bad disease and the vaccine worked remarkably well, resulting in a reduction in the average annual number of cases in the pre-vaccine era of 19 cases per year down to about 2 cases per year in the routine use era.

In terms of what is occurring more recently, rates of disease in Navajo children continue to be higher than in the general US population. While a spike in disease occurred in 2016, that spike was not observed in 2017 or 2018. It is known that Hib continues to circulate in this population. With a potential new vaccine that has undocumented immunogenicity following the first dose, there may be some potential for disease in that situation [Grant et al, Navajo Research Conference 2017].

In Alaska, similar results were seen with introduction of PRP-OMP vaccine resulting in dramatic reductions in Hib disease in children in both Native and non-Native populations. An increase in cases occurred in 1996, which was associated with a change in the recommendation in the Alaska vaccine schedule from routine PRP-OMP to an HbOC vaccine administered as TETRAMUNE™ to try to decrease the number of doses that were being given. Within 4 months of that recommendation, several cases of Hib disease occurred in rural Alaska Native infants. Over the course 2 years, about 16 Hib cases had occurred. Alaska responded quickly and made



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a change in the recommendation to use PRP-OMP as the first dose followed by HbOC given as TETRAMUNE™ for subsequent doses. However, that was still associated with an increased level of disease compared to the control that had been achieved with PRP-OMP vaccine. Even though PRP-OMP was recommended for the first dose, it was discovered that several children inadvertently received the HbOC vaccine which also was being stocked in the clinics for their first dose and were potentially left vulnerable because of that in these high transmission high burden settings. Since the state returned to a policy for PRP-OMP for all vaccine for all children, there has been sustained control of disease with occasional sporadic cases, but overall substantial reduction and sustained control having been achieved [Singleton, et al. J Pediatr 2000; 137:313-20 and CDC, unpublished].

This experience in Alaska contributed to a preferential recommendation for PRP-OMP for Native American children, and a preference on the part of IHS providers not to stock multiple types of vaccines that could create an opportunity for misadministration of the non-PRP-OMP vaccine as the first dose. The Committee on Native American Child Health (CONACH) issued a statement in 1999 that, “Because of the risk of invasive Hib disease at younger ages, the Indian Health Service (IHS) has recommended a preference for the PRP-OMP (PEDVAX-HIB) Hib conjugate vaccine based on seroconversion rates of 60% after the first dose of PRP-OMP, compared with rates of only 20% for other Hib conjugate vaccines.” That recommendation was published subsequently in the *Red Book* in 2000 [AAP Committee on Native American Child Health, *Pediatrics* 1999].

Possible introduction of a hexavalent vaccine would change several elements related to the Hib vaccine experience for Native children. First, the antigen load selected for hexavalent is 3.0µg versus 7.5µg in PRP-OMP. The hexavalent would be given at 2, 4, and 6 months of age and the booster dose would be given either as a PRP-T-containing vaccine like PENTACEL® or a single antigen PRP-OMP booster. There is some evidence to suggest that using a mixed regimen could be beneficial and provide greater immunity.

To briefly review some of the immunogenicity data, the first study evaluated Hib antigen concentrations at 3.0µg PRP-OMP vs. 6.0µg PRP-OMP vs. 12.0µg PRP-T compared to a control. Immunogenicity was evaluated at post-dose 3 at 7 months. As mentioned earlier, the immunogenicity was very good for both PRP-OMP at 3.0µg and PRP-OMP at 6.0µg. Because of the more favorable reactogenicity profile, the product moved forward with a 3.0µg PRP-OMP component[1]. The trial in Europe that evaluated a 2+1 schedule and assessed post-dose 2 immunogenicity of the hexavalent vaccine again showed that there was very good response post-dose 2 in terms of percent of responders and a 2.4 GMT[2] [[1]Diaz-Mitoma, et al., *Vaccine* 2011; 29:1324-1331; [2] Silfverdal et al., *Vaccine* 2016; 3810-3816].

Plotting the GMT of 2.4 in the context of a variety of historical data on post-dose 2 immunogenicity of PRP-OMP in Native American children, general US children, and the hexavalent from the European study, the data are very reassuring that the post-dose 2 immunogenicity is comparable to what has been observed and provides good protection. The post-dose 3 data also reflect a very good GMC.

When the available data are synthesized together in terms of what it means for use of hexavalent vaccine in Native populations, it is known that there are good protective GMCs for hexavalent vaccines post-dose 2 and post-dose 3. Overlaying the epidemiology of Hib disease in Native American infants, a substantial amount of disease is known to occur early in life. Given that there are no immunogenicity data for hexavalent post-dose 1, there is a question regarding whether there may be a window of vulnerability in a setting of continued circulation of disease. It



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may be that hexavalent provides great immunity after 1 dose, but given that the vaccine antigen load is lower, there just are no data to substantiate this.

In conclusion, Hib is still circulating in Native American rural and reservation-based communities. Post-dose 2 immunogenicity looks great, but post-dose 1 immunogenicity is unknown for the hexavalent vaccine and that may create a window of vulnerability in children between doses 1 and 2. This can be exacerbated depending upon timeliness of vaccine. Establishing immunogenicity post-dose 1 in high-burden Native American populations is important and could inform policy.

## Summary & Review of Work Group Considerations

**Sara Oliver MD, MSPH**
**CDC WG Lead, *Haemophilus Influenzae* Subject Matter Expert**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Oliver presented a brief summary of the information the WG reviewed, as well as the WG considerations. As a reminder, two policy topics under consideration were discussed by the WG, which were to: 1) consider if the new pediatric hexavalent vaccine should be included as an option in the VFC Program for the infant series at 2, 4, and 6 months of age; and 2) consider if the new pediatric hexavalent vaccine should be preferentially recommended for the American Indian and Alaskan Native population.

Information on a variety of topics was reviewed by the WG. The WG members and CDC SMEs for each relevant pathogen reviewed immunogenicity data for the pediatric hexavalent vaccine. In addition, the WG reviewed data on the safety of the hexavalent vaccine. Next, given that the Hib component in the hexavalent vaccine is PRP-OMP, they reviewed Hib epidemiology and the history of Hib vaccines in the AI/AN population. Finally, they reviewed available data on the pediatric hexavalent vaccine and the AI/AN population specifically. Dr. Oliver briefly summarized their discussion on each topic.

In terms of the immunogenicity data for the infant series, given that all components of the pediatric hexavalent vaccine are currently licensed and recommended, the immunogenicity studies conducted were non-inferiority studies comparing the new pediatric hexavalent vaccine to currently licensed vaccines. Overall, non-inferiority criteria were met, with 2 exceptions. First, non-inferiority was not met for the geometric mean concentrations for one pertussis antigen, FHA, at the post-dose 3 time point. However, it was achieved with the percent that met a pre-specified vaccine response. Next, one pneumococcal antigen, 6B, missed the pre-specified non-inferiority endpoint of 0.67 post-dose 3. However, it would have met the non-inferiority endpoints used in the PCV13 studies.

These data were reviewed with the WG. Overall, because antigen or serotype-specific correlates of protection are unknown, it is unclear whether these differences are clinically relevant. However, there are 5 pertussis antigens included in the vaccine, and only one antigen at one time point did not meet the pre-set non-inferiority criteria. In addition, the non-inferiority criteria were met for all other PCV13 antigens. Serotype 6B rarely causes invasive pneumococcal disease (IPD) among US children in the post PCV13 era. Therefore, the WG did not have serious concerns regarding the immunogenicity data, but did feel that post-licensure monitoring will be important moving forward.



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Next, the WG reviewed the safety data. The pediatric hexavalent vaccine has a safety profile consistent with the licensed component vaccines. Overall, there was a higher rate of fever, particularly when compared to pentavalent regimens. However, there was no increase in fever-related medical events, such as hospital visits or febrile seizures. The WG also had no serious safety concerns, but again felt that post-licensure monitoring would be important moving forward for safety as well.

After reviewing these data, the WG discussed including this vaccine as an option for the infant series. Overall, the WG is supportive of including this vaccine in the VFC program as a recommended option. The WG was in agreement on this.

Next, the WG discussed data that could inform a possible preferential recommendation for the pediatric hexavalent vaccine in the AI/AN population. In the pre-vaccine era, Hib disease occurred at a younger age among the AI/AN population compared to the general US population. In addition, PRP-OMP vaccines can achieve protective immunity in a majority of infants after the 1st dose. It is because of these factors, to provide protection early in infancy, that PRP-OMP vaccines have a preferential recommendation for the AI/AN population.

The new pediatric hexavalent vaccine, VAXELIS™, is the same antigen and manufacturer as the currently available PRP-OMP vaccine, PedvaxHIB®. However, there are different amounts of antigen in the 2 vaccines, as shown here:

- ❑ PedvaxHIB®: 7.5µg PRP-OMP
- ❑ VAXELIS™: 3µg PRP-OMP

In addition, as was just presented, the preferential recommendation for PRP-OMP vaccines was based on immunogenicity data after the first dose. The available data for VAXELIS™ shows a robust response. Data are available post-dose 2, post-dose 3, and post-toddler dose. However, there are no data post-dose 1. Therefore, considering these data, the current thoughts regarding a possible preferential recommendation are that the WG feels that immunogenicity data post-dose 1 is needed before ACIP considers a preferential recommendation. The WG also was in agreement on this.

Next, the WG will apply the EtR Framework to present during the June 2019 meeting in anticipation of a potential VFC vote.

**Discussion Points**

Dr. Bernstein inquired about the impact on nasopharyngeal carriage from PRP-OMP and how it compared to the other Hib vaccine, and specifically why there is continued Hib disease in the AI/AN population.

Dr. Oliver said that she did not know about nasopharyngeal carriage differential, but overall the Hib vaccines reduce carriage. The disease currently circulating is in a slightly older age group. Vaccinated children who are receiving disease are slightly older.

Dr. Hammitt added that there are good data from Alaska that PRP-OMP vaccine does reduce carriage, but the very high burden, high transmission setting drives this. The same is observed with pneumococcal colonization. Vaccine works well to reduce that, but does not fully reduce it to levels seen in the rest of the US.



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Dr. Walter asked whether a study is planned in the AI/AN population to acquire post-dose 1 immunogenicity data.

Dr. Lee indicated that this is of interest and Merck is assessing options on how to collect those data.

Dr. Frey expressed concern that the AI/AN incidence of pneumococcal disease occurred at 4 months in the post-dose 2 data, but after the hexavalent data this is not seen until 6 months and that is at 73%. While post-dose 3 looks great, 73% is somewhat low and she wondered how that compares to the pentavalent vaccine.

Referring to his Slide 18, Dr. Lee clarified that 73% referred to threshold of ≥ 1.0, which is the level associated with long-term protection. The percent ≥ 0.15 is the level needed for protection, which is quite high at 97%. Those results are quite reassuring.

## Agency Updates

### Centers for Disease Control and Prevention (CDC)

Dr. Messonnier provided CDC updates on measles, a Notice of Funding Opportunity (NOFO) for the 2019-2023 Immunization and Vaccines for Children (VFC) Cooperative Agreement, and an article recently published in the *Journal of Pediatrics*.

From January 1, 2019 to February 21, 2019, there have been 159 confirmed cases of measles reported from 10 states. Among these, there are 6 ongoing outbreaks: Clark County, Washington; New York State (Rockland County, Monroe County, and New York City); Harris County, Texas; and Champaign, Illinois. These outbreaks are generally linked to either unvaccinated US travelers who travel overseas, are exposed to measles, and bring them back to the US or travelers from outside the US visiting the US and exposing families and communities. The large outbreaks are definitely in close knit populations of smaller ethnic or religious persuasion who are clustering together and are by and large unvaccinated. The burden to respond is primarily on local and state health departments. In each of these outbreaks, there are thousands of contacts to trace in order to address outbreaks quickly. CDC is providing technical expertise, already has staff embedded in these states, has staff with boots on the ground, and has the communication team working the states to support their efforts. For comparison, in 2017 there were 17 outbreaks. Of those, 3 were in New York State, New York City, and New Jersey. These outbreaks were associated primarily with Israel where an extremely large outbreak is occurring. On February 26th, Dr. Messonnier testified before the House Committee on Energy and Commerce, along with Dr. Fauci from the National Institutes of Health (NIH), on the threat of measles and the threat to people who are unvaccinated. Everyone on the Committee was very supportive of the efforts to let people know that the threat is ongoing and there are safe and effective vaccines.

Second, the NOFO for the 2019-2023 Immunization and VFC Cooperative Agreement was released on February 25th. This is CDC's primary funding opportunity for eligible state, local, and territorial immunization programs and supports a wide range of programs, including VFC; adult and adolescent immunization initiatives; vaccine access, communication, and education; coverage assessments; registries; and pandemic preparedness. To begin planning, representatives from 64 currently funded programs visited CDC in January for a kick-off



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meeting. The 64 currently funded immunization programs represent all 50 states, the District of Columbia (DC), 5 cities, 5 territories, and 3 federally associated state entities.

The previous week, the *Journal of Pediatrics* published an article on the association of provider recommendations in HPV initiative among male adolescents aged 13-17. This is the first assessment of state-specific HPV vaccination among male adolescents by provider recommendations. Regarding a few of the findings, HPV vaccination coverage among males increased significantly. The prevalence of provider recommendations also increased from 14% in 2011 to 65.5% in 2016, which is a great sign of success. However, there is a difference in provider recommendations by state. It is definitely possible to do better, especially in states where parents report that provider recommendations are not so strong. It is known that the primary driver of vaccination in any age group, especially for HPV, is the strength of provider recommendations. CDC will be considering ways to target education and communication activities to focus on the states where there is still room to grow.

**Department of Defense (DoD)**

Dr. Deussing expressed DoD's appreciation for ACIP's and CDC's continued inclusion of the DoD in the ACIP meeting and ACIP WGs. He provided 3 updates for the DoD for ACIP's awareness. First regarding yellow fever (YF) vaccines, like so many others, DoD is happy to learn of the new YF vaccine facility that has been approved by the Center for Biologics Evaluation and Research (CBER) and awaits arrival of vaccine supply. It is anticipated that DoD will continue on its current restrictions of YF vaccine utilization until the nationwide vaccine supply exceeds demand. The second update is with respect to influenza vaccine effectiveness. DoD researchers have initiated a study called A Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED). This Institutional Review Board (IRB)-approved study assesses influenza vaccine effectiveness among egg-derived, cell culture-derived, and recombinant protein vaccines. Per protocol, the available licensed vaccines were randomly allocated to consenting volunteers who presented to receive influenza vaccine. These individuals are being followed to assess whether influenza attack rates differ based upon vaccine received. This study began in the fall of the 2018-2019 season across several DoD sites in the US. Finally, a note with respect to vaccine redistribution. Vaccine redistribution in the DoD continues to be a widely successful program. Individual DoD immunization sites have the capability to communicate near expiring vaccines surplus or a vaccine deficit through personnel at the Immunization Healthcare Branch (IHB) at the Defense Health Agency (DHA). IHB staff then can reach out to other immunization sites to redistribute vaccine as needed. In FY 2018, $740,000 worth of vaccines were successfully redistributed using this mechanism.

**Department of Veterans Affairs (DVA)**

Lori Hoffman-Högg reported that over 1.8 million veterans received free influenza shots during FY 2018. The VA continues to partner with Walgreen's during the current 2018-2019 influenza season. This partnership resulted in over 105,000 vaccines paid for by the VA during the 2017-2018 influenza season. VA also released an updated National Electronic Decision Support Tool, also called National Clinical Reminder, for HepB immunization. This clinical reminder can be used in the Veterans Health Information Systems and Technology Architecture (VistA), the VA's electronic medical record (EMR). The VA continues to align electronic measures with the Healthcare Effectiveness Data and Information Set (HEDIS). When VA is compared to HEDIS, HEDIS technically captures influenza vaccine information via survey methodology. VA collects influenza information using both survey and chart abstraction. VA exceeds HEDIS measures for influenza vaccines for both adults aged 18 to 64 and 65 and older.



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## Food and Drug Administration (FDA)

Dr. Fink reported notable approvals since the October 2018 ACIP meeting. VAXELIS™, the hexavalent pediatric vaccine indicated for use in children 6 weeks to 4 years of age, was approved in December 2018. A 0.5 mL dose of Fluzone® seasonal inactivated influenza vaccine (IIV) was approved for use in children 6 months to 35 months of age in January 2019. Also in January 2019, a second dose of Adacel® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine Adsorbed) was approved for use in individuals who received a first dose of either Adacel® or another Tdap vaccine at least 8 years prior, or at least 5 years prior in the case of wound management. In other FDA news, the Vaccine and Related Blood Products Advisory Committee (VRBPAC) will be convened on March 6-7, 2019 at the White Oak Campus in Silver Spring, Maryland. During the first day of this meeting, VRBPAC will be discussing strain selection for the 2019-2020 seasonal influenza vaccines. They are still waiting for the WHO recommendation for the H3N2 strain component of those vaccines, so they will not be able to make a recommendation during that meeting. VRBPAC is committed to ensuring minimal downstream effects on influenza vaccine availability for the 2019-2020 season, and they hope to have additional information about next steps during the March meeting. On the second day of the meeting, VRBPAC will be discussing the safety and effectiveness of Dengvaxia®, which is a live attenuated dengue vaccine intended for use in individuals 9 through 45 years of age with laboratory-confirmed prior dengue infection who live in endemic areas.

## Health Resources and Services Administration (HRSA)

Dr. Nair provided an update on the National Vaccine Injury Compensation Program (VICP). HRSA continues to process an increased number of claims. In Fiscal Year (FY) 2018, there were 1243 claims. In that same FY, petitioners were awarded $226 million and attorneys were awarded $26.9 million. That includes fees to attorneys for cases that are compensated or dismissed, as well as interim fees. For this FY, 411 claims have been filed as of February 1, 2019. Petitioners and attorneys have been awarded $74.4 million. Because of the increased number of claims in recent years, there is a backlog of 726 claims that are awaiting review by Medical Officers. More data about the VICP can be obtained on the HRSA website. To provide a broad picture for this program, from 2006-2017, HRSA received 6000 petitions that were adjudicated. Of those, 4000 (roughly 70%) were compensated. During that same time period according to CDC data, about 3.4 billion doses of vaccine were distributed in the US. For approximately every 1 million doses of vaccine distributed, the VICP compensates 1 claim.

## Indian Health Service (IHS)

Dr. Weiser reported that IHS has held regular calls with area and local Immunization Coordinators and clinicians to promote influenza vaccine uptake for 2019. Through its influenza surveillance system, IHS estimates that they have administered at least 295,000 doses of influenza vaccine with a population coverage estimate of about 35% among those 6 months of age and older. Uptake was highest among vulnerable populations, young children, and elders. Approximately 58% of children 6 months to 23 months of age received at least 1 dose of influenza vaccine. About 49% of elders 65 years of age and older received an influenza vaccine this season. IHS has a mandatory influenza vaccination policy for healthcare personnel (HCP). This policy requires HCP to receive the influenza vaccine each year. Healthcare employees are defined as anyone working within a healthcare facility. As of December 31, 2019, approximately 93% of all HCP working for IHS had received their influenza vaccination. The policy applies only to employees operated directly by IHS, not the Tribally-Operated 638 Programs or the Urban



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Indian Health Program (UIHP). However, those programs are encouraged to adopt this policy and many led the way for IHS by adopting the policy before IHS did. The IHS has not been directly impacted by the current outbreaks of measles in the Pacific Northwest or in other parts of the country, but has worked to get the word out about the benefits of measles vaccination and resources on the IHS website. IHS's first-dose measles, mumps, and rubella (MMR) coverage among children 19 months to 35 months is currently 86.5% as of December 2018. Among adolescents 13 through 17 years of age, 95.8% have received both doses of MMR vaccine. IHS continues to focus its efforts toward vaccination at all ages both with influenza and the routine schedule of vaccines. Dr. Weiser expressed IHS's appreciation for the discussion that was held the previous day regarding the Hib vaccine for Native American/Alaskan Native populations.

**National Institutes of Health (NIH)**

Dr. Beigel highlighted a few clinical trials and funding opportunities that might be of interest to ACIP. The NIH continues to have a focus on and intense interest in influenza, specifically H7N9. One H7N9 study was completed in November 2019 and two additional studies began since the last ACIP meeting, with and without adjuvant, in an effort to stay ahead of the need for an H7N9 vaccine. NIH also has begun a Phase I study for a tuberculosis (TB) vaccine, which is critical for controlling TB. This is a thermostable vaccine that holds a lot of promise, so NIH is very excited about this. There is an opportunity for Advancing Research Acute Flaccid Myelitis (AFM). New applications are being accepted to support basic, translational, and clinical research in that field. There also is an active program announcement for Research to Advance Vaccine Safety, which has been underway since 2009 and for which there are multiple awards. The links to all of these trials and announcements will be provided in the minutes.

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

Dr. Beckham, Acting Director of the NVPO and Director of the Office of HIV/AIDS and Infectious Disease Policy (OHAIDP), reported that NVAC released a report titled, "Strengthening the Effectiveness of National, State, and Local Efforts to Improve HPV Vaccination Coverage in the United States: Recommendations From the National Vaccine Advisory Committee in February 2018." Since the release of this report, NVPO has been working to address several of the recommendations from this report. NVPO, in coordination with offices within the Office of the Assistant Secretary for Health (OASH) and other agencies at the Department of Health and Human Services (HHS) such as CDC, have established a 3-pronged strategy for increasing HPV vaccination rates. The strategy focuses on engagement and communications, Integrated Delivery Network (IDN) health systems, and determining rural and faith-based needs. As part of its engagement in communication efforts, HHS will kick off communication activities on March 4th, which is International HPV Awareness Day." These activities are designed to engage a broad range of partners to raise awareness and share evidence-based practices for increasing HPV vaccination rates. The kick-off will include the release of an HHS statement on HPV; an HHS.gov blog from ADM Brett P. Giroir, MD, the Assistant Secretary for Health (ASH); and a Twitter chat with the Surgeon General and other partners. Everyone can join them in raising awareness by using #EndHPVCancers on social media or by joining the HHS Twitter chat and sharing resources from the HHS HPV Toolkit. Promotional efforts will continue through April 2019. They also will be working with CDC to engage IDN systems and a learning collaborative for sharing best practices. Regarding adult immunization, in addition to HPV activities, NVPO has been collaborating with a number of partners to improve adult immunization rates. Guided by the Adult Immunization Plan, NVPO is working closely with HHS regional offices to coordinate stakeholder meetings across the country. These meetings will focus on pressing regional immunization topics such as access, HepA, and HPV vaccination. Meetings are



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planned in Regions 1, 2, 4, and 10. For adult immunization, NVPO also is co-sponsoring the National Adult and Influenza Immunization Summit with CDC and the Immunization Action Coalition (IAC). The summit will be held at CDC May 14-16, 2019. The current National Vaccine Plan will expire in 2020. Over the next year, NVPO will be working with CDC, NIH, FDA, and other stakeholders to update this plan. The expectations are that this will involve a shorter timeframe of 3 to 5 years versus the previous plan, which was 10 years. This will allow for more flexibility and the ability to address emerging challenges and/or new technologies. In addition, the plan will include metrics for success and implementation strategies for meeting the goals. During the next year, NVPO will be holding listening sessions to gain feedback from stakeholders that will be used to inform the development of the plan. The next public NVAC meeting will be convened via webcast on March 25, 2019. This meeting will focus on access, and an agenda will be available in the coming weeks.

## Pneumococcal Vaccines

### Introduction

**Grace Lee, MD, MPH**
**Pneumococcal Vaccines WG Chair**
**Advisory Committee on Immunization Practices**

Dr. Lee reminded everyone that the Pneumococcal Vaccines WG's terms of reference are to: 1) Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines; 2) Review current recommendations considering up-to-date (UTD) evidence, including epidemiological studies conducted post-licensure, and assess strength of the evidence; and 3) Revise or update recommendations for pneumococcal vaccine use, as needed.

ACIP recommended pneumococcal conjugate vaccine (PCV)7 for children in 2000, followed by PCV13 in 2010 when that became available. In 2012-2013, ACIP recommended PCV13 for individuals with immunocompromising conditions. In 2014, ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age. Presently, the WG is re-evaluating the use of PCV13 in adults ≥65 years of age. When ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age in 2014, the rationale was that the recommendation was in the short-term because there was still a significant burden of disease among older adults, particularly due to pneumococcal pneumonia. The long-term public health benefits at that time were expected to be limited since the indirect effects from the pediatric PCV13 use were expected to increase. Therefore, the recommendation was made in 2014 with a commitment to re-evaluate this policy 4 years later and revise it as needed.

The policy question the WG is examining is, "Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?" The population of interest is immunocompetent adults ≥65 with and without chronic medical conditions, but not the immunocompromised population. The intervention is PCV13 in series with PPSV23 in the context of indirect effects. The comparison is PPSV23 alone, again in the context of indirect effects. The core outcomes are invasive pneumococcal disease (IPD), pneumonia, mortality, and safety.



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The following table is intended to emphasize that the WG is focused on the red box in the right upper half of the following table and looking at the PCV13 recommendation for those ≥65 years in immunocompetent patients with and without chronic health conditions. The WG is not re-considering the recommendation for immunocompromised persons, persons with functional or anatomic asplenia, Cochlear implants, or cerebrospinal fluid (CSF) leaks:

Table 1. Medical conditions or other indications for administration of PCV13 and PPSV23 for adults

| Medical indication | Underlying medical condition | PCV13 for ≥ 19 years | PPSV23* for 19 through 64 years | | PCV13 at ≥ 65 years | PPSV23 at ≥ 65 years |
|---|---|---|---|---|---|---|
| | | Recommended | Recommended | Revaccination | Recommended | Recommended |
| None | None of the below | | | | ✓ | ✓ ≥ 1 year after PCV13 |
| Immunocompetent persons | Alcoholism<br>Chronic heart disease[1]<br>Chronic liver disease<br>Chronic lung disease[2]<br>Cigarette smoking<br>Diabetes mellitus | | ✓ | | ✓ | ✓ ≥ 1 year after PCV13 ≥ 5 years after any PPSV23 at < 65 years |
| | Cochlear implants<br>CSF leaks | ✓ | ✓ ≥ 8 weeks after PCV13 | | ✓ If no previous PCV13 vaccination | ✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years |
| Persons with functional or anatomic asplenia | Congenital or acquired asplenia<br>Sickle cell disease/other hemoglobinopathies | ✓ | ✓ ≥ 8 weeks after PCV13 | ✓ ≥ 5 years after first dose PPSV23 | ✓ If no previous PCV13 vaccination | ✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years |
| Immunocompromised persons | Chronic renal failure<br>Congenital or acquired immunodeficiencies[3]<br>Generalized malignancy<br>HIV infection<br>Hodgkin disease<br>Iatrogenic immunosuppression[4]<br>Leukemia<br>Lymphoma<br>Multiple myeloma<br>Nephrotic syndrome<br>Solid organ transplant | ✓ | ✓ ≥ 8 weeks after PCV13 | ✓ ≥ 5 years after first dose PPSV23 | ✓ If no previous PCV13 vaccination | ✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years |

*This PPSV23 column only refers to adults 19 through 64 years of age. All adults 65 years of age or older should receive one dose of PPSV23 5 or more years after any prior dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine. No additional doses of PPSV23 should be administered following the dose administered at 65 years of age or older.

[1]Including congestive heart failure and cardiomyopathies

[2]Including chronic obstructive pulmonary disease, emphysema, and asthma

[3]Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)

[4]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy

Dr. Lee indicated that during this session, presentations would focus on the following topics:

- ❑ PCV13 Direct and Indirect Effects on Serotype 3 Disease
- ❑ PCV13 Direct Effects on Pneumonia Hospitalizations in Adults
- ❑ A comparison of Economic Analyses of PCV13 Use Among Adults ≥65 Years Old
- ❑ GRADE and EtR for PCV13 Use Among Adults ≥65 Years Old in the Setting of Sustained Indirect Effects

Given that the goal is transparency in the decision-making process, Dr. Lee indicated that the WG would like ACIP members to consider the following:

- ❑ What is the balance of desirable and undesirable effects of PCV13 use in immunocompetent adults ≥65 years, in the context of indirect effects from the pediatric program?

- ❑ Considering values, acceptability, resource use, and implementation issues, what is your overall assessment of continued PCV13 use in immunocompetent adults ≥65 years?



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- The WG also wanted to acknowledge head-on some of the unique challenges posed by this particular decision:
  - Although the focus was on the adult decision during this session, the WG wanted to emphasize that the pediatric vaccination programs are far more effective at reducing the overall burden of pneumococcal disease due to vaccine-type strains. Some of the members in the WG have found it challenging to consider these recommendations incrementally rather than holistically. Nonetheless, they would like ACIP to focus just on the particular question of interest during this session.
  - The second challenge for this WG has been the issue of framing bias. Even though the health and economic impacts of the intervention remain the same, whether implementing or de-implementing a recommendation, some of the WG members feel that it is harder to make the decision when it is framed as a loss instead of a gain.
  - The WG also is aware of potential new vaccines that will require .ACIP to re-evaluate this recommendation in the future
- What additional information is needed to help determine whether continued PCV13 use in adults ≥65 years is warranted?

In terms of the near future pneumococcal conjugate Vaccines, there are two new products in Phase 3 trials: PCV15 and PCV20. Both are conjugated to $CRM_{197}$ and both are working towards licensure in adults first. PCV15 includes PCV13 serotypes plus 22F and 33F, and is currently in adult Phase 3 trials. Based on information currently posted on clinicaltrials.gov, the manufacturer is projecting adult Phase 3 trial completion by approximately the third quarter of 2020. PCV20 includes PCV13 plus 8, 10A, 11A, 12F, 15B, 22F, and 33F. PCV20 also is currently in adult Phase 3 trials. The manufacturer is projecting adult Phase 3 completion by the end of 2019 or early 2020 according to what is posed on clinicaltrials.gov.

**PCV13 Effects on Disease Caused by Serotype 3**

**Tamara Pilishvili, PhD MPH**
**Respiratory Diseases Branch**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Pilishvili began by explaining the rationale for the focus on Serotype 3 (ST3) out of the 13 types that PCV13 vaccine covers. ST3 causes most of the remaining PCV13-type disease burden in the US and countries using PCV13. Evidence on PCV13 effectiveness against ST3 disease is not consistent across settings and studies. Assumptions around PCV13 effects on ST3 disease influence estimates of expected vaccine impact and results of economic analyses.

In terms of background, ST3 pneumococcal strains have unique genetic, phenotypic, physiologic characteristics associated with invasiveness and disease severity. Temporal variations in the incidence of ST3 have been reported that are potentially unrelated to vaccine introduction. To date in the literature, there are various mechanisms by which reduced effectiveness against ST3 is explained. Animal model studies have demonstrated that the very thick mucoid ST3 capsule releases free polysaccharides,[1] which interferes with antibody-mediated bacterial killing and protection. It also has been shown that there is reduced



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opsonophagocytosis due to increased thickness and density of the polysaccharide capsule[2] [[1]Choi et al. Clin Vaccine Immunol. 2016; [2]Poolman et al. Vaccine 2009].

A study conducted in the UK by Andrews et al had a primary objective to evaluate the effectiveness of PCV13 against individual serotypes using indirect cohort analyses. This study measured the effectiveness against ST3 to be 26%, with very wide confidence intervals of -69 to 68. As part of this study, the investigators also re-evaluated the serologic threshold for protection on a serotype-specific basis as opposed to the accepted 0.35 threshold, which is an aggregate for all serotypes. They estimated that for ST3, the threshold of protection was 2.83 and was much higher than for other PCV13 serotypes, which ranged from 0.16 to 1.00.[1] It is known that the threshold for protection against acquisition of nasopharyngeal (NP) carriage is much higher than those for IPD, which is what they estimated in this study and is what the 0.35 aggregate refers to. Studies to date have shown that there is no impact of PCV13 on acquisition of ST3 carriage.[2] Most of the studies showed lack of impact on carriage. Therefore, no herd effects are expected from the childhood PCV13 programs [**[1]**Andrews et al. Lancet ID 2014; and **[2]**Summary of systematic review for WHO SAGE Position paper. February 2019 (https://www.who.int/immunization/documents/positionpapers/en/)].

Dr. Pilishvili summarized what is known about PCV13 effects on IPD caused by ST3, presenting studies on effectiveness in children, population-level impact in children and adults (indirect effects), and effectiveness in adults.

Out of 6 studies on the effectiveness of PCV13 against ST3 IPD in children, only 2 were able to demonstrate significant effectiveness against ST3. A US study by Moore (2015) showed 80% effectiveness with ≥1 dose among children 2-59 months of age. This was conducted during the time that there was a transition from PCV7 to PCV13, so most of the children in this study received 2 or more doses of PCV13. Therefore, it is somewhat of an “apples and oranges” comparison” when looking across studies of how children were receiving PCV13 in these effectiveness studies.

A multi-center network study on pneumococcal disease surveillance that comes from the EU examined effectiveness by serotype and evaluated effectiveness by time since the last dose of vaccine was received. Even though for PCV7, PCV13, and 19A as a group they showed that effectiveness was similar at ≤12 months since the last dose and ≥12 months after the last dose, for ST3 they showed that there may be some evidence of waning of protection. At ≤12 months since the last dose, ST3 effectiveness was measured at 73% and was significant; whereas, at ≥12 months after the last dose, it was 30% and the estimate did not reach statistical significance [Hanquet G. and Savulescu C, unpublished data].

On February 22, 2019, WHO released a revised statement on pneumococcal vaccine use in children. This statement was informed by a very large body of evidence through systematic review of primary evidence on immunogenicity and effectiveness against IPD, pneumonia, and NP carriage for PCV10 and PCV13 in children for 2 products that are currently available in the world, PCV10 and PCV13. An excerpt directly from the statement that relates to PCV13 effects on ST3 IPD states that, “Despite immunogenicity data, evidence for a direct or indirect reduction in IPD due to serotype 3 after administration of PCV13 was inconclusive, although most studies showed no effect.” This evidence included effectiveness and impact studies. Of note, PCV10 does not contain serotypes 3, 19A, and 6A. There is a statement related to product choice in the same position statemen that, “Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine-type IPD, and NP carriage . . . PCV13 may have an additional benefit in



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settings where disease attributable to serotype 19A or serotype 6C is significant." Yet, there is no mention of ST3 because of the statement above.

Data from the Active Bacterial Core Surveillance (ABCs) system have been updated through 2017. These data reflect dramatic reductions in the incidence of vaccine serotypes among children less than 5 years of age. Most of the reductions were driven by serotype 19A, but significant reductions were observed in serotype 7F and the cross-reactive serotype 6C. While some overall annual changes have been seen in ST3, there has been no net impact on ST3 disease. Looking strictly at before versus after vaccine introduction, there was a non-significant 31% reduction (-67, 44). To understand whether there were any long-term changes in ST3 in children, a longer timeframe was examined from 1998-2017. Instead of trying to attribute any changes to vaccine introduction, a joint point analysis was conducted to allow the data to show whether the changes in ST3 disease trends occurred. This analysis found that ST3 rates seem to have been increasing before PCV7 introduction, and some time in 2003 (2000, 2008) began to decrease. The confidence interval is wide and does not include the PCV13 introduction timeline, in which reductions have been seen in type 3 disease. That trend started way before PCV13 was introduced in the US [Active Bacterial Core Surveillance, CDC unpublished data].

In another study from the same European network mentioned earlier, this time looking at the impact at a population level from various countries using PCV13 and others using PCV10. Countries exclusively using PCV13 initially saw what appeared to be a reduction in ST3 disease. However, they have seen increases since 2014 in ST3 in PCV13 countries. In countries using PCV10, 2 of which have a combination of PCV10 and PCV13, no changes have been observed in ST3 during the entire time period. The indirect effects among adults >65 years from the same network analysis showed very similar results as direct effects on disease among children. The rate ratios were below 1.0 through 2014 in PCV13 countries, suggesting that there might be a reduction in type 3 disease. However, increases since 2014 have returned to the same levels such that the net change was a 12% increase. There appears to have been more of a steady increase in ST3 in PCV10 countries, although the confidence intervals are very wide because fewer sites were included in this analysis [Hanquet G. and Savulescu C, unpublished data].

Returning to the ABCs system, between 2010 and 2014 reductions have been observed in all PCV13 serotypes with the exception of ST3 through indirect effects. Annual changes have been observed since adult vaccine introduction in 2014, though this has been less than 1 case/100,000. Overall, there has been no change in ST3 disease even after the 2014 recommendations. A similar joint point analysis was conducted in adults to determine where the change in ST3 occurred, with a very similar finding in which there seems to be a natural cycle of disease incidence which may have started decreasing sometime around 2000 (2000, 2003) before PCV7 was introduced. That trend continues and the epidemiology shows in recent years that in 2016-2017, ST3 caused most of the invasive disease infections in adults ≥65 years of age and none of the vaccine serotypes rank as the top 10 anymore. An effort also was made with the ABCs data to try to understand the contribution of the direct versus indirect effects to the observed trends. To that end, a mathematical model was constructed that uses the coverage data and the surveillance data before and after the vaccine was introduced. The bottom line results from that model in terms of the US, 190 (-470-870) cases were averted due to direct effects of PCV13 use in adults between August 2014 and May 2017. The very wide confidence intervals suggest that there may be no change. When ST3 was excluded in the same model, an estimated 580 (120, 1080) cases were prevented with a significant confidence interval. Again, showing that ST3 seems to be diluting the ability to evaluate the direct impact on adult disease [Active Bacterial Core Surveillance, CDC unpublished data].



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A case-control study evaluating PCV13 effectiveness among US Medicare beneficiaries ≥65 years of age by vaccine serotype group examined PCV13 types as a group and excluding ST3, with sufficient power also to assess ST3 alone. Looking at PCV13 types without ST3, the estimate was 67% (11, 88) and was significant. The estimate was lower for ST3 alone at 26% (-58, 65) and did not reach statistical significance CDC's [Active Bacterial Core Surveillance and CMS collaboration, unpublished data].

A post-hoc analysis of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), an RCT in the Netherlands of Dutch adults ≥65 years old (n=84,496), showed 100% efficacy. However, the objective of this trial was to evaluate the effectiveness against vaccine-type community-acquired pneumonia (CAP), so IPD and serotype-specific effectiveness were not the primary targets of this trial. This study was underpowered to look at ST3 IPD, with 0 cases in the PCV13 arm and 4 cases in the control arm. This translated into 100% efficacy (-52, 100), but the confidence interval is obviously not significant because the study was not powered to examine that [Bonten MJM, et al. NEJM. 2015; Gessner et al. In press].

Moving on to PCV13 effects on pneumonia caused by ST3, limited studies are available evaluating serotype-specific pneumonia burden and VE because there are no commercially available tests to detect pneumococcal serotypes causing non-bacteremic pneumonia. Dr. Pilishvili presented data from studies utilizing the Pfizer-developed serotype-specific urine antigen test (SSUAD), which are the only studies that can look at the specific outcome of PCV13 effectiveness against ST3 pneumonia. In the original CAPiTA trial population for the per protocol analysis for ST3 pneumonia, effectiveness was 56% (-12, 86) but the 95% confidence interval did not reach across the null value. For the ITT analysis in which individuals who were included who later developed immune compromise or other protocol violations that would have excluded them from per protocol analyses, effectiveness was 60% (5, 85) and confidence intervals were significant. Another post-hoc analysis from the CAPiTA trial among the same population looking at all clinical CAP and not just the x-ray confirmed as in the original trial showed close to 62% effective (18, 83).[1, 2] The test negative design study that is nested in the Louisville Cohort pneumonia surveillance presented previously to ACIP has demonstrated effectiveness of close to 53% (-100, 89) against ST3 CAP, but the confidence interval is very wide from that study[3] [[1]Bonten MJM, et al. *NEJM*. 2015; [2]Gessner et al. In press; [3]McLaughlin JM, et al. *Clin Infect Dis.* 2019].

The Louisville study demonstrated a 13% (8.5, 18.7) reduction in all-cause CAP and a 31% (8.3, 48.9) reduction in PCV13-type CAP.[1] From the same population with a shift in the timeline, although covering the same respiratory season from October 2014 to September 2015 as opposed to June 2014 to May 2015, the proportion of ST3 disease out of all-cause CAP was 0.78%.[2] In the same time period in the following year, the proportion of all-cause CAP that was ST3 was reported as 1.26%. These percentages were applied to the incidence of all-cause CAP, which results in 19/100,000 for ST3 CAP incidence in the October 2014 to September 2015 timeframe and 26.2/100,000 in the October 2015 to September 2016 timeframe. That was in a setting of about 36% PCV13 coverage.[3] Even though there was a reduction in PCV13-type CAP reported, there does not seem to be the same trend for ST3 incidence in the same population. A back of the envelope calculation relates to what is seen in IPD in which there may be some effectiveness, but no impact is seen at a population level. The calculation is: Expected incidence through direct effects in 2016 = (Incidence at baseline) x (VE) x (Coverage) = 18.8 x 61.5% (VE) x 35.6% (Coverage) ≈ an incidence of 14.7 cases/100,000 in a setting of this level of coverage. However, a level of 26.2 cases/100,000 is being observed [[1] Swerdlow et al June 2018 ACIP pneumococcal session presentation; [2] Courtesy of Pfizer, unpublished data; [3] Estimated by applying %ST3 to all-cause CAP incidence].



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To summarize what has been observed in children in terms of PCV13 effectiveness against ST3 IPD, there are inconsistent findings with most studies showing no effectiveness. The duration of protection may be shorter for ST3 than for other vaccine serotypes. At least a couple of comparisons in the literature, including the study highlighted for the US, suggest that toddler doses may be working better than infant series followed by a toddler dose. There is no population-level impact on ST3 IPD demonstrated in the US and countries using PCV13. What is known for adults in terms of PCV13 effectiveness against ST3 IPD is that non-statistically significant VE was shown in a CAPiTA post-hoc analysis, although that study was not powered to look at St#. The case-control study in the US was powered to look at ST3 and showed low and non-significant effectiveness. No population-level impact on ST3 IPD has been demonstrated in the US and countries using PCV13 among adults, indirect or direct. PCV13 effectiveness against ST3 pneumonia in adults, moderate and non-significant effectiveness against ST3 CAP was found among adults in 2 Pfizer supported studies (CAPiTA and Louisville TND). Significant effectiveness was demonstrated in a post-hoc and modified ITT analysis of CAPiTA. From the limited data on the population-level impact on ST3 pneumonia, there is no evidence of impact in one cohort study by 2016 in a setting of approximately 36% coverage.

In conclusion, PCV13 may provide some level of direct protection against IPD and pneumonia caused by ST3. There are inconsistent findings across studies and populations, and effectiveness is lower as compared to other PCV13-types. Given the VE measured, the point estimates, and PCV13 coverage to date, some population-level impact is expected. However, no evidence has been seen of population-level impact on type 3 disease to date. That could be due to limited duration of protection or the fact that there is no impact on carriage, which means that there is continued circulation and exposure in the community. With a sufficient number of susceptible individuals being exposed, this may lead to the disease rate persisting. A high-level of uncertainty remains in terms of the expected benefits of PCV13 against ST3 disease. Therefore, the WG felt that the assumptions around inputs for VE against ST3 disease for models estimating expected public health benefits from PCV13 use in adults should consider a range of values, which ranges from no effectiveness (VE=0%) to account for studies with 95% CI for VE cross the null value to point estimates for VE against ST3 IPD and pneumonia that does assume some effectiveness. Some of these ranges can be seen in some of the analyses presented later in the session.

**Discussion Points**

Dr. Gravenstein wondered whether there is any other way to assess attenuation of disease; for example, if there is some residual benefit with ST3. One way to do that might be to examine cost. There is a cost profile for Medicare beneficiaries, which could be assessed to determine whether even if patients got pneumonia perhaps they had fewer hospital days or some other unmeasured effect.

Dr. Pilishvili indicated that they could look through the CMS data and IPD data for hospitalized cases to examine the impact of severity.

Dr. Stephens requested further elaboration on the difference between the earlier US and German studies that showed significant effectiveness versus the ones that show little effectiveness.



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Dr. Pilishvili replied that the schedule is one of the hypotheses that has been raised. In terms of the populations in the studies presented, for the studies that did not reach statistical significance, it was clear that they were able to look at the schedule with 2 infant doses followed by a booster. There were no significant findings from those studies. From the 2 studies that reported significance, she could speak clearly only for the US which was clearly a very different population from the UK study because of the transition between PCV7 and PCV13 vaccine. Most of the children in that group were immunized with a toddler schedule. That has been raised as a hypotheses, but she did not think there were a lot of data to support that.

Referring to slide 12 pertaining to the EU network study, Dr. Bernstein pointed out that between 2011-2014 in the PCV13 countries, the vaccine seemed to be having a positive effect on ST3 and then declined. He requested further information about the explanation for those 4 years.

Dr. Pilishvili indicated that the investigators explained it as probably being due to some natural variations. Initially, they attributed it to vaccine use and indirect effects when the initial findings were reported. Now that they see an increase, they have attributed it to natural variation in ST3 incidence that coincided with the trends they were evaluating. The data shown for the US seems to suggest that there is variation every so many years. If two time periods in the US data were compared pre/post vaccine, it would be attributed to the vaccine and measure it as a vaccine impact. The longer term trends seem to suggest that the disease already was on the decline, making it harder to attribute the decline to the vaccine.

Dr. Bernstein asked whether it would be expected to mirror what is being seen in countries using PCV10.

Dr. Pilishvili indicated that countries using PCV10 did see more consistence increases, but the confidence intervals are very wide so it cannot be said with confidence that this related to the vaccine.

## Effectiveness of PCV13 in Adults Hospitalized with Pneumonia Using Centers for Medicare & Medicaid Services Data, 2014-2017

**Fernanda C. Lessa, MD, MPH**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Lessa presented on an analysis CDC performed in partnership with Acumen and CMS to evaluate the impact of the new PCV13 introduction in adults on pneumonia hospitalizations. She first acknowledged the Acumen team, who is a CMS contractor, and her CDC co-worker Trey Spiller for their dedication and commitment to this complex analytical project over the last 8 months.

The project goal was to evaluate the direct effect of PCV13 on pneumonia hospitalizations among persons ≥65 years of age given the new PCV13 recommendation among US adults. To address the project objective, CMS Medicare Parts A/B data were used. The study cohort included all Parts A/B beneficiaries who were 65 years of age and older on September 1, 2014. After September 1, 2014, only beneficiaries who enrolled in Parts A/B within 6 months of their 65$^{th}$ birthday were included in the cohort. Beneficiaries were observed until December 31, 2017 unless they died, moved out of the US, dis-enrolled from Parts A/B, or developed the outcome of interest before the end of the observation period. Pneumococcal vaccination status was



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divided into four categories: PCV13 only, PPSV23 only, both vaccines, or no pneumococcal vaccine.

Inpatient, outpatient, and physician Part B claims data were used to stratify the CMS Parts A/B beneficiaries into four mutually exclusive risk categories based on their underlying conditions and according to the previous risk-based pneumococcal vaccine recommendation for adults. The four mutually exclusive groups were High Risk 1 (HR1) only, High Risk 2 (HR2) only, both High Risk 1 and High Risk 2 (Both), and Low Risk. The most prevalent conditions for HR1 were CKD, generalized malignancy, and immunodeficiencies. The most prevalent conditions for HR2 were chronic heart disease, chronic lung disease, and diabetes, with special attention to diabetes and chronic lung disease for which the prevalence was around 42% in the CMS Medicare Parts A/B population. Therefore, those individuals in the HR1+HR2 conditions are likely to be those with diabetes and CKD or chronic lung disease with iatrogenic immunosuppression.

Three outcomes were evaluated based on inpatient claims: 1) CAP, which was defined based on discharge codes and a previously published algorithm by Griffin and colleagues; 2) non-healthcare associated CAP, which was defined as a CAP in a patient without an admission to a hospital or skilled nursing facility in the 30 days prior and without a prior healthcare-associated pneumonia hospitalization; and 3) lobar pneumonia, which was defined as discharge codes of lobar/pneumococcal pneumonia in any discharge position.

A discrete time survival model was used to calculate instantaneous hazard ratio, which is equivalent to incidence rate ratio (IRR). The outcome of interest was treated as a binary variable in each month of the study period. Generalized estimating equations (GEE) was used to adjust for correlations with the assumption of proportional hazard. VE was calculated as 1 minus the IRR multiplied by 100.

Four separate models were created that were stratified by influenza season and influenza vaccination status. Influenza season was defined as the months of October through April, while non-influenza season was the months of May through September. The rationale for the four models was related first to concerns with biological interaction between influenza vaccine and secondary bacterial pneumonia, including pneumococcal pneumonia. Second, the availability of current data showing that pneumococcal and influenza vaccines are not an independent observation. PCV13 coverage goes up during the period that influenza vaccine is available. Third, the current published influenza literature showing that underlying characteristics of influenza-vaccinated individuals are different compared to influenza-unvaccinated individuals. Each of the four models was adjusted for the following variables:

- ❑ Age group (5-year bands)
- ❑ High risk condition category
- ❑ State
- ❑ Race
- ❑ Gender
- ❑ Hospital visits in prior year
- ❑ Outpatient non-ER visits in prior year
- ❑ Charlson comorbidity index
- ❑ Reason to enter CMS (Age, ESRD, Disabled, other)
- ❑ Month of year (e.g., January, February)
- ❑ Year
- ❑ Interactions: vaccine and age group, vaccine and risk group, age and risk group



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These variables represent potential confounders related to immunization practices; for example, states with high incidence of CAP may have higher rates of PCV13 administration. Confounders related to selection bias on who receives the vaccine also were adjusted for; for example, older and sicker persons may be more likely to receive PCV13 compared to younger and healthier adults.

To calculate the number of hospitalizations averted, the number of hospitalizations for each outcome was first estimated in the absence of PCV13 using the observed number of episodes divided by the IRR based on model results, and then subtracted this expected number in the absence of PCV13 by the number of observed episodes.

At the beginning and end of the cohort, there were 26.5 million and 24.1 million beneficiaries ≥65, respectively. This represents approximately 57.6% of the US ≥65 population. Around 55% of the cohort was comprised of individuals 65-74 years of age. Despite the study design to only allow persons who enrolled in CMS Parts A/B within 6 months of their 65$^{th}$ birthday after the beginning of the study, the age distribution did not change from the beginning to the end of the cohort. Male distribution was similar at the beginning and the end of the cohort. PCV13 use increased from 0.8% at the beginning of the cohort to 41.5% at the end of our cohort. In terms of the high risk categories, the distribution was similar at the beginning and at the end of the cohort, with the HR1 only category being rare at about 5%. Most of the cohort were represented by either HR2 only or HR1+HR2. Also, over one quarter of the CMS Parts A/B beneficiaries had severe underlying conditions as represented by the Charlson Index and frequent healthcare exposure.

In terms of the characteristics of the beneficiaries who got PCV13 based on the last month of the study period, PCV13-vaccinated individuals tended to be older, sicker, with more contact with the healthcare setting, and substantially more likely to have received influenza vaccine compared to PCV13-unvaccinated adults. The average of CAP incidence across the study period was 148/100,000 person months. Non-healthcare-associated CAP is a subset of CAP and the average incidence was 115 per 100,000 person-months. Lobar pneumonia was relatively rare with an incidence of 6/100,000 person months. CAP incidence varied by age groups ranging from 86/100,000 person months for the age group 65-74 years to 334/100,000 person months for the age group 85+. CAP incidence also varied greatly by risk group. Those who had HR1 + HR2 condition had a CAP incidence almost 3 times higher compared to HR2 only and 14 times higher compared to the low risk group.

Moving to the model results, it is important to bear in mind the characteristics of the beneficiaries in each model in order to understand the PCV13 VE results. The influenza season models had the largest number of total person months compared to the non-influenza season models. The proportion of beneficiaries 65-74 years of age for the models with influenza-vaccinated individuals was around 48%, while the models with influenza-unvaccinated individuals was 59%-62%. A similar pattern was seen in terms of the proportion of HR1+HR2 and low risk. While the models with influenza-vaccinated individuals had 37% and 19% in the HR1+HR2 and low risk categories, respectively, the models with influenza-unvaccinated individuals had 28% of the individuals in HR1+HR2 and approximately 33% in the low risk group. Therefore, the models with influenza-unvaccinated individuals represent a heathier group of elderly compared to the models with influenza-vaccinated individuals.



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In terms of PCV13 VE against all-cause CAP across the four models, the VE point estimate ranged from 6% in the influenza season/influenza-vaccinated to 11.4% in the influenza season/influenza-unvaccinated. Regarding PCV13 VE against non-healthcare associated CAP across the four models, the VE point estimate ranged from 5% in the influenza season/influenza-vaccinated to 11.0% in the influenza season/influenza-unvaccinated. For PCV13 VE against lobar pneumonia, the VE point estimate ranged from 1.3% in the influenza season/influenza-vaccinated to 11.0% in the influenza season/influenza-unvaccinated model.

Based on these analyses, PCV13 averted 28,600 CAP hospitalizations, which includes 18,700 non-healthcare associated CAPs, and 1100 lobar pneumonia hospitalizations from September 2014 through December 2017. Of the 28,600 CAP hospitalization averted, 18,700 were averted during the last year of our study period from January to December 2017. The reason for most CAP hospitalizations to be averted in the later years is probably related to change in the risk distribution of the individuals who are getting the vaccine as PCV13 coverage goes up over time. The proportion of low risk individuals who are getting PCV13 only and for both PCV13 + PPSV23 increased between 2014 and 2017. This is likely the group who will benefit the most from the vaccine.

The study has several limitations. Despite all of the adjustments, all the biases inherent to administrative data probably were not eliminated. It has been shown that ICD codes fail to remove all confounding in pharmacoepidemiologic studies among seniors. A major problem is the lack of reliable ICD codes to measure functional status. The adjustments made for chronic conditions and healthcare utilization can reduce biases, but do not completely eliminate them. Also, based on the experience from the hospitalized influenza VE network and the ABCs surveillance, up to 30% of the individuals who had documentation of influenza or PPSV23 according to active surveillance were misclassified as unvaccinated in CMS data. Misclassification was uncommon for PCV13 vaccination status when ABCs data was compared to CMS data.

In summary, CAP incidence is highest among individuals ≥85 years of age and those with HR1+HR2 conditions. Individuals who got PCV13 were older, sicker, and had more healthcare exposures compared to those who were unvaccinated. Effectiveness of PCV13 was observed against first episode of CAP, non-healthcare associated CAP, and lobar pneumonia.

In conclusion, VE for PCV13 against all-cause CAP ranged from 6.0% to 11.4%, which is similar to what Gessner and colleagues published using clinical trial data from the Netherlands in the CAPiTA trial. Based on this analysis, approximately 28,600 CAP hospitalizations were prevented within 40 months after the implementation of the new adult PCV13 program. Of those, 65% or 18,700 were prevented in the last 12 months of the study period. The large proportion of cases averted in 2017 is likely related to the changes in the characteristics of the individuals who are getting PCV13 in more recent years. However, it is important to note that this number of cases averted represented only 5.1% of all-CAP hospitalizations in 2017.

## Discussion Points

Dr. Gravenstein observed that it was a very complicated process to try to adjust for an unhealthy population and compare them to others, especially when working with Medicare claims. He suggested that when looking at hospitalizations as an outcome, risk adjusting for prior hospitalizations might be a more effective strategy than just using disease categories. While the focus was specific to CAP, pneumonias also cause other outcomes. For example,



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30% of hospitalized pneumonias also relate to cardiac events. That might be another outcome of interest that could be prevented with pneumococcal vaccination.

Dr. Lessa indicated that the number of hospitalizations in the prior year was adjusted for in this model. She thought perhaps what he was suggesting was that they could exclude those who had hospitalizations the prior year.

Dr. Gravenstein said he was thinking of a prior event rate ratio as a specific approach.

Dr. Lessa indicated that they could look at other outcomes as well.

Dr. Bernstein pointed out that obesity plays a role in influenza disease as a high risk condition, and he wondered whether they have found the same in IPD or pneumonia.

Dr. Lessa indicated that they did not look specifically at obesity for this particular analysis, but it is a good point.

Dr. Stephens requested further information to sort out the effect between PPSV23 versus PCV13 in this analysis in terms of whether they are getting both vaccines, and if anything could be said about the efficacy of polysaccharide alone.

Dr. Lessa said that although she did not present those data, they did assess this. The way they looked at it may not have been the most appropriate way, because there is a waning effect of PPSV23. Their analysis included anyone who received PPSV23 in the last 5 years. The other thing they have found with this analysis is that the PPSV23 patient population is extremely sick. They know from the influenza study that it is important to adjust for functional status, but they were not able to do that for this analysis. When PPSV23 was compared to unvaccinated, no effect was seen. But again, she did not think the way they looked at this was the most appropriate way for PPSV23.

Dr. Szilagyi asked what percentage of all CAP were from the Low Risk group, and clarification that they were surmising that the increase in vaccination rates among that population might have accounted for some of the results even though they were unlikely to be hospitalized with CAP.

Dr. Lessa replied that the incidence among the Low Risk group is lower overall. In terms of overall VE with stratification of the HR groups, VE is higher among the Low Risk group.

Dr. Messonnier indicated that VE was stratified across the 4 models for PCV13 only compared to unvaccinated. The groups were HR1 + HR2 and HR2 only, and Low Risk. Across all of the models, even though the Low Risk group had a large confidence interval and the person months are small in this group and they have a lower number of events, they had a higher VE compared to the HR1 + HR2 and HR2 only.

Dr. Rockwell (AAFP) observed that as an outpatient family physician, this raised more questions than answers for her. Those in the Low Risk group who are least likely to be hospitalized do get diagnosed with pneumonia and get treated and get better. However, all of them who might benefit from the vaccine are not being captured.



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## Overview of Three Economic Analyses of Pneumococcal Vaccinations at age 65

**Andrew J. Leidner, PhD**
**Health Economist & ACIP Economics Lead**
**Berry Technology Solutions Federal Contractor for:**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Leidner indicated that this presentation would describe three cost-effectiveness models developed by three different teams: CDC, Pfizer, and Pittsburgh. A presentation and report for each model were given to the ACIP Pneumococcal Vaccines WG. All three reports went through the CDC economic review following the ACIP Guidance for Health Economics Studies. Completion of the economic review does not confer any explicit or implied approval of the model. The study question was, "Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?" The cost-effectiveness ratios (CERs) from the three models compared two scenarios: PCV+PPSV at age 65 years, which is the current recommendation, versus PPSV-only at age 65 years.

Beginning with the CDC model, the current CDC base case estimates that the cost per QALY is $562,000. This an adjustment from the $649,000 estimate presented in October 2018 in that two parameters were updated, VE and case fatality ratios (CFRs). In a sensitivity analysis with a higher VE-PCV(ST3), the cost per QALY was $222,000. This scenario turned out to be a very important parameter in the models. The Pfizer base case estimate is $199,000 per QALY. An alternate base case that included immunocompromised was $186,000. For the purposes of this summary presentation, the focus was on the scenario that excludes immunocompromised because the policy decision is more focused on the immunocompetent population and also brings the Pfizer scenario in closer alignment to what was used in the CDC model. The Pittsburgh model, the base case cost-effectiveness estimate is $765,000 per QALY. The Pittsburgh model was designed to investigate differences in Black and non-Black populations for which the cost per QALY is $814,000 and $761,000, respectively. For the purposes of comparability to the other models, the primary focus for this session was the total population.

Relative to the CDC model, the Pfizer model has: 1) higher VE-PCV assumptions most importantly the assumption against VE-PCV(ST3); 2) more severe case assumptions, meaning that there is a higher QALY loss per case and higher CFRs; and 3) lower indirect effects from childhood vaccination on older adults. The Pittsburgh model has: 1) higher VE-PPSV assumptions, which is one of the main reasons that this model estimate is higher than the other two estimates in the base case; 2) no indirect effects, making it slightly less comparable to the other two; and 3) more detailed modeling of Black and non-Black populations.

Regarding a few of the most important modeling assumptions, for indirect effects the CDC model assumes a 4.1% decline in incidences that are affected by the indirect effects every year until the model ends. The Pfizer model assumes 4.1% as well, but only for the first 3 years of the model. The Pittsburgh models includes no indirect effects. For utility loss for IPD and utility loss for inpatient pneumonia, the Pfizer model assumptions are higher than the CDC model and the Pittsburgh model. The CDC model has the lowest assumptions. The Pfizer model has higher case-fatality ratios for inpatient pneumonia than the CDC and Pittsburgh models.



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The Pfizer model assumes about 10% more VE-PCV (non-ST3) pneumonia in the first 5 years of the model, and they both converge to 0% after 20 years. For ST3 disease, the Pfizer model assumes the same thing it did in the non-serotype 3 case of about 40% for 5 years and then declining. The CDC model assumed 0% effectiveness in its base case for ST3 pneumonia. In the sensitivity analysis mentioned earlier, CDC had Higher VE (ST3), this assumption is increased to about 45% for 5 years and then it declines. The story is similar with IPD. The Pfizer model assumes about 10% more VE for non-ST3 IPD in the first 5 years, then the Pfizer and CDC models converge to 0% at age 85. The Pfizer model assumes a base case of 26% VE for the first 5 years for ST3 IPD and then declines, and the CDC model assumes 0% in the base case. In the sensitivity analysis in which the CDC model has higher VE ST3, the CDC assumption is the same as the Pfizer assumption for IPD.

To try to confirm what is thought to be occurring based on the differences in the assumptions, some of the results will be examined. Beginning with health outcomes, comparing the within model in-patient IPD burden averted, the inpatient pneumonia cases are much higher in the CDC and Pfizer models. Therefore, inpatient pneumonia is more important than IPD. The story is similar for averted deaths in that a greater number of deaths are predicted in all 3 models due to pneumonia as opposed to deaths due to IPD. In terms of QALYs gained in each of the models, Pfizer has the highest number due to a higher QALY loss estimate assumption per case, a higher CFR per case, and higher VE which averts more cases.

Moving to a more detailed look at some of the CERs, the Pfizer model assumes the CDC assumptions on VE-PCV in which the CER goes from about $200,000 per QALY to about $590,000 per QALY. This increase is due in most part to ST3 pneumonia and at least in part to ST3 IPD. The second most important category is non-ST3 IPD and pneumonia. The mirror image of that exercise done from the CDC model perspective in which the CDC model assumed a higher VE against ST3 brings it closer to, but not exactly the same, as the Pfizer VE assumptions. The base case CER now declines to $222,000 per QALY, putting it very close to the Pfizer base case estimate. By imposing the CDC assumptions for indirect effects, utilities, and CFRs on the Pfizer model base case, the CER estimate increases but not quite as dramatically as when VE was changed. When the Pfizer model assumptions on indirect effects, utilities, and CFRs were imposed on the CDC base case, the CERs declined. The largest decline was in CFR, but not as much as when the different VE assumptions were imposed.

Regarding the one-way and multi-way sensitivity analyses, the CDC and Pittsburgh models had a lot more variability and uncertainty in their outcomes than the Pfizer model. The extreme points in the CDC and Pittsburgh models were when they assumed a relatively high level of VE-PPSV against PPSV-type pneumonia of 45%. The lowest CER in the studies for one-way and multi-way analyses was in the Pfizer study, which assumed a relatively high VE-PCV against PCV-type pneumonia of 73%, higher PCV-type pneumonia incidence, and higher PCV-type pneumonia CFR.

In conclusion, VE appears to be the most important assumption in these models, especially VE of PCV against serotype 3 pneumonia. There were varied assumptions on VE for PCV and PPSV across all of the models. Other important assumptions were indirect effects, utility loss per case, and CFRs. The models assume different levels of uncertainty, with the Pfizer model having the least amount of uncertainty. The base case values ranged from about $200,000 to $765,000 per QALY averted. In the full range, the base case values ranged from about $46,000 per QALY averted to over $2 million per QALY averted.



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## Manufacturer Response

**Dr. Luis Jodar**
**Chief Medical Officer**
**Pfizer Vaccines**

Dr. Luis Jodar read the following statement into the record:

We are all here today trying to do the best for patients and for public health. PCV13 has already prevented thousands of hospitalizations and deaths in people 65+ in the United States. I think we all agree that we have a proven safe and effective vaccine against both IPD and community-acquired pneumonia caused by the 13 pneumococcal serotypes in the vaccine, including serotype 3. For this reason, and although today it has been moderated, Pfizer cannot agree with CDC's assigned value of zero for PCV13 vaccine efficacy, not effectiveness, efficacy against serotype 3 community-acquired pneumonia as the base case scenario for the cost-effectiveness model. It has been argued that this is a question of difference of opinions, or a different interpretation of the data. Pfizer argues that this is not a question of opinion, but a question of facts. I would like to review very quickly the data that Dr. Pilishvili has very eloquently reviewed for you on serotype 3. As you remember, CAPiTA, which is a randomized controlled efficacy trial among 85,000 adults aged 65+, served as the pivotal trial to confirm PCV13's indication against vaccine-type community-acquired pneumonia. This should be the primary source of the data for all of the estimations. Dr. Pilishvili mentioned, and she was right, that none of these trials were unfortunately powered to measure serotype-specific vaccine efficacy. However, in the modified intent-to-treat analysis, or mITT, vaccine efficacy against serotype 3 was 60% with confidence intervals from 5% to 85%. This result was submitted to the FDA in January 2015. Based on this analysis, the base case for serotype 3 just cannot be zero. Now, you did not see the data in the handouts, but I appreciate that Dr. Pilishvili included these mITT data in today's CDC presentation.

However, I do not think that that is yet recognized the CDC cost-effectiveness analysis. It is important to note that in the CDC cost-effectiveness analysis, the model used the CAPiTA mITT for all of the other parameters with the notable exception of serotype 3. As we have seen, had the CDC used the serotype 3 analysis as the base case in their model, the results would have been dramatically different. Dr. Pilishvili, in the summary tables, presented a different analysis, a post-hoc analysis, different from the mITT that I just mentioned. Just to be clear, that post-hoc analysis, which was also derived from CAPiTA, included all clinical community-acquired pneumonia regardless of the radiographic outcome. As shown in her presentation, the vaccine efficacy against serotype 3 was also high at 62% with confidence intervals from 18% to 83%, which supports the basic mITT analysis that I mentioned before. She mentioned also the Louisville data. There could be a debate about the epidemiological robustness or not, but when we pooled the data from serotype 3 for CAPiTA and the only other two adult test-negative design studies conducted so far, because Dr. Pilishvili did mention that yes Pfizer has the UAD which is validated by the FDA to measure serotype-specific, when you pool all of that data together, we showed a vaccine combined efficacy of 53% with confidence intervals from 6% to 76%. Again, this reaffirms that PCV13 provides a substantial level of protection against serotype 3.



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The second point that I want to emphasize today, because it was emphasized a lot here, is related to the surveillance population, the population impact data, which I think is a little bit more debatable. So, I agree with Dr. Pilishvili. It is true that serotype 3 has not gone down in the US. However, in countries that have not introduced PCV13, rates of serotype 3 in adults have notably increased. People have asked, "Well, I mean in the European Union you see a decrease in your data and then a slight increase, and in other countries a sustained increase, and it has been argued that these might be natural variations. Well, it is almost like there is an epidemiological conspiracy to get the same results in all of the countries that use PCV13 versus the countries that use other vaccines. What we have seen in all countries, and if you look at all surveillance studies, is that yes it goes down, and I think you explained it very well about coverage—it goes down and then starts to level, and then perhaps it slightly increases, with a difference in other countries that it is steadily increasing. What is more important is in countries that have a PCV13 program but no other program, and I'd like you to look at the UK and Germany, serotype 3 has dramatically increased in adults. The data suggest that a similar trend can be expected in the United States if the adults 65+ vaccination recommendation is removed. So, with all of this as a background, a key question for the entire community is, "Will taking this recommendation away lead to unnecessary hospitalizations and deaths from serotype 3 and from the other 12 serotypes in the vaccine?" Based on the data showing PCV13 direct efficacy against serotype 3 and given the surveillance trends that we are seeing elsewhere, we judge the answer is "yes." Thank you very much.

**Discussion Points**

Dr. Lee thanked Dr. Jodar for the scientific input on behalf of the Pneumococcal WG and ACIP. They are thankful for the impact that PCV13 as a product has had on overall disease burden in the US in both children and adults. With due respect to those comments, she said she wanted to pull them back a step because she felt like the bigger issue regarded thinking about the main issues related to disease burden. She does think the models are all very sensitive to VE, and perhaps what did not come across was that the CDC model was conservative on both serotype 3 VE and PPSV23 VE. Both were assumed to be zero. There is uncertainty on both of those estimates, so having a range of sensitivity analyses is incredibly important, but she thought it perhaps should be applied to both estimates. Applying it only to one and only to the other provides the two extremes since it seems like the Pittsburgh model had some PPSV23 effectiveness and no serotype 3. Conversely, the Pfizer model had serotype 3 effectiveness but no PPSV23. The CDC model happened to be in between.

Speaking from an outpatient perspective, Dr. Rockwell point out that the reality of publishing a complex recommendation such as, "All adults 65 and above should receive PCV13, and it needs to be in this order with this amount of time in between PPSV23, and it should be repeated if you do it wrong . . ." is that it takes more than a year to get that enacted, if not longer. In fact, it still may not always be done correctly. She wondered if they knew from the data how many of these adults actually get these vaccines in the correct order and if that was accounted for correctly, and if perhaps the data were being assessed prematurely since there has not really been sufficient time to look for longer trends if, in fact, the trends from other countries are showing different results.

Dr. Messonnier recalled that coverage data have been presented in previous meetings and they could share the data again, and she agreed that it is complicated and the answer is probably not one number.



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Dr. Pilishvili added that they have examined this at the population level and as part of the special studies that have been presented on effectiveness and efficacy for the CMS population. She thinks it is a combination of elements, such as the order in which vaccine was received. This is related to the fact that when the recommendations were made, there already was a large cohort of adults who had received polysaccharide vaccine. For newer cohorts, they do see the correct order. To what extent that occurs is hard to assume, because the surveillance data they have that tracks coverage does not have the power to assess the order in which the doses are received. That is a limitation.

Dr. Szilagyi said that while he understood that the models were most sensitive to VE, he was unclear about the large difference across the models in the utilities and wondered what they were based on.

Dr. Leidner explained that there were 3 different assumptions on utility. The CDC model used more or less research standard values from a 1993 survey in Massachusetts. The Pittsburgh model took a more expert opinion-like approach, but also used values that have been used several times recently and assumed a fixed level of utility of 0.4 if one was hospitalized and that hospitalization would last about a month. That is a standard assumption. The Pfizer model came from a sub-study of CAPiTA in which individuals who ultimately got pneumonia were matched with other individuals in the cohort who did not get pneumonia, and they compared the differences in utilities over a year across those two groups. It is a very new study, so it has not been used as widely in the literature thus far.

## EtR and GRADE for PCV13 Use Among Immunocompetent Adults ≥65 Years Old

**Almea Matanock, MD, MS**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Matanock summarized the EtR and GRADE evidence for PCV13 use among adults ≥65 years old in the setting of sustained indirect effects. As a reminder about the current adult recommendations for pneumococcal vaccines, in 2012 ACIP recommended PCV13 in series with PPSV23 for adults 19 years and older with an immunocompromising condition. This recommendation is not being reconsidered at this time. In 2014, ACIP recommended PCV13 in series with PPSV23 for all PCV13-naïve adults ≥65 years with the following considerations. The committee thought that the short-term use was warranted because of the remaining PCV13-type disease burden. However, it was thought at the time that the long-term utility may be limited due to anticipated indirect effects from pediatric PCV13 use. Therefore, ACIP proposed that the recommendations for routine PCV13 use among adults ≥65 years old be re-evaluated in 2018 and revised as needed, which led to this session.

The current policy question is, “Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?” The population is immunocompetent adults ≥65 years of age, with and without chronic medical conditions. The intervention is PCV13 at 65 years and older followed by PPSV23, in the context of indirect effects. The comparison is PPSV23 alone as that was the recommendation before this was enacted in 2014. The outcomes for this evaluation were IPD, pneumonia, mortality, and PCV13 safety. To evaluate this question, the ACIP EtR Framework was used.



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First to put things into context, Dr. Matanock reviewed what is known about the indirect effects from pediatric PCV use. From the time of first introduction of PCVs in 2000 to 2014, there was a 9-fold reduction in PCV13-type IPD amongst adults ≥65 years of age. Two-thirds of this reduction was in the first decade after PCV7 introduction. At the time PCV13 was recommended for older adults in 2014, there had been a 3-fold decrease in IPD from PCV13 use alone.[1] What was not known in 2014 is what the continued indirect effects would be. Since 2014, there has been a plateau in PCV13-type IPD. What has been observed in the US is similar to what other European countries have observed in terms of PCV13-type disease amongst older adults[2] [[1]Active Bacterial Core Surveillance, https://www.cdc.gov/abcs/reports-findings/surv-reports.html, comparing 2000 to 2014; [2]Hanquet et al. 2018].

In terms of the indirect effects from pediatric PCV use on pneumonia among older adults, most studies have demonstrated a decline in all-cause pneumonia since the introduction of PCV7 in 2000.[1] In the UK, where they are able to measure non-invasive pneumococcal pneumonia using an SSUAD, they observed a decrease of 88% in PCV7-type pneumonia and an additional decline of 30% in the PCV13 unique serotypes after PCV13 introduction in 2010.[2] In the US since pediatric PCV13 introduction, pneumococcal pneumonia hospitalizations have declined. Dr. Lessa's June 2018 presentation to ACIP showed declines in pneumococcal pneumonia for adults with the exception of adults 75 years and older where the credible intervals of the synthetic control model crossed one[3] [[1]Tsaban et al. 2017, [2]Rodrigo et al. 2015, [3]Lessa ACIP October 2018].

Additionally, for context presented here is the coverage for pneumococcal vaccines among Medicare beneficiaries aged 65 years and older. In 2016-2017, approximately 40% of older adults had received at least one dose of PCV13. Included in this number are the 24% who received both PCV13 and PPSV23; that is, those who had completed the recommended schedule of pneumococcal vaccines [https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/pcv13-medicare-beneficiaries.html].

PCV13-type IPD incidence has plateaued at 5/100,000 among adults ≥65 years. The remaining PCV13 serotypes account for 20% of all IPD plus an additional 3% when including 6C, a serotype not included in PCV13 but for which there is cross-protection. The most common PCV13 serotypes are 3, 19A, 7F, and 19F with 3 accounting for 66% of the remaining PCV13-type IPD in 2017. As discussed before, PCV13-type pneumonia incidence is more difficult to measure. The US-based serotype-specific incidence comes from Pfizer's Louisville study. The incidence measured in Louisville was 76/100,000 in the most recent year of the study, 2015-2016. The incidence presented by Dr. Lessa presented earlier in the session is close to this estimate from Louisville at 73/100,000 in 2015. Using the Surveillance for Non-invasive Pneumococcal Pneumonia (SNiPP), non-invasive pneumococcal pneumonia estimates results in a much lower estimate of 17/100,000, which as Dr. Matanock presented in October 2018, is close to the other estimates in the literature of pneumococcal pneumonia incidence. Again, this is not just PCV13 serotype-specific. The estimate there though is applying the ratio seen in IPD to what was observed in SNiPP. In the most recent year of data from the Louisville study, 2015-2016, serotype 3 was most common, accounting for 37% of all PCV13 types.



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Comparing the remaining PCV13-type disease burden among older adults to other vaccine-preventable disease for which there are vaccine recommendations for adults, PCV13 type pneumococcal pneumonia is less than that of zoster or influenza, for which there are universal recommendation for adults. PCV13 type pneumococcal pneumonia is greater than meningococcal serogroup B, for which the recommendation is based on individual clinical decision-making.

The WG perspective on the remaining burden of PCV13-type disease among older adults is that PCV13-type disease has been dramatically reduced through indirect effects, but some burden still remains in older adults. There is uncertainty about the burden of pneumococcal pneumonia and mortality associated with PCV13-type disease. Since the 2014 recommendation, no further reductions in IPD have been observed at the population level and inconsistent results from pneumonia impact studies. In answering the EtR question, “Is the PCV13-type disease burden still of public health importance?” the WG’s perspective was “Probably Yes.”

Now to look at the Benefits and harms using GRADE, just to remind everyone again that this is the policy question evaluated in GRADE, “Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?” In more detail, the outcomes of interest were: PCV13-type IPD, PCV13-type non-bacteremic pneumococcal pneumonia (NIPP), PCV13-type disease mortality, and SAEs associated with PCV13. The effect was evaluated by examining efficacy and effectiveness for individual-level effects associated with PCV13 use, and impact at the population level.

A systematic review was conducted of studies using Medline, Embase, CINAHL, Cochrane, and clinicalstrials.gov databases using search the search terms: (Pneumococcal Vaccin*) OR (pneumococcus vaccin*) OR (pneumonia* vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over 65) OR (older 65) OR >=65 OR =>65. Articles were reviewed from January 1, 2014 to July 3, 2018. Efforts were made to obtain unpublished or other relevant data, including presentations to the WG from industry and independent researchers.

For observational studies, studies were excluded with low PCV13 coverage in the population studied and in which the indirect effects would have been expected to be different than in the US population. For safety studies, studies were excluded in which PCV13 was co-administered with other vaccines since the SAEs in these trials could not be attributed to PCV13 alone. Additionally, RCTs were excluded in which there was no comparison to either PPSV23 or placebo. In the review process, 2239 title and abstracts were screened. Ultimately, 20 studies were GRADED after excluding studies that were in other population, had different outcomes than those in GRADE, or were examining pneumococcal vaccines other than PCV13.



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First to look at PCV13 efficacy, effectiveness, and impact on PCV13-type IPD, this table identifies the studies that were included:

**PCV13 Efficacy, Effectiveness, and Impact on PCV13-type IPD**

| Study | Population | Method | VE | (95%CI) |
|---|---|---|---|---|
| Bonten [1]* | Dutch adults ≥65 years old | Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) RCT (PCV13 vs placebo) (n=84,496) | 75% | (41, 91) |
| Gessner [2]* | Dutch adults ≥65 years old | CAPiTA RCT (PCV13 vs placebo) (n=84,496) + | 76% | (48, 89)+ |
| Pilishvili [3] | US adults ≥65 years old | Case-control; Active Bacterial Core Surveillance (ABCs) IPD cases and age- and zip code matched population-based controls (n=1,530) | 59% | (11, 81) |
| Pilishvili [4] | US adults ≥65 years old | Case-control; ABCs IPD cases enrolled in Medicare part B matched to controls on age group, census tract, and length of enrollment in part B (n=10,851) | 47% | (4, 71) |
| | | | % change | (95%CI) |
| Unpublished ABCs data [5] | US adults ≥65 years old | Pre-post analysis comparing incidence in 2013-14 vs 2016-17 (n=4,700,000) | -13% | (-26, 2) |

+All episodes of PCV13-type IPD using modified intent-to-treat (mITT)

*Pfizer funded studies

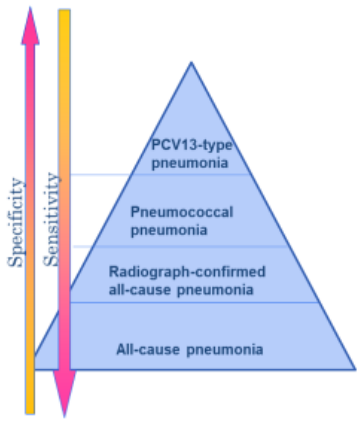
The first two rows are the estimates from the CAPiTA study, a very large RCT looking at the endpoint of pneumococcal pneumonia. The first estimate is per protocol and the second is all episodes in a mITT analysis. The two are very close and significant at 75% (41, 91) and 76% (48, 89). The second two lines are two case-control studies, both using ABCs IPD cases but with different controls. The point estimates from these studies are slightly lower, but still significant, with confidence intervals that overlapping those from the CAPiTA. In the last row is what has been seen at the population level in terms of impact on PCV13-type IPD. At the population level, it is not possible to separate out direct from indirect effects, but a statistically significant change in PCV13 type IPD incidence has not been observed using the period just before PCV13 introduction for older adults to the most recent data available, 2016-2017.

Before moving on to the second critical outcome, PCV13-type pneumonia, Dr. Matanock went through a schematic which she hoped would help to organize the various VE estimates available for pneumonia:

At the peak of the pyramid is PCV13-type pneumonia, as it is the most specific outcome. The studies evaluating this outcome use Pfizer's SSUAD test, which is not commercially available. There is no similar SSUAD being used for the other 75+ serotypes, so it is not possible to detect the serotype causing non-invasive non-PCV13-type disease.

At the base of the pyramid is all-cause pneumonia, which is the most sensitive but least specific outcome. The expected measure of effects is small due to a smaller proportion of vaccine-preventable disease for this outcome. Replacement with non-PCV13-types can obscure the impact on PCV13-type disease when examining all-cause pneumonia.

In presenting the effectiveness and impact for pneumonia, Dr. Matanock moved from the peak to the base.



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First for PCV13-type pneumonia including IPD, this table identifies the studies that were included:

**PCV13 Effectiveness and Impact on Pneumonia**
**— PCV13-type Pneumonia Including IPD**

| Study | Population | Method | VE (95%CI) |
|---|---|---|---|
| Bonten [1]* | Dutch adults ≥65 years old | CAPiTA RCT (PCV13 vs placebo) (n=84,496) | 45% (14, 65) |
| McLaughlin [7]* | U.S. adults ≥65 years old | Louisville cohort study [8] nested test negative design case-control; non-PCV13-type pneumonia as controls (n=2,034) | 71% (6, 91)[i] |
| Prato [9]* | Italian adults ≥65 years old | Test-negative design case-control; non-PCV13-type pneumonia as controls (n=186) | 38% (-131, 89)[ii] |
| | | | **% change (95%CI)** |
| Swerdlow [10]* | U.S. adults ≥65 years old | Louisville cohort study [8] pre-post analysis comparing incidence in Jun2014-May2015 vs Jun2015-May2016 (n=587,499) | -32% (-8, -49) |

[i]In the primary analysis, reported here, the controls were defined as all non-PCV13-type pneumonia. In a sensitivity analysis, where controls were defined as non-PCV13-type pneumococcal pneumonia, the VE was 69% (-47, 93).
[ii]*S. pneumoniae* confirmed in nasopharyngeal, sputum, bronchoalveolar-lavage, or sterile site on polymerase chain reaction (PCR) or culture

*Pfizer funded study

The first two rows are the efficacy from CAPiTA. The second two lines are two case-control studies. McLaughlin et al is Pfizer's Louisville cohort specifically using a nested case-control study to look at PCV13 effectiveness on pneumonia. Both of these estimates are statistically significant. In the observational study from Louisville, the confidence interval is both lower and higher than that seen in CAPiTA. There is one small study from Italy, Prato et al. This study did not use an SSUAD, so confirmed cases were from NP swabs, sputum, bronchial lavage (BAL), and other sterile site cultures. They had a non-significant estimate of VE. In the last row is the impact at the population level from the Louisville cohort for PCV13-type invasive and non-invasive pneumonia. At the population level, an impact is seen in this study in the two years that they used. Essentially, it is the first year of vaccine introduction when coverage was about 11% compared to the second year when coverage was about 36%.

Next are estimates from two studies looking just at PCV13-type non-invasive pneumonia. The first from CAPiTA (Webber) and the second from Louisville (McLaughlin). From CAPiTA, there is a statistically significant VE. From Louisville, the confidence interval at the lower end crosses 0 when excluding IPD.

Moving on to NIPP at the population level from surveillance for NIPP (Gierke), a statistically significant decline was observed between 2013-2014 versus 2015-2016. However, when the dramatic declines between 2013-2014 are not included and just 2014 is compared to 2016, there have been no declines.

And now at the base of the pyramid, PCV13 effectiveness against all-cause pneumonia.
The first row is from CAPiTA (Gessner), which found an 8% VE against all-cause pneumonia in a post-hoc analysis. The second row is the range of estimates from the stratified analysis presented earlier by Dr. Lessa of 6%-11%. Both of these estimates are significant, but are lower because this is a less sensitive outcome.



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PCV13-type disease mortality is the third critical outcome. There is very little information for this outcome. The first estimate is from CAPiTA (Bonten), which found 7% all-cause mortality in both the PCV13 and placebo arms over the course of the trial, but no VE against PCV13-type disease or all-cause pneumonia. Examining PCV13-type IPD mortality in ABCs comparing 2013-2014 to 2016-2017, A significant change is not observed in mortality since the 2014 recommendation was made.

With the burden of disease observed and the highest VEs from CAPiTA, every year roughly 26,300 older adults would need to be vaccinated with PCV13 to prevent 1 case of IPD. For inpatient pneumonia, between 3,000 to 14,000 older adults would need to be given PCV13 to prevent 1 case of inpatient pneumonia. Approximately 2,600 older adults would need to be given PCV13 to prevent 1 case of outpatient pneumonia.

Since 2014, the WG identified 4 published RCTs that reported SAEs: Bonten 0.8%, Jackson 2.3%, Juergens 0.6%, and Shiramoto 0.3%. Presented here is the total number of SAEs. However, it should be noted that in total these percentages represent very few SAEs, most of which were determined not to be related to the vaccine. In addition to the 4 RCTs, the WG identified 5 observational studies, which observed similarly low rates of SAEs: Durando 0.1%, Haber ,0.01%, Shiramoto 0%, Tinoco 1.2%, and Tseng1.2%-5.8%. When the results of Haber and Tseng were presented to ACIP by Tom Shimabukuro in June 2018, the conclusion was that there were no new safety signals or unexpected patterns observed, providing reassurance regarding continued use of PCV13 amongst older adults. The WG's conclusions after reviewing the literature remain the same.

To summarize GRADE, according to ACIP GRADE guidelines RCTs are initially given an evidence type of 1 and observational studies an evidence type of 3. The WG downgraded CAPiTA, the RCT, for the IPD outcome on indirectness because PCV13 was compared to placebo not PPSV23, which is the alternative in the policy question and for which there is an established efficacy against IPD. The WG downgraded CAPiTA as well for the mortality outcome on imprecision, but it should be mentioned that this was not the primary endpoint and that there were very few deaths overall caused by PCV13-type disease (2 in both the intervention and control arms). The WG downgraded the case-control studies for the IPD outcome based risk of bias from potentially unmeasured confounding and misclassification of vaccine status and indirectness for impact studies which looked at population level effects. Additionally, for pneumonia among the observational studies, the WG downgraded the risk of bias because of non-specific measures of the outcome. There was inconsistency between study results, and among the impact studies not only were they looking at population level effects, but also were looking over a short time periods of 2 years for the Louisville study and 4 years for SNiPP. The WG downgraded PCV13-type disease mortality since the only evidence comes from ABCs, which captures inpatient mortality and in the outpatient setting, deaths that occur very proximally to the diagnosis of PCV13-type IPD only. Lastly, the WG downgraded the RCTs for SAEs because some of the trials had modified blinding procedures, relatively short follow-up periods, and some used a control group other than PPSV23. The WG noted that the observational studies had inadequate or no comparison group, but upgraded these studies for the SAE outcome since there have been multiple large observational studies with consistent results. Here is the GRADE Summary Table showing the final evidence types for benefits and harms:



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| Outcome | Design | # studies [references] | Initial Evidence Type | Risk of Bias | Inconsistency | Indirectness | Imprecision | Evidence Type |
|---|---|---|---|---|---|---|---|---|
| **Benefits** | | | | | | | | |
| PCV13-type invasive pneumococcal disease (IPD) | RCT | 1 — [1, 2] | 1 | Not serious | N/A | Serious | Not serious | 2 |
| PCV13-type pneumonia | | 1 —[1, 2, 6] | 1 | Not serious | N/A | Not serious | Not serious | 1 |
| Mortality from PCV13-type disease | | 1 — [1] | 1 | Not serious | N/A | Not serious | Very serious | 2 |
| PCV13-type IPD | Observational | 4 — [3-5] | 3 | Serious | Not serious | Serious | Not serious | 4 |
| PCV13-type pneumonia | | 5 — [7, 9-12] | 3 | Very serious | Very serious | Serious | Very serious | 4 |
| Mortality from PCV13-type disease | | 1 — [5] | 3 | Serious | N/A | Serious | Very serious | 4 |
| **Harms** | | | | | | | | |
| Serious adverse events | RCT | 4 — [1, 13-15] | 1 | Serious | Not Serious | Serious | N/A | 2 |
| | Observational | 5 — [16-20] | 3 | Serious | Not Serious | Not Serious | N/A | 2 |

In summary, PCV13 is effective and efficacious in preventing PCV13-type IPD and efficacious in preventing NIPP, but the effectiveness against NIPP is inconsistent across studies. Since 2014, at the population level, no impact has been observed on IPD and data across studies for the impact on pneumonia are inconsistent. The remaining PCV13 disease burden is predominated by serotype 3. No impact has been demonstrated on mortality, and no concerning safety signals have been detected.

To summarize the WG's perspective on the benefits and harms of routine PCV13 use among older adults, PCV13 is effective in preventing disease amongst older adults, but the remaining disease burden is low and predominated by serotype 3. Based on this summary, the WG thought that the anticipated desirable effects would be small, but that the overall certainty of this evidence was judged to be low because of the limited and inconsistent results for pneumonia and mortality outcomes. For anticipated undesirable effects, no concerning safety signals have been seen since the 2014 recommendations were made with at least 40% coverage among adults 65 years and older. For these reasons, the WG's perspective was that the anticipated undesirable effects are minimal with a high certainty in the level of the evidence. In terms of the balance of benefits and Harms of PCV13 use among older adults, the WG thought that the benefits of continued PCV13 use are relatively small, but outweigh the risks, which also are small. Evaluating just the elements of the reviewed data to this point, the WG favored continuing routine PCV13 use for older adults.

Evaluating the values and preferences of the target population, there are very limited data for this element. In three patient-focused studies, participants perceived pneumonia as severe and sometimes fatal.[1-3] However, there was a low perceived personal susceptibility of pneumonia.[1-2] The WG's perspective was that the potential protection against pneumonia likely outweighs the side effects of PCV13 for older adults [[1] Doshi et al. 2016, [2] Brown et al. 2017 (PPSV23 only), [3]Kaljee et al. 2017].



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Assessing the available information in the EtR Framework, how older adults feel about the desirable effects balanced against the undesirable effects cannot be addressed with any certainty. However, the assessment by the WG was that there is possibly important uncertainty about how much adults ≥65 years old value the main outcomes. In summary, there is very little evidence on which to base a recommendation from this domain.

There are limited studies assessing acceptability among stakeholders as well, but the WG reviewed three studies directly addressing the policy question, which in summary raised the following themes. The current recommendations are confusing for providers.[1] However, providers when choosing to continue the recommendation or not, choose to continue with current recommendation.[2] Almost half of the immunization managers surveyed responded that keeping the current recommendations may be programmatically advantageous if new, higher valency conjugate vaccines were to be available soon.[3] While there is insurance coverage for the current recommendations, reimbursement for vaccine is still a programmatic issue[3] [[1] Hurley et al. 2018; [2] Pfizer sponsored provider survey, unpublished, 2018; [3] Association of Immunization Managers (AIM) survey, unpublished, 2018].

The WG has deliberated on the domain of acceptability of continued PCV13 use amongst older adults, taking into account the following considerations. The considerations for discontinuing PCV13 are that the overall impact on PCV13-type disease from vaccinating older adults is minimal in the context of indirect effects from pediatric PCV use. Considerations for continuing PCV13 included that PCV13 can provide individual-level protection against the remaining burden of disease, and that frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations and may present implementation challenges. With these different considerations, the WG's opinions did not coalesce around a single judgment for this domain.

In terms of resource use, as was summarized by Dr. Leidner in his presentation earlier in the session, there is important uncertainty for some of the inputs, primarily regarding what the VE against pneumonia is for both PCV13 and PPSV23. However, the majority of base-cases and sensitivity analyses provide an estimate that is 2 to 12 times higher than what it was in 2013. This table compares resources used in 2013 compared to 2019:

**Resources Used: Comparison of 2013 vs 2019**

| | | 2013 Model Projection for 2013 (2017$) | 2013 Model Projection for 2019 (2017$) | 2018 Model Projection for 2019 (2017$) (PCV13 VE for ST3 IPD and ST3 pneumonia 0%) | 2018 Model Projection for 2019 (2017$) (PCV13 VE for ST3 IPD 26% and ST3 pneumonia 45%) |
|---|---|---|---|---|---|
| Health Outcomes | IPD Cases | -226 | -163 | -76 | -84 |
| | Hospitalized Pneumonia Cases | -4,961 | -1,858 | -2,047 | -5,262 |
| | Non-hospitalized Pneumonia Cases | -7,252 | -2,715 | -2,205 | -5,611 |
| | Deaths due to IPD | -33 | -24 | -10 | -11 |
| | Deaths due to Pneumonia | -332 | -124 | -79 | -207 |
| | QALYs | 3,053 | 990 | 709 | 1,624 |
| | Life-years | 4,627 | 1,587 | 1,101 | 2,611 |
| Costs (million $) | Total Cost | $199 | $284 | $398 | $361 |
| | Medical Costs | -$139 | -$54 | -$25 | -$63 |
| | Vaccine Costs | $338 | $338 | $423 | $423 |
| Cost Ratios ($) | Cost/QALY | $65,306 | $286,855 | $561,417 | $222,132 |
| | Cost/Life-year | $43,087 | $178,848 | $361,367 | $138,122 |



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Comparing the results now with the evidence that went into the decision in 2014, in the first column are the 2013 model results. This was the estimated public health impact at the time of the decision. However, in 2014, it was anticipated that there may be additional indirect effects from pediatric PCV13 use, so the model was projected forward to 2019 when it was thought that the indirect effects would have reached their peak. Those model results are represented in the second column. The third and fourth columns are the current model estimates, first assuming no effectiveness against serotype 3 disease and then assuming 26% for ST3-type IPD and 45% for ST3 pneumonia. The assumptions have been updated with new information gained in the past 4 years. Roughly, the cost in 2013 was $65,000 dollars per QALY. It was projected to be $287,000 dollars per QALY. And now that it is actually 2019, the cost is estimated to be approximately $222,000 dollars per QALY assuming PCV13 effectiveness against serotype-3, and $561,000 dollars per QALY assuming PCV13 is not effective against serotype 3. In terms of the WG's perspective on the resources used, implicit in the economic models is the same level of uncertainty that exists in the evidence for the burden of disease and benefits from PCV13 use domains. However, with the updated information available now compared to 2014, the cost per QALY are estimated to be higher now than they were in 2013-2014 when the recommendation was made. The WG thought that PCV13 use among older adults was probably not a reasonable and efficient use of resources.

As the last domain in the EtR, the WG considered feasibility. The current recommendations are complex, but have been integrated into many health care and public health systems. Universal age-based recommendations are easier to implement than risk-based recommendations. Medicare currently covers the recommended pneumococcal vaccination series for adults ≥65 years old. If a change in the current recommendations is made, CMS will review the new recommendation and the supporting evidence. It was brought up by WG members as well that some state regulations that allow public health nurses and pharmacists to provide PCV13 are tied to ACIP recommendations, and that effective communication strategies will be needed if policy changes are considered. In answering the final question regarding whether the current intervention is feasible to continue, the WG thought "probably yes." PCV13 in series with PPSV23 is the current intervention, so continuing would mean continuing the status quo versus removing PCV13 and returning to the previous recommendations of PPSV23 alone for adults 65 years and older.

Now to bring everything together, the options for type of recommendations considered were the following:

A. We do <u>not</u> recommend the intervention (PCV13 in series with PPSV23 no longer recommended for immunocompetent adults ≥65 years old)

B. We recommend the intervention for individuals based on clinical decision-making (PCV13 in series with PPSV23 would be given to immunocompetent adults ≥65 years based on patient-provider judgement)

C. We recommend the intervention (continue PCV13 in series with PPSV23 for immunocompetent adults ≥65 years old)



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As of the most recent discussions, most WG members were either in favor of discontinuing PCV13 (A) or recommending PCV13 for individuals based on clinical decision-making (B). A small minority of WG members supported continuing current recommendations (C). However, there were many key issues raised when considering these different recommendation options. Here is a summary of the key issues:

| **Reasons Raised in Favor of Continuing Routine PCV13 Use** | **Reasons Raised in Favor of Discontinuing Routine PCV13 Use** |
|---|---|
| ❑ PCV13 is effective in preventing PCV13-type pneumococcal disease.<br>❑ PCV13-type disease has been reduced through indirect effects, but not eliminated.<br>❑ It is easier to adhere to universal prevention strategies than to risk-based ones.<br>❑ Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations, and may present implementation challenges. | ❑ The overall impact on PCV13-type disease from vaccinating older adults is minimal in the context of indirect effects from pediatric PCV use.<br>❑ The low remaining burden of PCV13-type disease limits the potential benefit from direct effects.<br>❑ There has been a lack of clear population-level impact on disease since 2014.<br>❑ This would be a more judicious use of resources.<br>❑ Discontinuing PCV13 for older adults would be a simplification of the recommendations. |

The next steps for the WG are to provide a brief summary of the EtR Framework to ACIP, including any updates from studies being finalized, including the following:

- ❑ The mathematical model estimating PCV13 direct and indirect effects against IPD
- ❑ The two case-control studies estimating PCV13 VE against IPD using ABCs IPD cases
- ❑ Trends by serotype from the Native American Adult Pneumonia Etiology Study, which was first presented in June 2018
- ❑ Results from a primary care provider survey focused on acceptability and feasibility

An ACIP vote is anticipated during the June 2019 meeting.

**Discussion Points**

Dr. Atmar observed that one of the issues he did not hear addressed regarded what resource utilization would result from removing the recommendation and then potentially re-initiating it within this population within a year or two when PCV15 or PCV20 become available. This is an important consideration, so any additional information that would inform ACIP's deliberations would be beneficial.

Dr. Messonnier said that CDC agrees that this is a complicated topic and appreciates everyone thinking through what additional information may be helpful. CDC probably needs to pose that complex question to CMS, which they will do in order to try to acquire some information for ACIP for June. She invited everyone to identify other information that would be helpful.



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Dr. Foster (APhA) suggested that pharmacists could weigh in on the acceptability issues for which the WG could not make a decision. Probably 100% of states permit pharmacists to administer this vaccine, so pharmacy is very much involved in this process. APhA puts a lot of resources into getting the recommendation understood within pharmacies throughout the country. He recalled some meningococcal discussions pertaining to $ACWY_{135}$ being kept in the schedule twice because of programmatic issues, so he thought this was a feasible thing to do. He thought that removing the recommendation now and then trying to implement something within one to two years if new vaccines do become available would be very difficult to do with the pharmacy setting. He also thought that in 2014 when the decision was made to revisit this in 2018, it was probably anticipated that there would be more data available. From the standpoint of pharmacy, he was supportive of continuing with the current recommendation until such time as additional vaccines are available.

Dr. Ault asked whether there are all-cause mortality data from the large Medicare and Medicaid dataset that was just presented.

Dr. Matanock indicated that they have some of that information and can provide it within the summary during the June 2019 meeting. They have assessed the CFR, but she was not sure whether mortality over time had been examined.

Dr. Ezeanolue said this reminded him of the decision ACIP had to make several meetings ago about LAIV in that there were the facts before them, as well as the programmatic issues that had to be considered. The majority of key issues Dr. Matanock reviewed for continuing versus discontinuing are programmatic. It is known from the data that there has not been any population-based impact, but there will be some important programmatic issues if it is removed. The question arises regarding what factors ACIP should consider in making its decision. The facts are before them that there has been no population-based impact. He requested further insight from CDC about how to weigh these two aspects in terms of whether the anticipated programmatic issues were enough to continue this vaccine.

Dr. Messonnier replied that programmatic issues are important enough. Dr. Wharton always reminds her when complicated issues such as this arise that this is why CDC has ACIP. She completely agrees that this is an incredibly complex issue that is at the boundary of data and judgment. Over the past couple of years and many of the issues that CDC poses to ACIP are in this same space in which it is not so obvious what to do. She thought Dr. Lee could comment on why this has been so difficult within the WG.

Dr. Lee commented that the reasons the “acceptability” box is so broad is because the entire WG as a whole has swayed from one side to the other, as have individuals on the WG. The problem is that they agree with all of the statements. There is nothing wrong with any of the arguments, so she thinks this is a judgment call they are going to be forced to make.

Dr. Stephens pointed out that this platform was introduced in 2014 and he did not think the impact of that has been realized. The order in which these vaccines are administered is important in that it really is a prime/boost strategy with a conjugate followed by a polysaccharide. To go back to a polysaccharide alone strategy seems to him to be a mistake based on his reading of the data. He did not think they had seen enough data with the proper use of the conjugate followed by the polysaccharide. He also would argue with the term “immunocompetent.” These are not immunocompetent individuals in the sense that many of them have conditions or significant conditions with medications and so forth. This is not “immunocompetent” as it would typically be defined. He urged them to think further about this



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issue. More data in terms of this platform is important, and he agrees about the coming introduction of potentially even better conjugate vaccines for this population.

Dr. Baker (IDSA) agreed with Dr. Stephens' statements.

Dr. Talbot asked if there is a population of Native Americans who are still at high risk for pneumococcal disease because they have not eliminated disease in children, whether that would require another WG and vote to include an indication just for them.

Dr. Cohn indicated that procedurally from an ACIP perspective, that group would have to be considered and voted upon separately as a high risk group. If the recommendation was taken away entirely, another WG would be needed. If individual clinical decision-making is kept, there potentially could be some broad-based decisions by IHS.

Dr. Weiser (IHS) emphasized that IHS is not the only group that provides immunizations for AI/AN. For example, the recommendations pertaining to influenza and treating influenza with antivirals has made a major impact on helping others who are not part of the IHS system to do the right thing. He would like to hear more about the Native American Adult Pneumonia Etiology Study during the next meeting.

Dr. Matanock indicated that the Native American Adult Pneumonia Etiology Study was presented initially in June 2018. At that time, Dr. Hammett presented information about what was known at that point amongst Navajo and Apache for etiology of pneumonia and the impact of PCVs overall in Alaska Natives and American Indians living in the Southwest. While there have been similar impacts, the rates of disease are still higher. The etiology study is not pre-2014, so it is not possible to look at impact from this. Dr. Hammett is going to try to estimate VE, but this is likely to be difficult given the very high coverage rates in that population.

Dr. Walter said he was still struggling with the first presentation in terms of the direct effects of PCV13 when ST3 is removed. The summary presentation accounted for all serotypes, and he wondered if that was the correct way to look at this. That is, ST3 was not removed in the last presentation but perhaps should be.

Dr. Pilishvili clarified that the study utilizes surveillance and coverage data in order to tease apart direct and indirect effects. They are using essentially what is observed and trying to attribute how much of it was due to direct versus indirect effects. When ST3 is removed, the trend looks very different. Therefore, more is to be attributed to direct effects given the coverage. When ST3 is included, the trend is flat and there is nothing to attribute to direct effect. This is not a direct effectiveness study which compares vaccinated to unvaccinated. She thought they should separate direct effectiveness where effectiveness was moderate to low when vaccinated are compared to unvaccinated and the impact over time.

Dr. Cohn added that further consideration can be given to whether ST3 should be removed, which can be presented during the next meeting.

Dr. Goldman (ACP) agreed that this is a complex issue and as a private practitioner, he always struggles with population health versus the individual patient in front of him. He always has been taught, trained, and still believes that his most important responsibility at that moment the patient is in front of him at that time until the next patient comes in and becomes the most important patient. While population health is of great importance to ACIP, he thinks they also must remember that even if they are reducing pneumonia risk in one patient as practicing



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physicians, that is of great concern. There needs to be leeway for individual clinical decision-making. While cost and health coverage are important, they must stress the fact the vaccine does have some benefits. It is not zero. It is not completely ineffective. Even if they are reducing the risk of a pneumonia-related death for one patient, it is 100% for that one patient.

Dr. Frey said it would help her think about the overall picture if they could find out where PCV10 and PCV15 are in their development and the timeline for potential applications/approvals.

Dr. Messonnier suggested that this be added to the list of items ACIP would like to hear about during the next meeting. They know what the companies will say and can include it, but as they all know and FDA will confirm, those timelines are always incomplete.

Dr. Grogg (AOA) emphasized that they finally got their physicians trained to give the Prevnar 13® Prevnar at 65 years of age and PNEUMOVAX® 23 at 66 years of age. There are questions about effectiveness and new vaccines are coming out, so his suggestion was to keep the recommendation as is until more is known.

Dr. Ezeanolue asked whether ACIP has to take a vote in June, or if it would be possible to defer that vote and allow the WG to continue in order to determine whether there will be an increase in uptake in that 20% uptake may be insufficient for them to judge whether there is going to be a population-based impact. It seems the infrastructure that already is built could wait until information on this and new products becomes available.

Dr. Cohn replied that ACIP does not have to vote on this issue. Not voting on this issue is essentially maintaining the current recommendation, so it is still a decision. In terms of implications and future data, ACIP has so many issues coming down the pipeline in the next couple of years, closing out this issue for a period of time would be helpful.

Dr. Ezeanolue emphasized that the problem is that they are not really closing it out. If they make a decision now and have to come back in a year or so, it will seem like they are not sure what they are doing.

Dr. Cohn indicated that they could discuss the WGs terms of reference and how they prioritize after there is more feedback on this particular decision. The answer is that they do not have to vote on this decision. That is up to ACIP.

Dr. Moore said she was one of three minds about this depending on the moment. It might help her to know what the potential inadvertent unintended consequences might be to particularly vulnerable populations if the recommendation was changed. Risk-based recommendations are difficult to implement and age-based recommendations are much easier to implement. This has been an age-based recommendation for a while. Perhaps it would be beneficial to hear about any data on subpopulations or vulnerable communities like AI/AN who might have special circumstances that ACIP has not discussed.

Dr. Coyle (AIRA) pointed out that from a systems perspective, it is very helpful for ACIP to consider what they want the provider to do, what information they want them alerted to, and how that reacts different. For example, if a provider is looking at the recommendation, does ACIP want that displayed ahead of time and recommended for all patients or a certain percent of that, or is it that the patient needs to know about the recommendation before they walk in the door? From a systems perspective, it would be helpful for ACIP to consider this as they evaluate their decisions.



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Dr. Bernstein expressed interest in knowing the annual NNV and cost per QALY for other vaccine-preventable diseases in comparison to this.

Dr. Cohn responded that this is not typically presented, as they think that these are each individual decisions and there is wide variation. Some background information can be provided for ACIP. She invited Dr. Baker to clarify whether her agreement with Dr. Stephens' statements was a personal opinion or an IDSA perspective that has been discussed.

Dr. Baker (IDSA) clarified that it was her personal opinion, but they are interacting officially with the IDSA, especially if there will be a vote because this is a very important issue. However, IPD is a very uncommon event due to the vaccine serotypes. There is a huge indirect effect due to pediatric and adult vaccine providers. It is very difficult to measure direct effects. For example, how many people 65 years of age and older who got PCV13 did not get IPD? How many people had mild CAP, went to the doctor, and got medication? It is difficult to be precise. Either she or Dr. Duchin will comment on the IDSA perspective during the June meeting. She suspects that for the people who are vaccinating within the IDSA, which includes pediatricians and adult providers, the issues pertaining to dismantling and re-mantling systems and future advance conjugate vaccines are all going to be very important. Immunizers are physicians and their duty is to deal with individual patients, and it is difficult.

Dr. Messonnier indicated that given the complexity of this situation, it would be very helpful for the liaisons to take this back to their organizations and be prepared in June to provide input. If organizations, especially those that are major stakeholders in this issue, want to take a position on this, it would be very helpful for the voting members to hear that feedback.

Dr. Atmar pointed out that one of the issues with influenza vaccine after the Medicare Demonstration Project and the increased uptake of influenza vaccine in the elderly population, was that there was great concern about being able to demonstrate population-based effects. They eventually moved to the test-negative design to show VE in various age groups. In fact, that may be similar here and perhaps they should seek input from the modelers on this. The lack of population-based effects may be somewhat troublesome, but he did not think it should be fatal. Some of the data showing evidence of continued direct effects should be given some import.

Dr. Szilagyi said that like everyone, he was really struggling with this. In terms of the 3 possible decisions, he thought it might be helpful for the WG to think through what guidance ACIP would be able to provide if there was individual-decision recommendation. As a primary care physician who administers vaccines, albeit it to children, he was having a hard time ascertaining what kind of logical guidance would help a primary care internist or family physician. This aligns with Dr. Stephens' comment that a 65 year old is not the same as a 75 year old. It is difficult to judge immunocompetence because there is an enormous range, and he personally would have a hard time trying to determine a patient's risk.

With some institutional memory having been on the committee for 5 years, Dr. Romero recalled a vote on meningococcal B vaccine and the discussion Dr. Frieden had with ACIP. To paraphrase that discussion, Dr. Frieden said that they should not be paralyzed by lack of data but should react on the data that they have, and project their decisions based on the facts present. They should make reasonable assumptions and if those assumptions need to be modified at a later date, so be it. They are tasked to come up with a plan or reasonable process forward, which is important for the committee to bear in mind.



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# Meningococcal Vaccines

## Introduction

**David S. Stephens, MD**
**Chair, Meningococcal WG**
**Advisory Committee on Immunization Practices**
**Emory University**

Dr. Stephens introduced the Meningococcal Vaccine WG session. Two serogroup B meningococcal (MenB) vaccines were licensed for persons aged 10 through 25 years in 2014 and 2015. The first is MenB-FHbp (Trumenba®, Pfizer), which is indicated for persons at increased risk for MenB disease. Trumenba® is administered as a 3-dose series at 0, 1-2, and 6 months. Healthy adolescents are recommended to receive a 2-dose series administered at 0 and 6 months. The second is MenB-4C (Bexsero®, GlaxoSmithKline), which is a 2-dose series administered at 0 and ≥1 month.

In February 2015, ACIP recommended that the following persons aged ≥10 years at increased risk for MenB disease receive a MenB primary series:

- ❑ Persons with complement component deficiency, including complement inhibitor use
- ❑ Persons with functional or anatomic asplenia
- ❑ Microbiologists routinely exposed to isolates of *Neisseria meningitidis* (*N. meningitidis*)
- ❑ Persons exposed during an outbreak

These groups are also recommended to receive a quadrivalent meningococcal conjugate, MenACWY, as a primary dose or series. A booster dose is recommended every 5 years thereafter for as long as increased risk remains.

In June 2015, ACIP also recommended that adolescents aged 16 through 23 years may be vaccinated with a MenB primary series based on individual clinical decision-making, with a preferred age of 16 through 18 years.

The question before the committee during this session pertained to MenB booster doses. ACIP does not currently recommend MenB booster doses for persons at increased risk for MenB disease. This recommendation would be off-label as booster vaccination currently is not licensed. Data and considerations for MenB booster doses were presented during the February 2017 ACIP meeting. ACIP requested further data to inform policy options. Additional data on immune persistence following a MenB primary series and immunogenicity, safety, and persistence of a MenB booster dose have been generated. However, the manufacturers have indicated that no further data are forthcoming.

In terms of activities, the WG has: 1) reviewed data on persistence of the immune response following a MenB primary series and immunogenicity, persistence, and safety of a MenB booster dose; 2) formulated policy questions and evaluated the quality of evidence for MenB booster doses; and summarized WG perspectives and developed potential MenB booster policy options for ACIP feedback.



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The agenda for this session included presentations on the following topics:

- ❑ A summary of the data on the immune persistence following a MenB-FHbp primary series and immunogenicity and safety of a MenB-FHbp booster dose
- ❑ A summary of data on the immune persistence following a MenB-4C primary series and immunogenicity and safety of a MenB-4C booster dose
- ❑ GRADE and EtR Framework for MenB booster doses
- ❑ WG interpretation of the data, considerations, and next steps

**Safety and immunogenicity of a booster dose of Trumenba® (MenB-FHbp)**

**Paul Balmer, PhD**
**Medical Development, Scientific, and Clinical Affairs**
**Pfizer Vaccines**

Dr. Balmer presented data generated on the safety and immunogenicity for a MenB-FHbp booster dose. As a reminder, MenB-FHbp is licensed for individuals 10 through 25 years of age for the prevention of serogroup B meningococcal disease. There are two dosing schedules: 1) For individuals at increased risk for meningococcal disease and for use during MenB disease outbreaks, ACIP recommends that 3 doses of Trumenba® be administered at 0, 1–2, and 6 months; and 2) When given to healthy adolescents who are not at increased risk for meningococcal disease, ACIP recommends that 2 doses of Trumenba® should be administered at 0 and 6 months.

As a reminder, Pfizer's MenB vaccine is based on a surface-exposed factor H binding protein (FHbp). Pfizer looked at an extensive collection of isolates from North America and Europe and found that FHbp is expressed in >95% of invasive MenB strains. Importantly, FHbp segregated into two distinct subfamilies, A and B. If a vaccine targets FHbp, it is very important to address this by including one protein variant from each subfamily. To do that, Pfizer included variants A05 and B01. Breadth of coverage is important for protein-based MenB vaccines. It is important to be able to deal with diverse MenB strains, but it is not possible to test against every possible MenB strain. The approach Pfizer took was to use the human serum bactericidal assay (hSBA), which is an established correlate to predict protection. Four MenB strains were selected that were the most prevalent in the US in terms of their clonal complex, including A22, A56, B24, and B44. Importantly, these variants are not matched to the vaccine components. This allows for true breadth of coverage [Madico et al. 2006; Schneider et al. 2006; Mascioni et al. 2009; Seib et al. 2009; Ala'Aldeen et al. 2010; McNeil et al. 2009; Jacobson, Moellig, Olcen 2009, McNeil et al. 2018].

In terms of study designs, these studies take a long period of time. Of the 3 parent studies, Studies 1010 and 1015 were 3-dose schedules. Study 1012 had groups who received either a 2-dose or 3-dose schedule. These subjects were then rolled over into Pfizer's Phase 3 Extension Study, 1033, in which persistence was evaluated for 48 months. A booster dose was then given to subjects who originated from Study 1012 and 1010 at 48 months and followed persistence out to 12 months and then 26 months.



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Regarding safety, what was observed was that a booster dose had a very similar safety profile compared to the primary series. Pain at the injection site was the most commonly reported local reaction, reported by 84.4% to 93.5% of subjects. Fatigue (51.9% to 65.6%) and headache (37.5% to 56.3%) were the most commonly reported systemic events. Of the subjects, 3.7% to 12.5% reported ≥1 AE. Among the subjects, 3 reported related AEs. One of those was an ILI that was classified as an SAE. This was among a group from Study 1012 who received a 2-dose schedule at 0, 2 months who did not roll through the entire persistence and post-persistence. There were no reported AESs during the persistence phase post-booster up to 26 months.

Dr. Balmer split the immunogenicity data into two sections in order to assess the 2-dose and 3-schedules separately. For the 2-dose schedule, looking at the proportion of subjects with a titer ≥1:4, at 1 month post-last dose, a significant proportion of individuals had an hSBA titer of ≥1:4. A decline was observed at 12, with a plateau at 48 months. Overlaying the booster data, a nice booster response was observed in terms of the proportion of individuals above this threshold 1 month after the booster dose. Looking at the data from 12 months and 26 months post-booster, persistence appears to have been improved. Those were the data for the four individual strains.

Looking at the data in terms of the proportion of individuals who were able to make a response at this threshold against all 4 strains, which Pfizer thinks of as evaluating the breadth of coverage the vaccine is able to give, the pre-vaccination data show that without vaccination, individuals found it difficult to mount an hSBA protective level across diverse strains. At 1 month after the 2-dose schedule, 73% of individuals were able to respond to all 4 strains. This declined at 12 months and plateaued out to 48 months. With the booster given at 48 months at the time of the plateau when immunity was at 23.8%, by 1 month post-booster the protective level across diverse strains was better at approximately 92%, at 12 months 62.7%, and at 26 months 42.1%.

From the parent studies, Study 1015 had a control group. This allowed for a comparison between the two groups vaccinated with MenB-FHbp and a control group at 1 month post-dose last dose (in this case 0, 2, 6 months) against the baseline at each time point. Similar to the 2-dose regimen, that declines after the nice response 1 month after the final dose. There is separation between the two groups until 48 months.

Looking at the individual 4 strains for the 3-dose schedule, the profile is exactly the same as the data for the 2-dose schedule with better persistence at 12 and 26 months. Looking at the response against all 4 strains, the profile is very similar at 1 month when approximately 84% of individuals are able to mount a response against all 4 strains. The persistence profile looks exactly the same. Looking at the booster dose data, there is a nice booster response with up to 100% of individuals responding to all 4 strains at 1 month. The persistence of individuals above this threshold remains higher post-booster.

The profiles for the 2-dose and 3-dose schedules are very similar in terms of their profiles. In terms of persistence post-primary series, no difference was observed irrespective of schedule. The parent study actually had groups with a shorter interval between the 2 doses as well. In terms of persistence post-primary series, a range was observed for the 4 strains. This is important because it provides an indication of the range that will be seen against strains which are diverse and not matching the antigen, and a feel for what persistence will be against diverse circulating strains. The profile looks very different after the booster, with a convergence of the range across the 4 strains. This indicates that there is maturation of the bactericidal response, and there probably is going to be a better persistence of breadth of coverage.



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For high risk groups, these data suggest that a 3-dose series followed by a booster dose will enhance persistence of breadth of coverage. For individuals at increased risk due to an outbreak, the data suggest that a single dose of MenB-FHbp can be given to those previously vaccinated with a primary series of MenB-FHbp regardless of whether it was a 2-dose or 3-dose schedule. These data on persistence of protective responses against diverse strains expressing non-matched FHbp variants post-booster dose provide further insights on the optimal way to use these protein-based vaccines to prevent MenB disease across adolescents within the population.

**Discussion Points**

Dr. Atmar asked whether Dr. Balmer could reassure them that the data for the persistence of antibody in the larger group, for the subgroup that had the booster, was similar or representative of what was seen if only the group who was boosted was analyzed. That is, somehow the booster group did not have baseline and persistent antibody to a greater degree than the larger group of whom did not get boosted.

Dr. Balmer indicated that in Study 1015, they received the 3-dose schedule and did not receive the booster dose. The data between that group plus the subgroup that ran through to booster were pretty similar.

**Update on BEXSERO® (MenB-4C) Regarding the Need for and Timing of MenB Booster Doses in Individuals at Increased Risk**

**Phil Watson, PhD**
**US Medical Affairs Lead**
**Meningococcal Vaccines**
**GlaxoSmithKline (GSK)**

Dr. Watson indicated that GSK's intention was to help provide information that could inform the booster recommendations for MenB vaccines. This presentation was created at the request of the ACIP Meningococcal WG and included a recap on the vaccine attributes and data pertinent to this particular policy question.

As a reminder, BEXSERO® comprises 4 major antigenic components: factor H binding protein (fHbp), *Neisseria* heparin-binding antigen (NHBA), (*Neisserial* adhesin A (NadA), and Porin A (NZ PorA P1.4). Each has a distinct target and antibodies to each component are independently bactericidal, but also can work in synergy. In the US, BEXSERO® has been licensed for persons aged 10 through 25 years of age since 2015 as a 2-dose series. It is licensed elsewhere in the world from 2 months of age, and several countries have implemented regional or national immunization programs.

BEXSERO® has been used extensively worldwide since licensure, with over 30 million doses distributed to date. Vaccination programs have been implemented in a range of settings, including populations with infants, children, adolescents, and university students. The largest program to date involved routine vaccination of all UK infants. In the 3 years since implementation, disease incidence has been significantly reduced in the vaccine-eligible cohort. The provisional estimate of VE is approximately 70%. UK authorities have also reported no significant safety concerns after the use of more than 3 million doses. A large regional campaign in Canada evaluated over 2 years after vaccination showed that disease risk was significantly reduced by vaccine use in a population ranging in age from 2 months to 20 years of age. These



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findings along with observations from Australia, the US, and elsewhere confirm that BEXSERO® provides direct protection and has an acceptable safety profile.

The data relating to the specific policy decision at hand come from 4 clinical trials in which BEXSERO® immune responses were evaluated in adolescents and young adults. These studies were undertaken in several countries (UK, US/Poland, Canada/Australia, and Chile), with follow-up periods ranging from 11 months to 7.5 years.

In terms of immune responses at 1 month after the primary series completion in each of these studies, robust responses to the 2-dose primary series were evident across the board with between 68% to 100% of subjects having protective titers against the individual vaccine components. The safety findings were consistent across all studies. Most events were mild or moderate and resolved by Day 7. There was no evidence of increasing severity after a second or subsequent dose.

Regarding immune responses at different timepoints after primary series completion, the follow-up interval increased from 11 months in the UK to 7.5 years in Chile. In the UK where responses were measured 11 months after vaccination, 85% to 97% of subjects retained protective levels of antibodies to the individual vaccine components. An additional analysis of the same data included in the FDA approved label in the US showed that serum from 66% of these individuals was actually bactericidal against all 3 of the indicator strains.

In the studies with longer follow-up periods, Canada/Australia and Chile, it is evident that antibodies may persist at protective levels for several years after primary series completion. After 4 years, between 9% and 84% of subjects maintained protective titers to the individual vaccine components. After 7.5 years, 29% to 84% of subjects maintained protective titers to the individual vaccine components. In every study, antibodies induced by each component waned at different rates. At the longer time points, fewer subjects retained protective titers for PorA, suggesting that antibodies to this component may wane relatively quickly. This was as expected and is consistent with observations with studies of other vaccines.

Importantly, the clinical impact may be limited as <1% of US MenB strains are covered only by this vaccine component. It also is worth noting that across all 4 studies, immune persistence data were available from only 18 US subjects. Caution should, therefore, be exercised in attributing more or less weight to any one of these individual studies when trying to generalize for the wider US population.

Moving on to booster responses, there are data from 2 studies in which a single dose of BEXSERO® was given after 4 or 7.5 years after primary series completion. For all 4 components, robust responses were evident to a booster given either 4 or 7.5 years after priming. The mean antibody titers after the booster doses were higher than the titers achieved 1 month after the 2-dose primary series. The kinetics of the booster dose also have been assessed by measuring GMTs up to 3, 7, and 30 days. In both studies, strong responses to all vaccine components were evident by Day 7. The reactogenicity of a booster dose has been evaluated in both studies as well. There was no evidence of increased reactogenicity after a booster dose compared with the primary vaccination, and AE rates were similar in the follow-on subjects and vaccine-naïve groups.



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The persistence of antibodies after a BEXSERO® booster have not been studied in clinical trials. Limited data are available from a study in which individuals were primed with BEXSERO®, followed for up to 2 years, and then boosted with an investigational MenABCWY vaccine, which contained all of the components of the BEXSERO® and those of a quadrivalent MenACWY vaccine. Of subjects, 45% to 100% of subjects had protective titers 1 year after MenABCWY. The extent to which these responses accurately reflect antibody persistence after a BEXSERO® booster dose is unknown, but they were included for completeness and consideration.

When trying to predict the longevity of disease protection after BEXSERO® vaccination, the respective contribution of each vaccine component must be considered. As a reminder, circulating MenB strains are highly diverse and the prevalence and expression level of each antigen varies among strains. In the US, it is predicted that 91% of circulating strains are covered by BEXSERO® and more than 47% of these strains are covered by two or more vaccine components. NHBA and fHbp are the two vaccine components that contribute the most to strain coverage (83% and 53%, respectively). Since the prevalence of each antigen is known among circulating strains and the rates at which antibodies to each component wane, it is possible to integrate these two datasets and use modeling to predict overall disease protection over time.

The results of this modeling come from the immunogenicity data from the US/Poland and Canada/Australia studies. Whichever immunogenicity data are used, overall protection is predicted to last several years after primary vaccination. This sustained effect can largely be attributed to the relatively slow waning of fHbp and NHBA antibodies, the vaccine components that contribute the most strain coverage. The more rapidly waning of PorA antibodies mentioned previously has relatively little impact on protection over time, because less than 1% of strains rely solely on this antigen for vaccine coverage.

Modeling also has been used to predict the duration of protection after a BEXSERO® booster dose. As one might expect, responses are predicted to be sustained for longer after a booster dose than after priming. It also is worth noting that these predictions of protection may be conservative because the underlying assays, hSBA and MATS, do not capture the synergistic effects between antibodies to each antigenic component.

Before summarizing, Dr. Watson reminded everyone that the immunogenicity and safety of BEXSERO® has been studied in individuals with increased risk due to underlying medical conditions. These data were presented previously by CDC in 2017. Response in children with asplenia or splenic dysfunction were similar to responses in healthy children. However, there was a trend toward reduced immune responses in children with complement deficiencies and those on eculizumab therapy.

To summarize the data, experience from large vaccine programs demonstrates the impact, field effectiveness, and tolerability of BEXSERO® in populations of all ages. Vaccine-induced antibodies persist to varying degrees for up to 7.5 years after a 2-dose primary series. The integration of immunogenicity and strain coverage data suggests the protective benefits of a 2-dose series may be sustained for several years. A single booster dose administered up to 7.5 years after priming elicits robust responses by Day 7. Higher titers have been observed after the booster dose than after priming, which is predictive of a more sustained response.



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In terms of MenB vaccination policy considerations, it remains the case that sporadic exposure actually accounts for the majority of MenB cases in the US—not outbreaks. In an outbreak where risk is substantially elevated, the priority is to quickly achieve high titers in the population at risk. In these circumstances, previously vaccinated individuals may already be protected from their primary series. In addition, these individuals can be boosted quickly within 7 days of a single dose. By contrast, vaccine-naïve individuals will need 2 or 3 doses over a period of 1 to 6 months, depending on the vaccine. Recent publications have shown that series completion in this setting can be challenging and problematic. Taken together, these considerations highlight the value of MenB vaccination at age 16 to 18 years to help provide protection during the period of increased age-based risk.

**Discussion Points**

Dr. Quash (NACI) requested clarification regarding what the primary series schedule was.

Dr. Watson indicated that in all of the studies he described, the schedule was 0,1 months with the exception of the small study, which had the MenABCWY follow-up where the initial series was 0,2 months.

**EtR and GRADE: MenB Vaccine Booster Doses for Persons at Increased Risk for Serogroup MenB Disease**

**Catherine Bozio, PhD, MPH**
**Epidemiologist, Division of Bacterial Diseases**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Bozio presented on the EtR Framework, including the grading of recommendations, assessment, development, and evaluation (GRADE) for MenB vaccine booster doses for persons at increased risk for MenB disease. She first presented some background on meningococcal disease and the WG's over-arching policy question, and then delved into the EtR criteria, including GRADE, during which she presented evidence for each criterion and provided the WG's interpretation.

Meningococcal disease is a rare but severe infection that can progress rapidly. Among persons with meningococcal disease, 1 in 10 die despite proper antibiotic treatment and 1 in 5 survivors have long-term sequelae. The incidence of meningococcal disease has been low, and rates are declining. A decline also has been seen in serogroup B disease, which accounted for approximately 40% of cases in 2017.

ACIP recommends that persons at increased risk for MenB disease receive a MenB primary series. Available evidence suggests that antibodies wane in the years following completion of the primary series, and MenB booster doses may be necessary to sustain protection. However, the goals of a booster dose differ by the reason for the increased risk. Persons with underlying conditions or microbiologists need protection for as long as the increased risk remains; whereas, among persons at-risk during an outbreak, rapid, short-term protection is prioritized.



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The WG's over-arching policy question was, "Should persons vaccinated with a MenB primary series who remain at increased risk for MenB disease receive a MenB booster dose?" The population was persons who were at increased risk due to specific underlying conditions and microbiologists, and persons during a MenB disease outbreak. The intervention was either a MenB-FHbp or MenB-4C booster dose, and the comparison was no MenB-FHbp or MenB-4C booster dose. The outcomes of interest related to the MenB booster dose were vaccine effectiveness, immunogenicity, persistence of the immune response, immune interference due to co-administration with other vaccines, and SAEs. For GRADE, there were four PICOs, two for each group at increased risk and two for each MenB vaccine.

For the evidence retrieval, a systematic review was conducted of studies in any language from PubMed, Medline, Embase, CINAHL, Cochrane, Scopus, and clinicalstrials.gov databases using the search string: "booster" AND ["serogroup B meningococcal vaccine" OR "recombinant meningococcal B vaccine" OR "MenB vaccine" OR "Bexsero" OR "MenB-4C" OR "rMenB±OMV NZ" OR "4CMenB" OR "Trumenba" OR "rLP2086" OR "Factor H binding protein vaccine" OR "FHbp"]. Efforts were made to obtain unpublished data. Studies were included that presented primary data on MenB booster doses in subjects who received a licensed MenB primary series at at least 10 years of age. An investigational combined serogroup vaccine, MenABCWY, booster dose was included as a proxy for MenB booster dose if the MenB vaccine component was identical to the licensed MenB formulation. One study with unpublished data was identified based on presentations to the WG. Additionally, 131 references were identified in the database search. After screening the title, abstract, and article, 4 studies were included in the GRADE analysis.

Short-term immunogenicity of the booster dose, persistence of the immune response to the booster dose, and SAEs from the booster dose were included in the evidence profiles. Given the differences in the populations and the goals of the booster dose, EtR was completed separately for each population at increased risk. The data reviewed as part of the GRADE analysis were included as supplementary slides, and the evidence included in the profiles is the same for both populations at increased risk.

Dr. Bozio presented EtR for persons with underlying conditions and microbiologists, starting with stating the problem. The burden of serogroup B meningococcal disease among persons at increased risk is not well-known due to limitations in national surveillance. The magnitude of increased risk in these persons can be up to 10,000-fold. Based on the population estimates for each group, these persons comprise less than 0.1% of the US population aged at least 10 years.

Regarding benefits of the MenB booster dose, no data are available on its effectiveness or duration of protection in persons with underlying conditions. Additionally, immunogenicity and antibody persistence to the MenB vaccine may differ in persons with underlying conditions. In a GSK study examining the MenB-4C primary series, the immunogenicity in children and adolescents with asplenia was similar to that in healthy persons, but was lower in persons with complement deficiencies. Further, meningococcal vaccination may confer little to no protection in persons taking eculizumab. Regarding potential harms, evaluations including more than 69,000 healthy adolescents and adults have demonstrated the safety of both MenB-FHbp and MenB-4C primary series. The undesirable effects of repeated MenB booster doses or in persons with underlying conditions have not been assessed.



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For GRADE, the WG evaluated data on the MenB-FHbp booster from one unpublished study by Pfizer. This observational study was an extension study that included participants who were previously enrolled in an RCT on the MenB primary series in four European countries. Healthy persons received the MenB-FHbp booster dose 48 months after the 2- or 3-dose MenB primary series. No data on a comparison group were available. Short-term immunogenicity, persistence of the immune response, and SAEs were outcomes of interest. As a reminder, the data reviewed for the GRADE analysis were included as supplementary slides.

For the MenB-FHbp booster dose, the WG evaluated evidence for short-term immunogenicity, persistence of the immune response, and SAEs from one observational study, though not all criteria were applicable. For all outcomes, the WG had serious concern for risk of bias, specifically selection bias. All of the subjects enrolled in the extension study related to the booster dose accounted for 14% of those who participated in the parent study. The WG downgraded for indirectness because data were available for healthy persons, but not for persons with certain underlying conditions. The WG also downgraded for imprecision because the small number of subjects resulted in wide confidence intervals regarding persistence of the immune response and may not be able to detect rare SAEs. The evidence type across these outcomes was a 4, indicating studies with important limitations, and the overall certainty of evidence was very low.

Moving onto the MenB-4C booster, data were available from three studies. The two observational studies from Nolan 2019 were both extension studies that included participants who were previously enrolled in RCTs on the MenB primary series in Australia, Canada, and Chile. Healthy persons received the MenB-4C booster dose 4 or 7.5 years following the 2-dose MenB primary series. For both studies, the comparison group was MenB vaccine-naïve subjects who received 1 MenB-4C dose. Short-term immunogenicity results were presented for each study, and data on serious adverse events from these studies were combined and analyzed as one study, as per the vaccine manufacturer.

The study from Szenborn 2018 was an RCT in the US and Poland and also was an extension study. Healthy subjects were randomized to receive a booster dose based on the primary series they received. The intervention was the MenABCWY booster dose, with MenB component identical to that of licensed product, 2 years after the primary series. The comparison group included subjects who were received the MenACWY vaccine as the primary series, but were MenB vaccine-naïve, and one MenABCWY dose. The outcomes of interest were short-term immunogenicity, persistence of the immune response, and SAEs.

For the MenB-4C booster dose, the WG evaluated evidence for short-term immunogenicity from two observational studies. The WG had serious concern for risk of bias, specifically selection bias. All of the subjects enrolled in these extension studies accounted for 41% of those who participated in the parent studies. In the Australia and Canada extension study, the racial distribution differed among those who enrolled versus those who did not enroll. The WG had no serious concerns with inconsistency, but downgraded for indirectness because data were available for healthy persons, but not for persons with certain underlying conditions. The WG had no serious concerns with imprecision, and there were no other considerations.



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Evidence also was available from one RCT, but not all criteria were applicable. The WG had no serious concerns with risk of bias, but downgraded for indirectness because data were available for healthy persons, but not for persons with certain underlying conditions. Additionally, the intervention was an investigational MenABCWY vaccine, which was used as a proxy for the MenB-4C booster. The WG also downgraded for imprecision because the confidence intervals were wide due to the small number of subjects. For persistence of the immune response, the WG evaluated the same RCT and had the same conclusions about the quality of evidence for all criteria.

For SAEs, the WG evaluated evidence from one observational study. They had serious concern for risk of bias, as previously mentioned. The WG downgraded for indirectness because data were available for healthy persons, but not for persons with certain underlying conditions. The WG also downgraded for imprecision because the number of study subjects may be too small to detect rare events. In addition, the WG evaluated the same RCT and had the same conclusions about the quality of evidence for all criteria. The evidence type across these outcomes was a 4, indicating studies with important limitations, and the overall certainty of evidence was very low.

Moving on to the additional EtR considerations, from October 2014 through July 2018, 8% of persons aged at least 10 years with specific underlying conditions in commercial claims data received at least 1 MenB dose as part of the primary series. In comparison, 26% of these patients received at least 1 MenACWY vaccine. The low uptake in this group may reflect that the target population or their providers do not value the intervention, are unaware of the need for MenB vaccination, do not feel MenB vaccination is programmatically or financially acceptable, and/or encounter barriers that limit feasibility. In a survey of provider MenB vaccination practices, 81% of pediatricians and 56% of family physicians reported recommending the MenB vaccine for children aged at least 10 years at increased risk for serogroup B meningococcal disease, which may reflect their level of acceptance, awareness, or feasibility of MenB vaccination. Regarding resource use and cost, no published cost-effectiveness analyses on the use of a MenB primary series or booster dose are available in this population. As far as feasibility, the data previously presented on MenB vaccine coverage and provider practices may signal feasibility challenges in implementing the MenB primary series recommendation. Consequently, feasibility challenges may be encountered for booster doses as well.

For this population at increased risk, serogroup B meningococcal disease is a problem of public health importance. The desirable effects of the MenB booster dose may vary in persons with underlying conditions versus healthy microbiologists. However, the undesirable effects are likely minimal, but safety data on multiple doses are not available. The intervention of the MenB booster dose is favored, but there is very low certainty of the evidence. The target population may feel uncertain that the desirable effects are large relative to undesirable effects, though there is important uncertainty in how much these persons value the main outcomes. A MenB booster dose is probably acceptable to key stakeholders, though it is uncertain whether the intervention is a reasonable and efficient allocation of resources or is feasible to implement. Although the WG did not reach a full consensus on whether to propose a recommendation for persons with underlying conditions and microbiologists, the majority of its members was in favor of proposing a MenB booster recommendation for this population.



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Moving to the EtR for persons at risk during a serogroup B meningococcal disease outbreak, starting with stating the problem, serogroup B meningococcal disease outbreaks have occurred, accounting for 7% of all serogroup B cases in the US. Most of the organization-based serogroup B outbreaks are college-based, and 11 college-based serogroup B outbreaks were reported during 2013-2018. College students are the primary group at risk for these outbreaks who may have received a MenB primary series as healthy adolescents. While evidence presented here applies for all serogroup B outbreaks, all remaining data related to outbreaks are focused on college students.

Regarding benefits and harms of the MenB booster dose, including GRADE, no data are available on its effectiveness or duration of protection in US adolescents or adults. In the 4 years following mass MenB-4C vaccination of persons aged <20 years during a regional outbreak in Canada, VE was estimated to be 79%, though the confidence interval was very wide. As far as indirect effects of the MenB vaccine, no evidence suggests that MenB vaccines reduce or prevent serogroup B meningococcal carriage, and therefore herd immunity is unlikely. Regarding potential harms, evaluations following mass vaccination campaigns during outbreaks at US universities have demonstrated the safety of the MenB primary series.

For GRADE, the WG evaluated the same data that pertained to the other population of interest. For the MenB-FHbp booster, they evaluated data from an unpublished study by Pfizer. This observational study was an extension study, in which healthy persons received the MenB-FHbp booster dose 48 months after the MenB primary series. For the MenB-FHbp booster dose, the WG evaluated evidence for all outcomes from one observational study, though not all criteria were applicable. For all outcomes, the WG had serious concern for risk of bias, for the same reason previously mentioned. The WG had no serious concerns with indirectness, but downgraded for imprecision because the small number of subjects resulted in wide confidence intervals regarding persistence of the immune response and may not be able to detect rare SAEs. The evidence type across these outcomes was a 4, indicating studies with important limitations, and the overall certainty of evidence was very low.

Moving to the MenB-4C booster, data were available from three studies, which also were evaluated for the other population of interest. The two observational studies were both extension studies. Short-term immunogenicity results were presented for each study separately, and data on SAEs were combined and analyzed as one study, as per the vaccine manufacturer.

The last study was an RCT in the US and Poland and was also an extension study. For the MenB-4C booster dose, the WG evaluated evidence for short-term immunogenicity from two observational studies. The WG had serious concern for risk of bias, for the same reason previously mentioned. They had no serious concerns with inconsistency, indirectness, or imprecision, and there were no other considerations. Evidence was available from one RCT, but not all criteria were applicable. The WG had no serious concerns with risk of bias, but downgraded for indirectness because the intervention was an investigational MenABCWY vaccine, which was used as a proxy for the MenB-4C booster. The WG also downgraded for imprecision because the confidence intervals were wide due to the small number of subjects. For persistence of the immune response, the WG evaluated the same RCT and had the same conclusions about the quality of evidence for all criteria.



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For SAEs, the WG evaluated evidence from one observational study. They had serious concern for risk of bias, as previously mentioned. The WG had no serious concerns with indirectness, but downgraded for imprecision because the number of study subjects may be too small to detect rare events. The WG also evaluated the same RCT and had the same conclusions about the quality of evidence for all criteria. The evidence type was a 3 for the RCT across the outcomes and was a 4 for the observational studies, indicating RCTs with notable limitations and observational studies with important limitations. Thus, the overall certainty of evidence was low.

In terms of the additional EtR considerations, all 11 universities that had serogroup B outbreaks implemented MenB vaccination, which demonstrates acceptability of MenB vaccination by key stakeholders. First-dose MenB vaccination coverage varied from 14% to 98% across these universities and may reflect the target population's value and acceptability of MenB vaccines; parents' acceptability and encouragement for their children to receive MenB vaccine; feasibility concerns, especially at large universities; and differences in the student population, campus culture, and perceived risk of disease.

Despite acceptability from stakeholders, MenB mass vaccination requires substantial resources. At one large university with approximately 20,000 undergraduate students, the total costs of vaccination were $1.7 million dollars, but the projected costs to achieve 100% primary series coverage were $7.7 million dollars. However, the strategy of MenB mass vaccination for outbreak response is estimated to be more cost-effective than universally vaccinating all students at college entry. Overall, the high costs incurred by universities may reflect the belief that these campaigns were a reasonable and efficient allocation of resources. Since the booster would require fewer doses than the primary series, it is anticipated that MenB booster doses will be viewed similarly.

In terms of feasibility, outbreaks require intensive coordination, significant human resources, and action among multiple stakeholders to efficiently respond within a short time. As MenB vaccines are not interchangeable, determining whether a MenB primary series was completed, the vaccine product, the date of the last dose, and ensuring availability of both MenB vaccines may impact feasibility during an outbreak. Universities have demonstrated the feasibility of conducting mass vaccination campaigns for the MenB primary series under challenging circumstances, so administering MenB booster doses is anticipated to be feasible as well.

For this population at risk during an outbreak, serogroup B meningococcal disease is a problem of public health importance. The desirable effects of the MenB booster dose may be large, with minimal undesirable effects. The intervention of the MenB booster dose is favored, but there is very low certainty of the evidence. The target population may feel that the desirable effects were large relative to undesirable effects, and there was probably variability in how much these persons value the main outcomes. The WG considered that the intervention of a MenB booster dose is acceptable to key stakeholders, a reasonable and efficient allocation of resources, and feasible to implement. Therefore, the WG proposed recommending a MenB booster dose for persons at risk during a serogroup B outbreak.

In summary, despite very low evidence quality, the majority of WG members favored MenB booster doses and proposed recommending this intervention for both populations at increased risk for serogroup B meningococcal disease.



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## WG Interpretation, Considerations for Policy Options, and Next Steps

**Sarah Mbaeyi, MD, MPH**
**CDC Lead, ACIP Meningococcal Vaccines WG**
**National Center for Immunization & Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Mbaeyi reviewed the WG's interpretation of the persistence of the immune response following a MenB vaccine primary series and immunogenicity and persistence of a MenB booster dose, discussed the WG's considerations for MenB booster doses in persons at increased risk for serogroup B meningococcal disease, and requested ACIP's feedback on potential policy options for MenB booster doses. She began with persistence of the immune response following a MenB primary series, and reviewed the data for MenB-FHbp.

To summarize data for both a 3-dose and a 2-dose MenB-FHbp primary series from baseline through 48 months post-primary series for each test strain, 2 studies measured seroprotection as the proportion of subjects who achieved an hSBA titer at or above the lower limit of quantification of the assay (either 1:8 or 1:16, depending on the strain), which is more conservative than the 1:4 threshold used in other studies presented earlier in the session. In these studies, initial antibody waning was observed 6 to 12 months following completion of the primary series, and then remained stable. Thus, the WG's interpretation was that antibodies wane by 12 months following completion of a MenB-FHbp primary series, and then remain stable for up to 4 years in healthy adolescents [Adapted from: Marshall H, Lancet Infectious Diseases 2017 and Vesikari, Vaccine 2019].

Regarding data for MenB-4C, 4 studies were conducted to assess immunogenicity and persistence to each of the 4 vaccine antigens through 7.5 years post-primary series. The WG was particularly interested in the results for FHbp and NHBA, as these antigens contribute most to strain coverage in the US. Because the study populations and time points assessed were different for the various studies, and generally speaking, antibody waning patterns for the 4 antigens were not consistent, Dr. Mbaeyi walked through each study in more detail.

A study in UK adolescents demonstrated a high proportion of subjects with seroprotection at 11 months following completion of the primary series. However, baseline antibody titers were high in this study, reaching nearly 70% for FHbp, and no data were available for NHBA. In a study from Chile, evidence of persistence through 18 to 23 months was observed, though subjects in this study also had elevated baseline titers. Although a substantial proportion remained seroprotected by 7.5 years, this proportion was not significantly different than baseline titers for most of the antigens. The WG felt that the US/Poland study and the Canada/Australia study were most representative of the US context.

In the US/Poland study, antibody waning was evident by 2 years following completion of the primary series, though confidence intervals were wide, with relatively consistent results by 4 years in the Canada/Australia study for most antigens. Persistence following a MenB-4C primary series was difficult to generalize due to the heterogenous results by vaccine antigens, different time points assessed in different studies, elevated baseline titers in two studies, and limited persistence data for NHBA. In light of this, the WG's interpretation was that antibodies wane by 2 years following the primary series in healthy adolescents and adults, though they may wane earlier [Adapted from Read RC, Vaccine 2017; Block SL, Vaccine 2015; Szenborn L, Pediatr Infect Dis J. 2018; Perrett KP, Vaccine 2015; Nolan T, Vaccine 2019; Santolaya ME,



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Lancet 2012; Watson PS, Expert Review of Vaccines 2019, and results on clinicaltrials.gov; * hSBA titer of 1:5 used in US/Poland study].

In summary, given the variable rate of waning between vaccine types and between studies, antibody persistence following a MenB primary series could not be generalized. It also must be noted that the two vaccines are completely different, and evaluations of immunogenicity and persistence were conducted using different strains and immunologic endpoints, and thus cannot be directly compared. However, the WG felt that by 1 to 2 years following a MenB primary series, booster vaccination is indicated for persons who remain at increased risk.

Regarding immunogenicity and persistence of a MenB booster dose starting with MenB-FHbp, immunogenicity and persistence of a booster dose 4 years after completion of either a 2 or 3 dose primary series demonstrates a robust immune response at 1 month with gradual waning and evidence of persistence through 26 months post-booster dose. Thus, the WG's assessment was that the immune response to a MenB-FHbp booster dose persists for at least 2 years in healthy adolescents, and given the gradual antibody decay pattern, may last longer [Adapted from Pfizer data presented to ACIP meningococcal WG].

For MenB-4C, regardless of timing since completion of a MenB-4C primary series (whether 2, 4, or 7.5 years), a robust immune response was demonstrated 1 month post-booster. No studies assessed persistence of a MenB-4C booster dose. However, following a MenABCWY booster dose in the US/Poland study, antibody persistence was observed through 12 months post-booster. Thus, the interpretation of the WG was that the immune response to a MenB-4C booster dose likely persists for several years in healthy adolescents and adults. This interpretation was primarily derived through demonstration of good persistence of a MenABCWY booster dose through 12 months and modeled data presented earlier in this session by GSK suggesting persistence for several years. However, no further precision in the estimate was possible due to the lack of observed data [Adapted from Szenborn L, Pediatr Infect Dis J. 2018; Nolan T, Vaccine 2019; Watson PS, Expert Review of Vaccines 2019;* hSBA titer of 1:5 used in US/Poland study].

To summarize, a MenB booster dose elicits a strong immune response, and the persistence appears to exceed that of a MenB primary series. Thus, the WG's interpretation was that antibody persistence of a MenB booster dose is likely at least 2-3 years, and may be longer, in healthy adolescents and adults.

To summarize the WG's deliberations for MenB booster doses in persons at increased risk, Dr. Mbaeyi first explained why the WG is reviewing policy considerations for MenB booster doses at this time. ACIP recommended a MenB primary series for persons at increased risk 4 years ago during the February 2015 meeting. Starting in late 2018, several cases of serogroup B meningococcal disease were reported in fully vaccinated people, both in healthy persons and those with underlying conditions. Strain coverage analysis is still ongoing to assess whether these cases should have been averted through vaccination. Regardless, the WG expects future breakthrough cases to occur, and thus felt it was time to start considering MenB booster doses. In addition, serogroup B outbreaks among college students continue to occur. As MenB vaccination coverage in healthy adolescents increases under the Category B recommendation, an increasing number of vaccinated college students will be exposed during an outbreak. Finally, both vaccine manufacturers have indicated that no further data are forthcoming. Additional data on effectiveness and duration of protection may take years to generate. Thus, the WG moved forward on reviewing data on the persistence of the immune response following a MenB primary series, and immunogenicity and persistence of a MenB booster dose. The WG



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did not reach a consensus on either the need for or timing of MenB booster doses. A minority of WG members felt there was insufficient evidence on safety and efficacy of MenB booster doses to inform policy options. However, the following represents the views of the majority of WG members.

In terms of the need for MenB booster doses, the WG's primary consideration was that meningococcal disease is a devastating infection and the groups at increased risk represent small, targeted populations. Available evidence suggests waning of the primary series, and a booster dose elicits a robust immune response. However, this is based on hSBA titers, which is the serologic correlate of protection, but may not accurately represent the level of expected clinical protection. In summary, the WG felt that MenB booster vaccination is necessary to sustain protection in persons who remain at increased risk.

Studies reviewed by the WG indicate antibody waning by 1-2 years following the primary series, and persistence of a booster dose for at least 2 years and likely longer. However, immunogenicity and persistence of MenB vaccination may be limited in persons with underlying conditions, especially those with complement deficiency or complement inhibitor use. Thus, the WG suggested that a MenB booster dose is indicated at 1 year following completion of the primary series. Greater persistence is expected after the booster dose, and thus, a longer interval for repeat booster doses may be considered. Clinical trials and other observational studies have demonstrated the safety of the MenB primary series. Limited data are available on booster doses, though no SAEs have been reported. There are no data on safety in persons with underlying conditions, and no data on repeat booster doses. Despite this, given the serious nature of meningococcal disease, the WG felt that the potential benefits of MenB booster vaccination outweigh potential risks in this population.

The WG also discussed programmatic considerations for MenB booster doses. While harmonization with MenACWY is desired, the WG felt that the data do not support a 5-year interval for MenB booster doses, and thus, harmonization is not the main priority. Additionally, the WG felt that the booster dose recommendations for MenB-FHbp and MenB-4C should be harmonized to minimize unnecessary complexity in booster dose schedules. Outbreak situations come with additional challenges, and booster dose eligibility may be difficult to rapidly determine. Additional clinical guidance, such as updated language in CDC's outbreak guidance, will be necessary to facilitate booster dose implementation.

Based on these deliberations, the WG considered potential MenB booster policy options for persons at increased risk. In persons at increased risk due to certain underlying conditions or occupational exposure, the WG felt that the available data supported an initial 1 year booster dose followed by repeat booster doses every 2-3 years. This conservative approach was felt to be reasonable in order to maximize protection in persons in whom immunogenicity and persistence may be reduced, or in microbiologists who may experience increased exposure. The WG also felt that allowing a flexible range of every 2-3 years would allow for some harmonization for meningococcal booster doses, as both a MenACWY and MenB booster dose could be given together every other time, which may reduce missed opportunities for vaccination. However, there are some potential downsides to this more complicated schedule, which may be more conservative than necessary.



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The WG also considered a standard interval such as every 2 or 3 years, as it is more straightforward and prescriptive, but WG members felt that this may leave the target groups with insufficient protection for greater periods of time. During serogroup B outbreaks, the majority of WG members favored a booster dose if it has been at least 6 months since completion of the primary series in order to boost immunity prior to antibody waning, thus maximizing individual protection during a short-term period of increased exposure. However, this is a more conservative approach than that proposed for other persons at increased risk, without substantial evidence to support this distinction. Additionally, a 6 month interval may send an inaccurate message on duration of protection of MenB vaccines, leading to reduced vaccine confidence. Thus, a 1 year interval also was considered, as most people are expected to have protective antibodies through 1 year post-primary series, though there may be some who do not. Additionally, a minimum 1 year interval would be consistent with the proposed booster interval for other groups at increased risk. Regardless, the WG favored flexibility given the unique circumstances of each outbreak.

Given these considerations, the WG requested ACIP's feedback on these potential policy options:

- For persons with complement deficiency, complement inhibitor use, asplenia or microbiologists, a MenB booster dose 1 year following completion of a MenB primary series, followed by MenB booster doses every 2-3 years thereafter, for as long as increased risk remains.

- For persons at increased risk during an outbreak, a one-time MenB booster dose is recommended if it has been ≥1 year since completion of a MenB primary series. A booster dose interval of ≥6 months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk.

The WG expressed interest in hearing ACIP's feedback on the WG's interpretation for the need and timing of booster doses, including whether the booster dose interval should be the same for both vaccines and whether there were any additional data ACIP would like to see. Based on ACIP's feedback, the WG planned to present policy options for a vote during an upcoming ACIP meeting.

## Discussion Points

Dr Talbot asked whether both of these vaccines are T-cell independent; that is, just because the antibodies wane, does that mean that there is no T-cell response or does T-cell response take too long? In addition, it appeared that at least 1 antigen was similar between the two vaccines. If so, she wondered if a trial could be conducted giving the alternate vaccine as a booster. She was trying to visualize a college campus trying to purchase vaccine and vaccinate, and trying to figure out which vaccines they had previously.

Dr. Stephens indicated that these vaccines do induce some memory response, which is what the booster is showing. There is a feeling that memory alone will not protect against meningococcal disease because of the short incubation period within 7 to 10 days of acquisition.

Dr. Mbaeyi indicated that both vaccines contain fHbp. One of the major challenges to feasibility is that the vaccines are not interchangeable. The WG recognizes that this is going to be one of the major challenges, and it is a major challenge for the primary series as well.



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Dr. Szilagyi said he supported the WG suggestions. For patients with complement deficiencies or asplenia, data were presented about “values” based on the low vaccination rate. However, he suggested that those were not really data about values. Most of these patients are also taken care of by pediatric subspecialists. Data also were presented that 81% of pediatricians favor vaccinating these patients. He thought this was more of a rollout or lack of information rather than a concern about values.

Dr. Atmar expressed concern about the booster data in that the intervals of when the boosters have been given were longer, at least for the first vaccine discussed, than what was proposed. At least with other vaccines, the interval of boosting can affect the magnitude of response. The concern is a reasonable one, and it sounded like they would have to make a decision without a lot of data. He would be interested in knowing whether any additional information would be available by June about apparent vaccine failures in terms of the strain and duration of time from completion of primary series to infection, in order to get some idea of when these failures occurred and if the proposed intervals make sense in light of those kinds of data.

Dr. Mbaeyi indicated that the WG does anticipate having more information available in the coming months and could present an update. They wanted to at least signal this issue to ACIP, though they did not have all of the information yet related to the strain coverage, underlying conditions, et cetera. It is something the WG can prepare.

Dr. O’Leary (PIDS) said his understanding was that serogroup B is not usually the issue for immunocompromised patients, and asked what the burden of disease is in that population in the last several years.

Dr. Mbaeyi replied that they did not present these data because they do not have great information at this point. Some of this information is collected historically through ABCs, which represents less than 15% of the population. Meningococcal disease is so rare right now that it is not going to be very representative and is a small number. Some additional information has been collected through enhanced meningococcal disease surveillance for the past couple of years. Through more in-depth chart reviews for ABCs, it has been observed that few patients report having complement deficiency tested for, let alone a diagnosis. Thus, they are not confident that this information is being captured through the surveillance mechanisms. There just is not a great estimate on the number of cases and their serogroup distribution at this time.

Dr. Walter wondered in an outbreak situation under what conditions a 6-month interval would be utilized versus 1 year and how that would play out in the outbreak by public health officials.

Dr. Moore responded that it is known that this vaccine has less impact on nasal carriage than MenACWY does, and there has been evidence of breakthrough disease occurring in people after mass vaccination on a college campus. One of the outbreaks included a case and a visitor that occurred after everyone else was vaccinated because the strain was still circulating. The concern was for an outbreak starting at the beginning of a school year among a population who is 10 or 11 months out from their primary series and whose increased risk of exposure may occur throughout the entire school year, as opposed to an outbreak identified at the end of a school year right before everyone disperses. There are also questions about how easily records can be obtained, and how strict they want to be about a 1-year interval. It was the incredibly specific practical operational considerations that could come into play that might result in a campus opting to conduct only one mass vaccination campaign. That is the reason that it says it should be considered by public health officials as opposed to individual clinicians.



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Dr. Zahn (NACCHO) pointed out that while thinking through how to vaccinate thousands of students in a school and figuring out who should receive a booster when there has been a potential exposure is complicated. However, it already is pretty complicated. Either they vaccinate everyone and inadvertently vaccinate some people with the wrong booster, or they get aggressive in making sure it is exactly correct and will vaccinate a lot less because they will not get their vaccination schedule.

Dr. Maldonado (AAP) pointed out that AAP has struggled with the Category B recommendation as it is for healthy children. In terms of persons at increased risk during an outbreak, this puts healthy people into an at-risk group. That is a huge step and raised questions about how those risk groups will be defined. Do they fall under risk only during outbreaks? If they are backing that definition out, does that mean everybody should be considered at risk if they are going to college? She thought they already had dealt with that issue in terms of the very small numbers of cases in that age group, half of whom are not even in college. She emphasized that this needs to be very clearly defined, because pediatricians are struggling with this. While 7% coverage was mentioned for the first category at risk, she wondered about the percentage of coverage for persons at increased risk during an outbreak or in healthy children otherwise. Following up on the previous question, it seemed that if someone knows they have been immunized, they should get a booster during an outbreak. It was not clear to her how they were going to differentiate this, especially in the midst of a large outbreak.

Dr. Mbaeyi indicated that the coverage data based on NIS-Teen suggest that about 14.5% of 17 year olds have received at least 1 dose of MenB vaccine. There is no information from that survey regarding series completion, but other sources of data suggest that 50% or less so far have actually completed a series who have started it. It is low, but has been steadily increasing since the recommendation was made. They do not have any information on coverage specifically among college students. They expect that it is probably higher than for the general adolescent population. What they mean for this group is people who have been identified by public health officials to be in the at-risk group during an outbreak. In most of the university outbreaks that have occurred so far, it has been all undergraduate students. Those are decisions that are not part of the ACIP language. Public health officials make the determination of what groups are at-risk during an outbreak, then vaccination recommendations are made and there is outbreak guidance.

Dr. Messonnier indicated that a representative from AAP is on the WG. Perhaps AAP could help CDC work offline through how they might suggest addressing this. The clinical difficulty is clearly recognized, but there also is the issue regarding the data on waning immunity.

Dr. Bernstein asked whether there are any data about the use of vaccine type. Given that the vaccines are not interchangeable, he wondered what data colleges are collecting in terms of the specific products that have been received by their students.

Dr. Mbaeyi indicated that what they have heard from their colleagues in college health, including those on the WG, is that a lot of colleges do not have this information readily at their disposal. MenB vaccination is not mandated by most universities at this time, so there is very little record-keeping and it is a challenge during an outbreak to know vaccine status. That is true even for the primary series.



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Dr. Bernstein said he understood that a growing number of colleges are requiring MenB vaccine, and he wondered whether it should be more explicit in terms of which product is being received. He also understood that an increasing number of camps are requiring receipt of MenB vaccine before attending camp, beginning at the age of 10.

Dr. Even (ACHA) confirmed that it is true that there is not a good record. Very few schools require MenB vaccines. They receive vaccination records for students, so that information is known. However, the students do not know what they have had. The records are typically in a scanned database or otherwise not easily accessible when an outbreak occurs. There is variability of entering students in terms of MenB vaccine, but there are definitely more entering students who have been vaccinated than before. Knowing that a campus may experience an outbreak at some later point and since immunity wanes, the outbreak recommendation is still the strongest one. The ability to mobilize is important even though it is so difficult, but it happens so infrequently that having public health recommendations to identify the smallest group at the earliest opportunity to begin vaccination is feasible. In a prolonged outbreak, there are really just 2 months in which the 6-month parameter would fall, June and July. Otherwise, it would be during the months classes are in session.

## Zoster Vaccines

### Introduction

**Kelly Moore, MD, MPH**
**ACIP Chair, Zoster WG**
**Vanderbilt University School of Medicine**

Dr. Moore reminded everyone that in October 2017, ACIP made the following recommendations:

1) Recombinant zoster vaccine (RZV, SHINGRIX) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years.

2) RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL, [Zostavax]).

3) RZV is preferred over ZVL for the prevention of herpes zoster and related complications.

Its publication in 2018 was a supplement to the existing recommendations for the use of ZVL in immunocompetent adults aged ≥60 years [Dooling et al. *MMWR* Jan 25, 2018].

Since June 2018, there have been 6 WG meetings during which the following topics were discussed:

- ❑ Burden and pathophysiology of herpes zoster in immunocompromised persons
- ❑ RZV vaccine performance in immunocompromised persons
- ❑ Post-licensure safety and uptake monitoring of RZV



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Dr. Moore indicated that the presentations for the February 2019 session would focus on the preliminary results of RZV safety and uptake.

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

**Tom Shimabukuro, MD, MPH, MBA**
**Immunization Safety Office**
**Centers for Disease Control and Prevention**

Dr. Shimabukuro reminded everyone that RZV is an adjuvanted glycoprotein vaccine that was reactogenic in clinical trials, with rates of SAEs similar between RZV and placebo groups. He also clarified a few of the terms that are used in the context of vaccine safety monitoring and research, which are shown in the following table:

**Vaccine Safety Monitoring and Research Terms**

| Term | Explanation |
|---|---|
| Adverse event | An adverse medical or health event following vaccination (a temporally associated event), which may or may not be related to vaccination (i.e., coincidental). |
| Adverse reaction | An adverse health event following vaccination where substantial evidence exists to suggest the event is causally related to vaccination. |
| MedDRA | A clinically-validated international medical terminology used by regulatory authorities to describe health outcomes and events. |
| ICD-10 and 9 | A system used by physicians and other healthcare providers to classify and code diagnoses, symptoms and procedures associated with healthcare. |
| Automated analysis | Analysis on administrative or claims data or non-chart/health record confirmed data. |
| Chart confirmed/medical record confirmed case | A case where review of medical charts and records by physicians or medical personnel confirms the diagnosis as valid and with accurate onset relative to timing of vaccination. |
| Incident case | A new case occurring for the first time ever or during a specified time period. |
| Historical/prevalent case | A case that has been diagnosed in the past prior to vaccination or prior the study period that has become part of the patient's past medical history and therefore is not new. |
| Biologically plausible risk interval | The time interval following vaccination where it is biologically plausible, based on the best available science, that an observed adverse event could be related to vaccination. |
| Statistical signal | A finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold; a statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn. |

This session focused on post-licensure safety monitoring of RZV during initial uptake period based on data from Vaccine Adverse Event Reporting System (VAERS) monitoring and preliminary results from the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA).

VAERS is a national passive surveillance system for AE that is co-managed by the CDC and FDA. The strengths of VAERS are that it can rapidly detect safety signals and can detect rare AEs. It is subject to the limitations of spontaneous reporting in general. Reports of AEs are received in VAERS, some of which may be true AEs and some of which may be coincidental events and not related to vaccination. All reports are accepted without judging causality or the seriousness of the event. Because of the limitations, generally causality cannot be assessed from VAERS data as it is a hypothesis generating system. During this session, Dr. Shimabukuro presented an update on the publication titled *Postlicensure Safety and Surveillance of Recombinant Zoster Vaccine (Shingrix)—United States, October 2017-June 2018*.

The descriptive analysis Dr. Shimabukuro presented included all RZV reports received from October 20, 2017 through December 31, 2018. Reporting rates were calculated based on doses distributed in the US market. CDC's colleagues at FDA conducted an Empirical Bayesian (EB) data mining to detect disproportional reporting for VAE pairings. Reports were clinically reviewed, including medical records when available, for 22 pre-specified outcomes listed here alphabetically:



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**Pre-Specified Outcomes** (based on pre-licensure trials and ZVL reports)

- Acute myocardial infarction
- Amyotrophic lateral sclerosis
- Anaphylaxis
- Autoimmune disorders
- Autoimmune vasculitis
- Bell's Palsy
- Co-administration with another adjuvanted vaccine
- Death
- Gout
- Guillain-Barré syndrome
- Herpes zoster
- Idiopathic thrombocytopenia
- Inflammatory eye disease
- Lymphadenitis
- Meningitis
- Neuropathy
- Optic ischemic neuropathy
- Osteonecrosis
- Post-herpetic neuralgia
- Seizures / convulsions
- Stroke / CVA
- Supraventricular tachyarrhythmias

During the analytic period, 14,381 reports were received following RZV. Of those, 97.6% were classified as non-serious. Based on 8.59 million doses distributed during this period, the reporting rate for all reports was 167 per 100,000 doses distributed and 4 per 100,000 for serious reports. Those rates are similar to what is observed for other vaccines administered in this age group. A serious report is defined by the Code of Federal Regulations (CFR) as "death, life-threatening illness, hospitalization, or prolongation of hospitalization or permanent disability." Again, these are reports occurring in temporal association and no judgement is being made on causality.

Systemic signs and symptoms and injection site reactions were the most commonly reported AEs. No unexpected patterns were detected by physician reviewers of reports of the 22 pre-specified outcomes. EB data mining detected one finding, which was a "product administered to patient of inappropriate age" when looking at individuals aged 19-44.9 years old, an age group for which RZV is not approved.

In summary, RZV post-licensure safety monitoring findings in VAERS are generally consistent with the safety profile observed in pre-licensure clinical trials. Self-limited systemic signs and symptoms and injection site reactions were the most commonly reported AEs. SAEs were rarely reported at 2.4% of reports, which is similar to other vaccines given in the same age group. There were no EB data mining findings for any RZV-AE pairings except for "product administered to patient of inappropriate age."

Moving to the VSD RCA for RZV, the VSD is a collaboration between CDC and several integrated healthcare plans. It is a large linked database that is used for surveillance and research. Vaccination records, health outcomes, and patient characteristics are linked by unique patient IDs. RCA is a powerful and sophisticated tool for near real-time vaccine-safety monitoring. It is a surveillance activity, which is not the same as an epidemiologic study. It requires careful thought and customization in the design, set-up, and interpretation. It employs an automated analysis that uses ICD-coded diagnoses from claims data. It is designed to detect statistical signals (e.g., values above specified statistical thresholds). Not all statistical signals represent a true increase in a risk for an AE. When a statistical signal occurs, CDC conducts a series of evaluations using traditional epidemiologic methods. Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment.



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The primary analysis for RZV RCA is a historical comparator design. Monthly near real-time sequential monitoring of pre-specified outcomes is done. There will be 18 planned monthly analyses, which began at 6 months after January 2018, with an 18-week data lag. This data lag accounts for the risk windows plus time to let the claims data settle and mature. As mentioned, this is an automated analysis using ICD-10 or ICD-9 codes depending upon the dates. The third analysis has been completed, and the test statistic is an adjusted likelihood ratio test. Observed events are compared in one risk window for current recipients to what is expected for the historical ZVL recipients from 2013-2017. There are 10 high priority pre-specific RZV RCA outcomes:

| High Priority Pre-Specified Outcomes* | Risk Interval (Days) |
|---|---|
| Acute myocardial infarction | 1-42 |
| Anaphylaxis | 0-1 |
| Bell's palsy | 1-42 |
| Convulsion | 1-42 |
| Giant cell arteritis | 1-42 |
| Guillain-Barré syndrome | 1-42 |
| Optic ischemic neuropathy | 1-42 |
| Polymyalgia rheumatica | 1-42 |
| Stroke | 1-42 |
| Supraventricular tachycardia | 1-42 |
| *Footnote: gout, keratitis, local reactions, non-specific adverse effects, pneumonia, systemic reactions, uveitis and retinitis, and zoster ocular disease | |

There also are other outcomes for descriptive analysis only, including those listed in the footnote of the table. These outcomes are based on outcomes of historical concern for vaccine safety, plus outcomes that were described in the pre-licensure submissions to FDA, plus outcomes monitored for ZOSTAVAX® as well.

Secondary analyses for RZV RCA in the VSD uses 2 concurrent comparators, including individuals who: 1) had an ICD-10 coded well-visit during the RZV uptake period; or 2) received some other vaccine (e.g., for pneumonia, Td, Tdap, IIV) during the RZV uptake period. For the third analysis, roughly 106,000 doses were administered through August 2018. The follow-up for outcomes is through December 2018. For 9 of the high priority outcomes, there was no preliminary statistical signal (e.g., no evidence of an increased risk). There was one preliminary statistical signal for Guillain-Barré Syndrome (GBS), which was detected initially during the second analysis. In the third analysis, there were 4 observed GBS events in the risk interval compared to 0.8 expected events for a relative risk of 5.06. The likelihood exceeded the critical value, so this is a statistical signal. When there is a statistical signal, one of the first steps is to conduct a [chart review]. One of the major activities in the RCA is to review those cases in the VSD. Here is a table with a short chart review of automated cases:



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**Signal Assessment:**
**Short Chart Review of Automated Cases**

| Description of the four ICD-10 coded cases of GBS | Adjudication |
|---|---|
| 65 y/o with a history of GBS diagnosed years prior, no recurrence or exacerbation after RZV | Historical case, not a true incident ( i.e., 'new') case |
| 72 y/o with a history of GBS diagnosed years prior, no recurrence or exacerbation after RZV | Historical case, not a true incident ( i.e., 'new') case |
| 68 y/o female who received concurrent PCV13 and had ZVL 7 years prior, had GBS symptom onset 13 days post-vaccination and was hospitalized 15 days post-vaccination | Short chart review confirmed case, Brighton Criteria level 2* |
| 59 y/o female who received concurrent hepatitis B vaccination had chart documented GBS onset no later than 1 day post-vaccination, but sx may have started prior to vaccination. Patient had some signs and sx in the month prior and in the days leading up to vaccination suggestive of an infection (i.e., vague sx and respiratory and GI sx prior to GBS admission) | Short chart review confirmed case, Brighton Criteria level 1*, actual GBS symptom onset uncertain |

*Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

The short chart review is not the full clinical narrative. It is basically an abbreviated review in which key data are extracted to allow for a rapid assessment of the cases. The first two cases are individuals with a history of GBS diagnosed years prior. There is no recurrence or exacerbation after RZV. An incident case is a case that is either new in general, or new onset during the specified time period. These cases were diagnosed years in the past and then appeared because there was some type of health encounter after vaccination during which this was captured in the VSD database.

The third case was a 68-year old female who received concurrent PCV13 and had ZVL 7 years prior, with GBS onset 13 days post-vaccination and was hospitalized 15 days post-vaccination. The short chart review confirmed this case, which was classified as Brighton Criteria Level 2. Brighton is a standardized case definition used in vaccine safety, with 1 being the highest level of diagnostic certainty. The fourth case was a 59-year old female who received concurrent HepB vaccination and had chart documented GBS onset no later than 1 day post-vaccination. The symptoms may have started prior to vaccination, as the patient had some signs and symptoms in the month prior and days leading up to vaccination suggestive of an infection, such as respiratory and gastrointestinal (GI) symptoms. This was adjudicated as a short chart review confirmed case, Brighton Criteria Level 1, with actual [timing of] GBS onset symptoms being uncertain.

After the initial chart review of these cases, 2 were ruled out, 1 appeared to be a confirmed case in the risk window, and the last case was confirmed but questionable because GBS symptom onset is uncertain. Even if it was 1 day, that is a pretty short onset after an exposure for GBS. It is important to note that a case in the risk window does not equate to a causally associated case. It means there was a vaccination and then a case in the risk window that fell within this window of biological plausibility.

In summary, after the third analysis of 18 planned analyses, there have been 106,121 doses of RZV administered in VSD from January-August 2018. There is no evidence of increased risk for any of the pre-specified outcomes except GBS in the automated ICD-10/9 analyses. A statistical signal for GBS was detected in the primary analysis and consistently elevated relative risks across other comparators: RR=5.06 for ZVL comparators, RR=2.95 for well-visit comparators, and RR=3.25 for received some other vaccine comparators. Full clinician narratives have been requested for review for the 2 valid GBS cases (i.e., symptoms and onset, physical findings,



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relevant testing, physician assessments, et cetera). There also are plans to chart review the GBS cases following ZVL in the historical comparator group.

Part of the signal assessment was to re-review the VAERS reports for GBS. There were 35 reports that had a MedDRA Preferred Term (PT) for GBS assigned. Upon review, 19 case reports met Brighton criteria for GBS level 1 (1), level 2 (15), or level 3 (3). Of the case reports, 6 did not meet Brighton criteria or had insufficient information, but were explicitly described as physician-diagnosed GBS. The remaining 10 reports did not meet Brighton criteria and were not physician diagnosed. Of the 25 cases that met Brighton criteria levels 1-3 or were physician diagnosed, 24 had symptom onset within a 0-42 day risk window following RZV. That translates into a reporting rate of 2.8 GBS cases per million RZV doses distributed.

Proportional Reporting Ratio (PRR) analyses also were performed that did not detect any disproportional reporting for RZV-GBS when either ZVL, IIV, or PPSV23 vaccines were used as comparators. This is similar to FDA's EB data mining in terms of looking at disproportionality or disproportional reporting. Looking at comparator groups of specific vaccines, no disproportional reporting was detected for RZV GBS when either ZVL, IIV, or PPSV23 were used as comparators.

In terms of next steps, FDA is exploring options for an analysis of GBS following RZV in the Center for Medicare and Medicaid Services (CMS) database. CDC will continue to monitor this preliminary VSD RCA statistical signal for GBS following RZV by tracking additional counts of GBS, and will continue enhanced monitoring for RZV in VAERS to include clinical review of all GBS reports following RZV. In terms of the timeline, this signal was detected in November 2018 and rapidly evaluated. Colleagues in the immunization program and FDA were notified, and the ACIP Zoster WG was engaged and heard presentations twice in February 2019, and during this meeting.

In closing, this is still the initial uptake period for RZV and early in the post-licensure monitoring process. Overall, the safety profile of RZV is consistent with pre-licensure clinical trial data. The VAERS data indicate that systemic and local reactions are commonly reported, with no findings of disproportional reporting for GBS or any other pre-specified outcomes. A limited number of doses have been administered in the VSD at this point. A statistical signal was detected in the VSD RCA based on a small number of GBS cases using automated data. There are currently 4 ICD-10 coded GBS cases. Upon review, there is 1 confirmed case in the risk interval, 1 confirmed case with questionable onset timing and possible infectious trigger, and 2 historical cases that have been ruled out. The post-licensure safety monitoring systems and surveillance methods are designed to be rapid, sensitive, and allow for quick assessment of statistical signals. The policy is to be transparent and communicate vaccine safety information in a timely manner. These preliminary data are insufficient to conclude that a safety problem exists for GBS, but further evaluation and continued vigilance are warranted. The RZV-GBS statistical signal detection and assessment demonstrates the robust and responsive US vaccine safety monitoring system in action, working as intended. CDC will update the Zoster WG as information comes available and will be available to update ACIP as requested.



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## Herpes Zoster Vaccines Update

**Dr. Kathleen Dooling MD MPH**
**Herpes Zoster Work Group Liaison**
**National Center for Immunization and Respiratory Diseases**
**Centers for Disease Control and Prevention**

Dr. Dooling reminded everyone that during the June 2018 ACIP meeting, she showed a table summarizing CDC's plan for monitoring RZV coverage, uptake, and 2-dose series completion. During this meeting, she planned to present preliminary data from 3 of those systems including: 1) data from the Immunization Information Systems (IIS) in 6 jurisdictions; 2) vaccine administrative claims data from Medicare beneficiaries and CMS; and 3) VSD data (presented by Dr. Dr. Shimabukuro).

In terms of the preliminary results for RZV uptake in IIS, the observation period for this analysis was October 17, 2017 through December 31, 2018. Data were contributed from 6 jurisdictions: Minnesota, Michigan, Oregon, North Dakota, Wisconsin, and New York City. The inclusion criteria for analysis were age ≥50 years and a record of at least one RZV vaccination dose within the IIS during the observation period. Data were pulled between February 7-14, 2019 and are dynamic; that is, reports may still be received within the system. The analysis provided by IIS Sentinel Site awardees in each jurisdiction. A total of 751,405 doses of RZV were reported in IIS during the study timeframe. Of those, 21% (155,594) of those doses were administered to persons 50-59 years of age, 41% (304,365) were received by persons 60-69 years of age, 28% (210,487) were received by people 70-79 years of age, and 11% (80,959) were received by individuals 80 years of age and older.

Looking at the number of RZV doses recorded in IIS by month from October 2017 through December 2018, the doses administered increased sharply in March and April. After that, between approximately 60,000 and 100,000 doses were administered each month in these settings. Regarding the proportion of RZV administered in pharmacy versus non-pharmacy settings, a minority (39%) of people in their 50s were vaccinated in a pharmacy. That proportion increases to 54% for people in their 60s, and to a full 70% of people in their 70s and 80s. It should be noted that these estimates varied substantially by state, ranging from 28% overall in one jurisdiction to 85% in another. However, in all jurisdictions older age was associated with increased chance of being vaccinated in a pharmacy setting.

With regard to preliminary results for RZV uptake among Medicare beneficiaries, similar to the previous analysis, the observation period was October 1, 2017 through December 31, 2018. The inclusion criteria for beneficiaries was that they had to age into Medicare by October 2017 and that they were continuously enrolled in Medicare Part D from October 2017 to vaccination date. Data were pulled during February 13-14, 2019 and the data are dynamic. This analysis was provided by Acumen, LLC through a collaboration with FDA, CMS, and CDC.

In terms of the characteristics of Medicare beneficiaries who received at least one dose of RZV, in this analysis over 1.5 million beneficiaries were vaccinated with RZV under Medicare Part D. The mean age was 75 years, the vast majority were younger than 80 years of age, and 59% were female.



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Regarding the number of ZVL and RZV vaccinated Medicare beneficiaries by month during the analysis time period, ZVL administration declined toward the end of 2017. The first dose of RZV began to rise steeply in March and April, with the second dose increasing 3 months later in June and July. As mentioned, just over 1.5 million beneficiaries received the first dose and over 750,000 received a second dose during the same time period.

The second dose of RZV is recommended 2 to 6 months following the first dose. This table shows RZV series completion and timing of the second dose for Medicare beneficiaries vaccinated in 2018:

| Month of First RZV Vaccination | Number of Beneficiaries With First Vaccination | Proportion of Vaccinated Beneficiaries Who Have Received Second Vaccination (Cumulative Time Since Vaccination) | | | |
|---|---|---|---|---|---|
| | | 2nd month (60 Days) | 3rd month (90 Days) | 6th month (180 Days) | 9th month (270 Days) |
| Jan 2018 | 11,217 | 8% | 47% | **78%** | 86% |
| Feb 2018 | 32,412 | 7% | 43% | **77%** | 85% |
| Mar 2018 | 89,471 | 4% | 37% | **76%** | |
| Apr 2018 | 196,464 | 3% | 31% | **77%** | |
| May 2018 | 202,537 | 2% | 33% | **76%** | |
| Jun 2018 | 153,839 | 3% | 35% | | |
| Jul 2018 | 135,398 | 3% | 32% | | |
| Aug 2018 | 175,008 | 2% | 29% | | |
| Sep 2018 | 188,710 | 3% | | | |
| Oct 2018 | 149,585 | | | | |
| Nov 2018 | 103,033 | | | | |
| Dec 2018 | 87,037 | | | | |

As reflected in the table in the highlighted box, at least 75% of beneficiaries for whom at least 6 months had elapsed received the second dose. This is strong series completion despite challenge with shortages of RZV. It also must be taken into account that these Medicare beneficiaries are highly motivated vaccine seekers who received the first dose within the first 5 months of CDC recommendations when the vaccine supply was just becoming available.

Moving on to RZV status, GSK plans to manage RZV supply by continuing order limits during 2019. Therefore, providers will continue to experience shipping delays. In response to demand for the vaccine during 2018, GSK has taken two steps. The first was to increase the number of doses available for the US market in the second half of 2018. The second was to plan for more frequent, higher volume shipments to increase supply and deliver doses more consistently for all customer types during 2019.

In conclusion, the following points summarize the HZ WG discussions. RZV demand continues to outpace supply. Approximately 8.59 million doses were distributed in the US through 2018, with a greater number of doses expected in 2019. The 2-dose RZV series completion within 6 months was >75% among Medicare beneficiaries. While this is strong series completion, it is important to continue monitoring as the supply stabilizes and immunization providers can expand their reach beyond the most highly motivated vaccinees. A preliminary statistical signal for GBS among RZV recipients has been observed based on 4 claims in administrative data. Because claims data are not medical records, they require verification and investigation. In fact, in a brief chart review, it was confirmed that onset of GBS predated receipt of RZV in 2 cases. The HZ WG agreed that there is insufficient evidence at this time to support a change in



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policy or practice. More investigation is required to determine whether this statistical signal is or is not a safety problem. In order to do that, clinical validation is necessary and is underway. Evaluation also is needed of near real-time data in multiple systems, which also is underway. The HZ WG will be updated on each step as soon as information becomes available. The WG commits to reporting interpretation of those data to ACIP at the earliest opportunity.

**Discussion Points**

Dr. Leonard Friedland (GSK Vaccines, Medical Affairs) emphasized that GSK's top priority is patient safety and GSK is committed to monitoring and assuring the safety of all of its products, including SHINGRIX. GSK recognizes the importance of the VSD and a comprehensive review of pre-clinical studies, clinical trials, and post-marketing reports to GSK have not indicated an increased occurrence of GBS following vaccination with SHINGRIX. GSK remains confident the favorable benefit-risk profile of SHINGRIX for the prevention of herpes zoster (HZ), and GSK will continue to work closely with the CDC and the FDA to actively monitor the safety of SHINGRIX.

Dr. Hunter inquired as to whether the definition of the risk window started for RZV with the first or second dose.

Dr. Shimabukuro indicated that the risk windows for dose 1 and dose 2 are being assessed separately. For this analysis, the 4 cases were all after the first dose.

Dr. Bernstein wondered whether the HepB vaccine that was given with the SHINGRIX was the new adjuvanted HEPLISAV-B®. His understanding was that there are no data regarding co-administration of two adjuvanted vaccines.
Dr. Shimabukuro said that he would have to check on that. There is very limited use of the new HEPLISAV-B® vaccine except in one site that is conducting a post-marketing study for the manufacturer.

Ms. McNally said she was curious regarding the evaluation of other vaccines beyond HepB that may be given at or near the same time, and whether this was flagged as an issue with the GBS cases.

Dr. Shimabukuro indicated that there is intensive monitoring of influenza vaccines each season, as well as SHINGRIX. They certainly document co-administration, but are not specifically monitoring on co-administration. There is a period of intense enhanced monitoring after any newly licensed and recommended vaccine, and they will capture information when possible on co-administration. In VAERS, that is one of the 22 priority pre-specified conditions. Anytime RZV is co-administered with adjuvanted influenza vaccine, the new adjuvanted HepB vaccine, or all three together, those reports will be reviewed regardless of seriousness. Two of the cases had co-administration. One had PCV and the other HepB vaccine. However, co-administration has not been flagged specifically in the monitoring overall as problematic.



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# Hepatitis Vaccines

## Introduction

**Kelly L. Moore, MD, MPH**
**Chair, Hepatitis Vaccines WG**
**Vanderbilt University School of Medicine**

Dr. Moore indicated that the terms of reference for the Hepatitis WG with respect to hepatitis A (HepA) are to: 1) update the HepA vaccine recommendations that were last comprehensively published in 2006 [ACIP Routine Recommendation for Hepatitis A Vaccine, *MMWR* 2006 May 19;55(RR-7):1-23]; and 2) address persons living with HIV (PWHIV) as a risk group for HepA vaccination.

Recommendations published since October 2018 include the following:

- ❑ Doshani M, Weng M, Moore K, Romero J, Nelson NP. Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for Persons Experiencing Homelessness. *MMWR* Morb Mortal Wkly Rep 2019;68:153-156.

- ❑ Nelson NP, Link-Gelles R, Hofmeister MG, Romero JR, Moore KL, Ward JW, Schillie SF. Update: Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for Postexposure Prophylaxis and for Preexposure Prophylaxis for International Travel. *MMWR* Morb Mortal Wkly Rep 2018;67:1216–1220.

Between November 2018 and February 2019, the WG has convened four meetings focused on HIV as an indication for vaccination and has applied the EtR Framework and GRADE.

Dr. Moore indicated that during this ACIP meeting, members would hear presentations on PWHIV as a risk group for HepA vaccination with a vote at a future meeting. She first set the stage for this discussion in terms of why PWHIV should be considered for routine HepA vaccination, given that HIV alone does not increase the risk of exposure to HepA virus (HAV), nor does it necessarily lead to more severe disease. Studies suggest that HAV infection increases HIV replication in PWHIV. Studies also suggest that HIV infection delays HAV infection resolution, which may lead to a longer period of transmissibility. Studies also suggest that PWHIV can mount a protective antibody response to vaccination, although that protection may be less robust.

The next steps for the WG include presenting the full updated HepA vaccine statement for a vote, and to continue its deliberations on adult HepB vaccination topics.



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## Background: Hepatitis A among Persons Living with HIV

**LCDR Mark Weng, MD MSc**
**National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention**
**Centers for Disease Control and Prevention**

Dr. Weng presented background information on HepA epidemiology; HepA vaccines; HAV ongoing outbreaks, including a small case study from Tennessee; and some statistics on HIV in the US. In 2016, there were 2007 reported cases. However, it is known that the reported cases will be much higher in 2017 and 2018 due to the ongoing HAV outbreaks in multiple states among people who use drugs and people experiencing homelessness.[1] When comparing the 2016 HepA rates for all age groups, adults aged 20-49 years had the highest rates per 100,000 population.[2] Overall data from the National Health and Nutrition Examination Survey (NHANES) show the prevalence of antibody among US residents is about 26.5% indicating that <1/3 of the US population had protection against HAV infection in 2009-2010. The lowest percentages of protection were among adults aged 30-49 years[3] [[1]National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. *Pediatrics* 2007;119:e22-9; [2]NNDSS, http://www.healthypeople.gov/2020/topicsobjectives2020/pdfs/Immunization.pdf; [3]NHANES, National Health and Nutrition Examination Survey Murphy TV et al. Progress Toward Eliminating Hepatitis A Disease in the United States. MMWR Suppl. 2016 Feb 12;65(1):29-41].

Groups at increased risk of HAV infection or severe HepA disease are recommended to receive HepA vaccine. The recommended groups to receive HepA vaccine and year of recommendation are shown here:

- ❑ Travelers (1996)
- ❑ Men who have sex with men (1996)
- ❑ Users of injection and non-injection drugs (1996)
- ❑ Persons with clotting-factor disorders (1996)
- ❑ Persons who work with nonhuman primates (1996)
- ❑ Persons with chronic liver disease (1996)
- ❑ Persons who anticipate close personal contact with an international adoptee (2009)
- ❑ Persons experiencing homelessness (2019)
- ❑ Persons living with HIV (proposed)

This presentation regarding HIV and HepA vaccination focused on adults, since children are recommended for HepA vaccination as part of the routine childhood vaccination schedule at age 12-23 months or as part of permissive catch-up vaccination. During licensing trials, it was found that HepA vaccines licensed in the US are highly immunogenic in immunocompetent persons aged greater than 18 years, when administered according to the recommended schedules. Protective antibody levels were identified in 94% to 100% of immunocompetent adults 1 month after the first dose. After the second dose, all immunocompetent persons had protective levels of antibody with high GMTs [Clemens R et al. J Infect Dis 1995;171(Suppl 1):S44–9. Nalin DR. VAQTA™: hepatitis A vaccine, purified inactivated. Drugs of the Future 1995;20:24–9. McMahon BJ, et al. Immunogenicity of an inactivated hepatitis A vaccine in Alaska Native children and Native and non-Native adults. J Infect Dis 1995;171:676–9].



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In pre-licensure trials, adverse reactions to HAVRIX®, VAQTA®, and TWINRIX® were mostly injection site reactions and mild systemic reactions. Post-marketing surveillance for AEs following receipt of HepA vaccines has been performed primarily by two systems in the US, VAERS and VSD. No unusual or unexpected safety patterns were observed for any of the HepA vaccines licensed in the US. More information on vaccine safety will be presented as part of the GRADE presentation [Vaccine Information Statement (VIS) https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-a.htmlMMWR 2006;55(RR-7)].

In terms of immunogenicity, the antibody to HAV has been shown to persist in vaccine recipients for at least 20 years in immunocompetent adults administered inactivated vaccine as children with a 3-dose schedule.[1] At least 20-year antibody to HAV persistence was demonstrated among immunocompetent adults vaccinated with a 2-dose schedule as adults.[2] Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and antibody to HAV kinetic studies.[2,3] Protection following natural infection is lifelong and may also be lifelong following vaccination. For persons with immunocompromising conditions or co-morbidities, protection may be less [[1]Plumb ID, et al. J Viral Hepat. 2017 Jul;24(7):608-612; [2]Theeten H, et al. Vaccine. 2015 Oct 13;33(42):5723-7; [3]Hens N, et al. Vaccine. 2014;32(13):1507-1513].

In adults the ≥2 doses vaccine coverage was much lower than in children and adolescents in 2016 at 9.5% for adults ≥19 years, 13.4% for adults 19-49 years, and 5.4% for adults ≥50 years. When considering recommended risk groups for HepA vaccination, for adults aged 19-49 years, greater or equal to 2 doses vaccine coverage was 19% for Travelers and 24% for persons with chronic liver disease (CLD) [Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016.https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/NHIS-2016.html#hepA].

The epidemiology for HAV has shifted. In the past, large community outbreaks were associated with asymptomatic children infecting the adults who cared for them who then transmitted the virus to other adults. With widespread adoption of the universal childhood vaccination recommendations, asymptomatic children are no longer the main drivers of outbreaks. Although the overall incidence rate of HAV infection has decreased within all age groups, most adults are not immune because they have not been vaccinated and were not infected naturally. Older people are more likely to be symptomatic and experience severe disease and adverse outcomes such as hospitalization, fulminant liver disease, fulminant liver failure, and death. For the at-risk adults for which vaccination recommendations do exist, uptake is low. The number of cases has risen sharply since 2015. Person-to-person transmission is currently the most common source of HAV transmission in the ongoing outbreak [Collier M, et al. Hepatology 2015; Ly KN, Klevens RM. J Infect Dis 2015; Epson E, et al. Public Health, 2015; Murphy TV, et al. MMWR Suppl 2016; Foster M, et al. MMWR 2018].

HAV outbreaks have been ongoing in multiple states among people who use drugs and/or people experiencing homelessness, as well as continued reports of men who have sex with men (MSM) cases. Since these outbreaks were first identified in 2016, more than 13,000 cases and 7,400 hospitalizations have been reported, for a 57% hospitalization rate. Over 100 deaths have occurred nationwide because of these outbreaks. Hospitalization rates have been higher than typically associated with HAV infection, probably reflective of more serious illness among the vulnerable populations impacted by these outbreaks. HAV is highly transmissible from person-to-person, so prolonged community outbreaks have been challenging to control.



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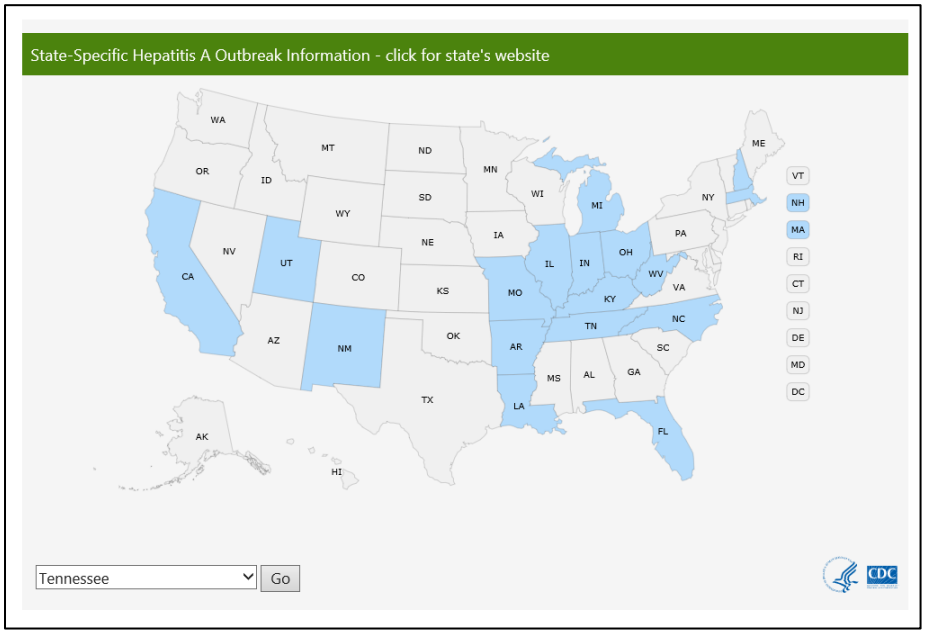
This map shows in blue the 17 states that have been or are affected by the person-to-person HepA outbreaks:




Division of Viral Hepatitis Outbreak Website Map:
https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm

During the course of the outbreak, multiple states reported cases among persons living with HIV who had a history of unknown or at least partial HepA vaccination. These reports prompted CDC to request case reports from affected states and to perform a systematic review to investigate the risk of HAV infection and course of infection, and to evaluate the response to Hep A vaccine among persons living with HIV. Complete case information was not available from all states. Data from the Tennessee Department of Health were provided during this session.

In Tennessee, 14 persons living with HIV were infected with HAV. Of the 14, 5 (36%) were previously vaccinated with at least 1 dose of either combination or single-antigen HepA vaccine at least 1 month prior to hepatitis exposure. The other 8 had no or unknown vaccination history. Of the 14, 13 (93%) had an indication for HepA vaccine prior to becoming ill with HAV. Previously vaccinated HAV cases among persons living with HIV raise concern about susceptibility to HAV among PWHIV and HepA vaccine long-term immunogenicity. These data represent missed opportunities for vaccination among persons with an existing recommended risk factor for vaccination of up to 8 patients (57%), and potential waning immunity among persons previously vaccinated of up to 43% [Courtesy: Julia Brennan and Tennessee Department of Health].

The following definition of HIV infection will be utilized:

> *The term refers to persons diagnosed with HIV infection, regardless of the stage of disease at diagnosis (i.e., HIV infection Stage 0, 1, 2, 3 [AIDS], or unknown), from all 50 states, the District of Columbia, and 6 U.S. dependent areas (American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, the Republic of Palau, and the U.S. Virgin Islands)* [Centers for Disease Control and Prevention. HIV Surveillance Report, 2017;



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vol. 29. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2018. Accessed 2.19.2019].

At the end 2015, an estimated prevalence of 1.1 million people ≥13 years old were living with HIV infection, including 162,500 people (14.5%) whose HIV infection had not been diagnosed [https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-23-1.pdf].

In 2017, the number of new HIV diagnoses was 38,739 and was mostly among adults. The highest numbers were among ages 20-39. CDC classifies HIV diagnoses into six transmission categories to which transmission may be attributed (perinatal transmission is not shown here):

**Diagnoses of HIV Infection by Transmission Category**

- CDC classifies HIV diagnoses into six transmission categories to which transmission may be attributed

| Transmission Category | Adult and Adolescent Males | Adult and Adolescent Females | Total |
|---|---|---|---|
| Male-to-male sexual contact | 25,748 | NA | 25,748 |
| Injection drug use | 1,373 | 1,016 | 2,389 |
| Male-to-male sexual contact and injection drug use[a] | 1,252 | NA | 1,252 |
| Heterosexual contact[b] | 2,829 | 6,341 | 9,170 |
| Other[c] | 37 | 44 | 81 |

[a] Includes infections attributed to male-to-male sexual contact *and* injection drug use (men who reported both risk factors).
[b] Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
[c] Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

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The categories shown in red represent existing recommended risk groups for HepA vaccination. Based on this classification, approximately 24% of persons living with HIV do not have another risk group for which HepA vaccination is recommended.

The Medical Monitoring Project (MMP) was used, which looks at a nationally representative sample of persons living with HIV, to answer the question, “What percentage of PWHIV do not have an existing risk factor for which HepA vaccine is recommended?” The percentage of persons living with HIV without a recommended risk group for HepA vaccination is higher when looking at more specific risk factor data. MMP includes the following risk groups for which HepA vaccination is recommended: MSM, injection and non-injection drug use, persons experiencing homelessness, chronic liver disease, and clotting factor disorders. Up to 40% of persons did not have a risk factor for which HepA vaccination is recommended. Some risk factors for which HepA vaccine is recommended could not be evaluated (e.g., occupational risk, travel risk, or exposure to an international adoptee from an endemic country). However, this illustrates that persons living with HIV might be missed for HepA vaccination if they do not have an existing factor for which HepA vaccine is recommended or they do not seek services for the other risk factors.



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In summary, HepA vaccine is largely responsible for the marked reduction in HAV cases. An increasing proportion of adults in the US are susceptible to HAV due to reduced exposure to HAV early in life, significant decreases in seroprevalence of anti-HAV antibody in older adults, and because low two-dose vaccination coverage exists in adults, including high risk adults (e.g., travelers, or those with chronic liver disease). The ongoing HAV outbreaks illustrate the shifting epidemiology and person-to-person transmission among unvaccinated, vulnerable populations. About 1 million persons are living with HIV in the US. Finally, up to 40% of PWHIV HIV do not have a risk factor for which HepA vaccination is otherwise recommended.

## GRADE: Use of HepA Vaccines Among Persons Living with HIV Infection

**Alaya Koneru, MPH**
**National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention**
**Centers for Disease Control and Prevention**

Ms. Koneru presented on GRADE for HepA vaccine among PWHIV. This is an overview of the GRADE process, which is to:

- ❑ **Develop policy questions**
- ❑ **Consider critical outcomes**
- ❑ **Review and summarize evidence of benefits and harms**
- ❑ **Evaluate quality of evidence**
- ❑ **Assess population benefit**
- ❑ Evaluate values and preferences
- ❑ Review health economic data
- ❑ **Considerations for formulating recommendations**
- ❑ **ACIP recommendation and GRADE category**

The bolded bullets are the components followed by the WG for evaluation of HepA vaccine for PWHIV. The policy question for consideration was, “Should routine 2-dose vaccination vs. no routine vaccination to prevent HAV be given to adult HIV-positive persons regardless of another indication for vaccination?” The population of interest was adult HIV-positive persons regardless of another indication for vaccination. The intervention of interest was routine 2-dose HepA vaccination. The comparison of interest was no routine 2-dose HepA vaccination. The outcomes the WG considered and included in the evidence profile were HAV infection (designated as critical), mild AEs (designated as important), and SAEs (designated as critical).

For evidence retrieval, a systematic review was conducted of data on HepA vaccine and PWHIV, including a search of Medline, EMBASE, CINAHL, Cochrane Library, and ClinicalTrials.gov through January 17, 2019. Search terms included: (((Hepatitis OR HAV OR hepatovirus) AND vaccin*) OR HepA OR Vaqta OR avaxim OR epaxal OR havpur OR Havrix OR nothav) AND (HIV OR human immunodeficiency). No language restrictions were placed on articles based on language or country of origin. Articles were excluded based on the following criteria:

- ❑ Articles focused solely on children or that did not have information on ages of included individuals
- ❑ Articles with no data on HAVRIX® or VAQTA®, which are the two single antigen HepA vaccines currently licensed in the US



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- ❑ Articles that that did not provide new data, only included safety data not in the target population of persons living with HIV infection, discussed vaccine introduction, made recommendations, or proposed guidelines
- ❑ Articles that could not be obtained full-text or in English
- ❑ Articles on animals other than humans
- ❑ Clinical trials with no results available

A total of 927 unique abstracts were identified. Of these, 584 abstracts were excluded due to irrelevance. This left 343 articles for full-text review. Another 319 articles were eliminated due to irrelevance or publication prior to 1996, which was when HepA vaccine was introduced in the US. Studies also were excluded with populations that were a subset of other included studies. A total of 24 studies were included in the GRADE analysis.

In terms of reference values and corresponding units used throughout the presentation, for HepA vaccine, the correlate of protection is generally accepted to be 20 mIU/mL though this varies from 10 to 33 in the literature. There are two monovalent HepA vaccines licensed for adults in the US, VAQTA® and HAVRIX®. The dosage for VAQTA® is 50 units. The dosage for HAVRIX® is 1440 ELU. For the CD4 cell count, the normal range is 500 to 1500 cells/cells/mm$^3$. Less than 200 cells/mm$^3$ indicates severely immunocompromised. For HIV viral load, undetectable is defined as HIV ribonucleic acid (RNA) less than 20 to 75 copies per mL depending upon the assay used.

The studies assessed for Outcome #1, HAV infection, varied in how data were collected and reported and the thresholds for seroconversion also varied by study. The Kemper 2003 study demonstrated that seroconversion was 68% among those with CD4 counts ≥200 and 9% among those with CD4 <200. This finding was significant. Launay 2008, a study from France, found in their ITT analysis that seroconversion was 69.4% among the 2-dose group and 82.6% among the 3-dose group. Wallace 2004, a US study, found an overall seroconversion of 94%, with 87% in the CD4 <300 group and 100% among the CD4 ≥300 group. Armstrong 2010, a US study, found a seroconversion rate of 60% overall, with 62.5% among those with CD4 >400 and 55.56% among those with ≤400. Cheng 2017, a study from Taiwan, found a seroconversion rate at month 12 of the study of 87.3% and 88.9% among those receiving 2- and 3-dose, respectively. Crum-Cianflone 2011, a US study, found an overall seroconversion of 89%, with 78% among those with a CD4 <350 and 94% among those with CD4 ≥350. Horster 2010, a German study, found a seroconversion rate of 63.6%. Jablonowska 2014, a study from Poland, found a seroconversion rate of 79.5% after the second dose and immunogenicity of 75.5% 5 years after vaccination.

Jimenez 2013, a US study, determined an overall seroconversion rate of 53.5% with 54% in the HAVRIX® group. Kourkounti 2012, a study from Greece, found a 74.4% seroconversion rate. Kourkounti 2013 and 2014 found seroconversion rates of 77% and 76%, respectively. Lin 2018, a study from Taiwan, determined a seroconversion rate of 63.8% in their ITT analysis and 93.7% in the per-protocol analysis. This study found an overall VE of 96.3%. Mena 2013, a study from Spain, found an overall seroconversion rate of 73.4%, with 80.7% in the HAVRIX® group. Overton 2007, a US study, found a rate of 49.6% overall. Tsachouridou 2017, a study from Greece, found 80.7% seroconversion within 3 months of HepA series completion. Tseng 2013, a study from Taiwan, found a 75.7% seroconversion rate among those receiving 2-dose vaccination. Weinberg 2012, a US study, found a 52% seroconversion rate in those who were HAV-seronaive and received vaccine. Weissman 2006, a US study, determined a seroconversion of 48.5%. Rimland 2005, a US study, found a rate of 60.7%. Valdez 2003, a US



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study, found a rate of 88% among highly active antiretroviral therapy (HAART)-only recipients. Lederman 2003, a US study, found a seroconversion rate of 46%.

In terms of the studies assessed for Outcome #2, mild AEs, Kemper 2003 found that 1.6% of all subjects experienced severe headache, and 1.6% in the vaccine group experienced severe fatigue within 4 days of vaccination. Minor injection site soreness was found after 35% of vaccine doses were administered versus 8% of placebo doses administered. This study also found that reported post-vaccination bacterial, viral, and fungal infections was 24% versus 26%, among patients receiving vaccine versus placebo, respectively. Wallace 2004 reported local reaction at the injection site of 57% on the vaccine group versus 60% in the placebo group. Systemic AEs were predominantly headache and fever. Tseng 2013 reported mild tenderness at the injection site in 51.6% of all subjects within 24 hours of vaccination.

Regarding the studies assessed for Outcome #3, SAEs, Castro 2009, an RCT from Spain, found that vaccinations in successfully treated PWHIV were safe, not associated with increased detectable viral load, and not associated with developing genotypic resistance mutations. Horster 2010, a study from Germany, found that there were no adverse reactions after vaccination for those receiving HepA vaccination. No statistically significant difference between pre- and post-vaccination CD4 T-cell counts and HIV plasma load was observed in this study. Launay 2008 found that there were no SAEs associated with vaccine and there were no significant changes in CD4+ T cell counts or plasma HIV-1 RNA levels. Bodsworth 1997 found no adverse outcomes attributable to vaccination. They also noted that there were no significant differences between the case and control groups for progression to AIDS, death, or mean CD4 cell decline. Wallace 2004 determined that vaccination had no adverse effect on CD4 cell count or HIV viral load.

Moving the GRADE summary, the evidence types are displayed here for reference:

| | |
|---|---|
| **High/Evidence Type 1** | We are very confident that the true effect lies close to that of the estimate of the effect. |
| **Moderate/Evidence Type 2** | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| **Low/Evidence Type 3** | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| **Very low/Evidence Type 4** | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

The limitations of the articles described are that there were few studies that directly compared a standard 2-dose vaccination versus no vaccination in adult HIV-positive persons; there were limited studies with HAV infection as a study endpoint; and seroconversion thresholds for HepA antibodies and timing of the testing after vaccination varied by study.



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The benefit outcome, Hepatitis A Infection, for RCTs was graded as an Evidence Type 2. The WG downgraded for inconsistency due to variability of HepA antibody seroconversion thresholds used. The benefit outcome, HAV infection, for observational studies was graded as an Evidence Type 4. The WG downgraded for inconsistency due to variability of HepA antibody seroconversion thresholds used and for indirectness due to limited studies comparing a 2-dose standard intervention to no vaccine. The harm outcome, mild AEs, for RCTs was graded as an Evidence Type 1. The harm outcome, mild AEs, for observational studies was graded as an Evidence Type 3. The harm outcome, SAEs, for RCTs was graded as an Evidence Type 3. The WG downgraded indirectness for use of multiple non-HepA vaccines and for imprecision due to small study population size. The harm outcome, SAEs, for observational studies was graded as an Evidence Type 4. The WG downgraded indirectness for use of multiple non-HepA vaccines and for imprecision also due to small study population size.

## ACIP EtR Recommendations Framework: Use of HepA Vaccines among PWHIV

**LCDR Mark Weng, MD MSc**
**National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention**
**Centers for Disease Control and Prevention**

For the EtR framework, Dr. Weng reviewed the policy question and background and went through each of the 10 criteria, other considerations, balance of consequences, and ACIP recommendations. The policy question was, “Should routine two-dose vaccination vs. no routine vaccination to prevent HepA be given to HIV-positive adults, regardless of another indication for vaccination?” The 10 criteria are:

1. Is the problem a public health priority?
2. How substantial are the desirable anticipated effects?
3. How substantial are the undesirable anticipated effects?
4. Do the desirable effects outweigh the undesirable effects?
5. What is the overall certainty of the evidence for critical outcomes? GRADE
6. Does the target population feel that the desirable effects are large relative to the undesirable effects ?
7. Is there important uncertainty about or variability in how much people value the main outcomes?
8. Is the option acceptable to stakeholders?
9. Is the option a reasonable and efficient allocation of resources?
10. Is the option feasible to implement?

Dr. Weng noted that for the rest of this presentation, although the question refers to 2-doses, routine vaccination also can consist of a 3-dose schedule when combined HepA and B vaccine (Twinrix®) is administered.

Data suggest up to 87% of PWHIV are susceptible to HAV infection.[1-6] Of newly diagnosed PWHIV, 75% are at risk for HAV infection.[2] MMP shows that up to 40% of PWHIV had no indication for HepA vaccination.[7] Of HAV cases that did report risk factors, 56.2% indicated no risk factors for HAV.[8] Of note, nearly half (45.7%) of these HAV cases were missing data on risk factors for HAV [[1]DeGroote 2018; [2]Moon 2018; 3Adejumo 2010; [4]Sun 2009; [5]Overton 2007; [6]Sheth 2006; [7]CDC MMP 2016; [8]CDC Viral Hepatitis Surveillance 2016].



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***Criterion 1: Is the problem a public health priority?***

**JUDGEMENTS:**
□ No □ Probably No □ Uncertain □ Probably Yes ☒ **Yes** □ Varies

**RESEARCH EVIDENCE:**
- ❑ PWHIV are at increased risk of HAV infection due to their immunocompromised state and missed opportunities for vaccination.[1,2]

- ❑ Outbreaks that include PWHIV can have prolonged HAV transmission.[3,4] HAV viremia in PWHIV tends to be higher and more durable.[3]

- ❑ Infectious Disease Society of America (IDSA)[5] and 11 other review articles recommend or permissively recommend vaccinating all PWHIV.[1, 6-15]

- ❑ Spain, Italy, and Australia report routinely vaccinating all PWHIV, at least in some parts of those countries.[16-20]

[1. Koziel 2007; 2. Lin 2017; 3. Puoti 2012; 4. Yotsuyanagi et al, 1996; 5. Aberg 2013; 6. Crum-Cianflone 2014; 7. Pham 2011; 8. Crane 2009; 9. Kresina 2007; 10. Schiff 2007; 11. Brook 2006; 12. Gleeson 2006; 3. Sidiq 2006; 14. Laurence 2005; 15. Kwong 1999; 16. Mena 2015; 17. Lugoboni 2012; 18. Turnbull 2011; 19. Rivas 2007; 20. Van Damme 2003].

Susceptibility in the HIV+ population is high, even among those with recommended risk factors for HepA vaccination. Several publications reporting on the HIV+ population showed that a substantial portion of PWHIV remain non-immune to HAV infection, including: 87% of high-risk patients at a New York HIV clinic, 58% at a Baltimore HIV clinic, 42% from the MMP, and 31% of active HIV clinic patients at Washington University. Where available, the characteristics of the HIV+ population, non-immune to HepA, are described. They are non-immune to HepA virus infection despite existing risk factors for HepA vaccination.

***Criterion 2: How substantial are the desirable anticipated effects? (Beneficial effects of vaccination)***

**JUDGEMENTS:**
□ Minimal □ Small □ Moderate ☒ **Large** □ Don't know □ Varies

**RESEARCH EVIDENCE:**
- ❑ HAV infection may increase HIV replication, potentially increasing HIV transmission.[1]

- ❑ HAV infection in PWHIV is prolonged and can lead to longer transmission period.[1-9]

- ❑ It is known that HepA vaccine is a highly effective vaccine in the general population.[10] Seroconversion rates in PWHIV are 49.6%–94% from a 2015 published paper.[11] A similar range was seen in Ms. Koneru's presentation.

1. Gallego 2011; 2. Lee 2018; 3. Ciccullo 2018; 4. Comelli 2018; 5. Lin 2017; 6. Ida 2005; 7. Laurence 2005; 8. Fonquernie 2001; 9. Lombardi 2019; 10. Fiore 2006; 11. Mena 2015



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***Criterion 3: How substantial are the undesirable anticipated effects? (serious adverse events)***

**JUDGEMENTS:**
☒ **Minimal** ☐ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies

**RESEARCH EVIDENCE:**
- ❑ HepA vaccine is safe.[1-3] The main side effect is mild, transient local soreness at the injection site based on follow-up of hundreds of millions of doses after 104 clinical studies in 27 countries.

- ❑ There are similar rates of SAEs in PWHIV vs. HIV-negative persons,[4] with no unexpected vaccine AEs reported among PWHIV, 1990-2016.[5]

- ❑ HepA vaccine does not increase HIV viral load, CD4 cell count, or progression to AIDS.[3,4,6-9]

1. WHO 2013; 2. Fiore 2006; 3. André 2002; 4. Dlamini 2018; 5. Su 2018; 6. Phung 2012; 7. Shire 2006; 8. Kemper 2004; 9. Wallace 2003

***Criterion 4: Do the desirable effects outweigh the undesirable effects?***

**JUDGEMENTS:**
☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ **Yes** ☐ Varies

**RESEARCH EVIDENCE:**
- ❑ Protection against HAV in PWHIV can be achieved, despite lower seroconversion rates in PAWHIV compared to persons without HIV.[1-3]

- ❑ Out of 130 PWHIV, 85% maintained seropositivity 6-10 years after a 2-dose vaccine series.[4] However, vaccination at higher CD4+ counts is associated with better vaccine-induced immune response, which supports vaccinating PWHIV earlier in the course of HIV diagnosis.[1,4-7]

1. Mena 2015; 2. Crum-Cianflone 2014; 3. van Damme 2003; 4. Crum-Cianflone 2011; 5. Huang 2019; 6. Armstrong 2010; 7. Kemper 2003

***Criterion 5: What is the overall certainty of the evidence for critical outcomes? GRADE***

**RESEARCH EVIDENCE:** Outcome measures included in evidence profile just presented by Ms. Koneru:

| OUTCOME | IMPORTANCE |
|---|---|
| ***Benefits*** | |
| **(1) Hepatitis A infection** | Critical |
| ***Harms*** | |
| **(2) Mild adverse events (any)** | Important |
| **(3) Serious adverse events (any)** | Critical |



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***Criterion 6: Does the target population feel that the desirable effects are large relative to the undesirable effects?***

**JUDGEMENTS:**
□ No □ Probably No □ Uncertain ☒ **Probably Yes** □ Yes □ Varies

**RESEARCH EVIDENCE:**
- ❑ Few have studied PWHIV preferences regarding HAV, expert opinion has been sought from select advocacy groups and from among the ACIP WG members who work clinically with the HIV population to arrive at the "Probably Yes" judgment.

- ❑ Qualitatively, frequent reasons for non-vaccination in one study were lack of recommendation by providers, lack of expected effectiveness, and fear of vaccine adverse effect.[1]

1. Zadeh 2010

***Criterion 7: Is there important uncertainty about or variability in how much people value the main outcomes?***

**JUDGEMENTS:**
□ No ☒ **Probably No** □ Uncertain □ Probably Yes □ Yes □ Varies

**RESEARCH EVIDENCE:**
- ❑ There are few studies specific to the PWHIV on valuing protection against HAV, but expert clinical opinion was sought to arrive at the "Probably No" opinion.

- ❑ Among people who use injection drugs (PWID), (of whom 24.2% were PWHIV), convenience was an important determining factor for initiating HepA/HepB vaccination.[1]

1. Campbell 2007

***Criterion 8: Is the option acceptable to stakeholders?***

**JUDGEMENTS:**
□ No □ Probably No □ Uncertain □ Probably Yes ☒ **Yes** □ Varies

**RESEARCH EVIDENCE:**
- ❑ There are parallels to the recommendations for HepB vaccination in PWHIV.[1] Seroresponse is lower also with HepB vaccination for those with low CD4 counts. But, it is still recommended that all persons living with HIV receive their first dose of HepB vaccine during their first HIV care visit. Even though the vaccine is less immunogenic at lower CD4 counts, people at any CD4 count can and have responded.

- ❑ Routine HepA vaccination would be less confusing to clinicians than having a different approach for the two types of vaccinations.

1. J. Weiser 2019, communication. CDC Division of HIV/AIDS Prevention.



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### *Criterion 9: Is the option a reasonable and efficient allocation of resources?*

**JUDGEMENTS:**
□ No □ Probably No □ Uncertain ☒ Probably Yes □ Yes □ Varies

**RESEARCH EVIDENCE:**
- ❑ Adult HepA vaccines are licensed only for certain high-risk groups, and cost-effectiveness data on its use for these indications are limited.[1,2]

- ❑ It is known that outbreak campaigns incur high medical cost, productivity losses, disruption of other public health services, and diversion of public health resources and extensive human resources.[3,4] For instance, the cost of a HepA outbreak among PWID (n=590, Washington) was $3.3 million. The cost of an outbreak among MSM (n=136, Ohio) was $520,039.[1]

- ❑ The cost of routine immunization through HIV and primary care clinics may be lower per capita than cost of large, rapid vaccination campaigns for outbreak response.[1-4]

1. Luyten 2009; 2. O'Connor 1999; 3. Epson 2016; 4. Van der Hilst 2009

### *Criteria 10: Is the option feasible to implement?*

**JUDGEMENTS:**
□ No □ Probably No □ Uncertain ☒ Probably Yes □ Yes □ Varies

**RESEARCH EVIDENCE:**
- ❑ Simplifying provider guidance may improve protection of at-risk PWHIV.[1,2]

- ❑ Vaccine response improves if PWHIV are vaccinated earlier in the course of HIV infection[3], when patients have higher initial CD4 counts[4-9] and lower HIV RNA viral load.[6, 10, 11]

- ❑ Despite recommendations to vaccinate based on specific risk factors, there is inadequate screening and vaccination for HAV among PWHIV, even in HIV clinics.[1, 5, 12] In a US study, only 23.3% eligible outpatient PWHIV received 1 dose of HepA vaccine.[1] In a British study, HepA vaccine was indicated in 75% of PWHIV but had been delivered to 36% of eligible individuals.[12]

1. Tedaldi 2004; 2. Mena 2015. Medicina Clínica.; 3. Crum-Cianflone 2014; 4. Kemper 2013; 5. Kourkounti 2013; 6. Sell 2013; 7. Mena 2012; 8. Rimland 2005; 9. Wallace 2004; 10. Tseng 2013;11. Overton 2007; 12. Quinn 2012

In terms of other considerations, PWHIV may experience milder clinical course of HAV infection because of less immune response and liver injury, but infection is prolonged and can lead to a longer transmission period. Early small case series indicated persons living with HIV who became infected with HepA virus developed increased HIV viral load, increased liver enzyme levels, and significant declines in CD4 after pausing antiretroviral therapy (ART)[1-3]. Some of these small studies showed that HIV viral load increased in 38% of PWHIV with HAV infection,[4] and that delayed resolution indicated by ALT remaining over 5 times the normal limit for over 2 weeks after diagnosis of HAV infection.[1] Larger recent studies showed less severe, but prolonged HAV course[5-13]. Host immune response may be the main pathogenic mechanism of liver injury in HAV.



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WG considerations regarding the factors favoring vaccination of PWHIV include the following: HAV infection may increase HIV replication, potentially increasing HIV transmission. Resolution of HAV infection may be delayed, potentially prolonging the infectious period. Up to 40% of PWHIV do not have a risk factor for which HepA vaccination is otherwise recommended. For PWHIV with an existing risk factor for HepA vaccination, another opportunity for vaccination would be provided for PWHIV who are missed or who do not seek services for other risk factors. Vaccine is safe and efficacious in PWHIV.

WG consideration regarding the factors not favoring vaccination of PWHIV include the following: Illness from HAV infection may be less severe. Seroconversion may be lower or take longer among PWHIV vaccinated while they have low CD4 counts. Immunity may wane in PWHIV who have low CD4 counts. HIV infection alone is not a risk for HAV infection.

In the balance of consequences, desirable consequences probably outweigh undesirable consequences in most settings. The WG does recommend that routine, 2-dose vaccination versus no routine vaccination to prevent HAV be given to adult persons with HIV, regardless of another indication for vaccination.

Future considerations if HepA vaccination is recommended for PWHIV are to consider additional protection with immunoglobulin and/or additional vaccine following a known high-risk exposure regardless of vaccination history, and consider periodic anti-HAV antibody testing and/or booster doses for persons with an ongoing risk for exposure, as with HepB. Data on VE among persons living with HIV should be evaluated for proximity of vaccination to HIV diagnosis and CD4 count at vaccination and at exposure to HAV.

**Discussion Points**

To put this into perspective, Dr Nelson indicated that this pertains to about 1 million PWHIV up to 40% of whom do not have an existing risk factor for which HepA vaccine is currently recommended. Therefore, up to about 400,000 additional people would be recommended to receive HepA vaccine.

Dr. Bernstein wondered whether there would be any value in suggesting knowing laboratory criteria before administering the vaccine.

Dr. Nelson indicated that that would be a next step for WG discussion, but that she would say they would vaccinate at any CD4 count. However, persons who were vaccinated with a count lower than the cutoff would require data monitoring such as post-vaccination testing as is done for HepB vaccine.

Dr Romero pointed out that this also would mean that if ACIP makes this recommendation, at first contact with a healthcare provider, this would be an option. It would go into effect immediately such that newer populations would be immunized very early on rather than waiting for lower CD4 counts.

Dr. Fryhofer (AMA) thought the levels of 20 were antibody titers. In the past with her patients, she has checked qualitative antibody titers from time to time, but never a quantitative antibody titer. She wondered whether that came up in the review as something that practitioners should be checking to ensure that patients are immune.



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Dr. Nelson indicated that post-vaccination testing is not usually recommended. They do think that there is some waning of antibody as opposed to immunity, but this has been studied more closely in terms of HepB.

Dr. Atmar said his understanding was that the qualitative test is relatively less sensitive, so the threshold for being called “positive” is somewhat higher than the quantitative assays described in these studies. If someone is seropositive by qualitative test, they are likely to be above the threshold. If they are seronegative, it is uncertain. Regarding the comments about CD4 counts, of all of the studies that were shown the only one with a threshold of 200 had only a poor 9% seroconversion rate. Biologically, 200 has been a pretty important number. Therefore, he would want the WG to strongly consider recommendations with that in mind.

Dr. Lee observed that the question about public health burden is interpreted somewhat differently by different WGs. Perhaps something to consider would be how to consistently think about overall population burden as well as transmissibility, and whether individual health benefits should be considered as well. She understood why perhaps there is not a need for a formal cost-effectiveness analysis, but it would be helpful to get a sense of what the estimated cost would be of vaccinating the population and a smaller number of people, and “back of the envelope” calculations on disease burden averted and economic burden averted.

Dr. Messonnier said she was thinking the same thing. CDC will give thought to what that would look like so that they are not holding different groups to different standards, and perhaps work with the Economics WG to figure out what a “light” version would look like.

Ms. Hayes (ACNM) inquired as to how Dr. Weng’s data break down by gender. The risk factor for HepA is different in MSM than it is for women.

Dr. Weng replied that those data are available, Dr. Weiser added that they have not yet been analyzed, and Dr. Nelson agreed that they would present those data during the next meeting.

In terms of WG consideration around timing and CD4 counts, Dr. Moore thought they would want to assess this but it was not clear whether that would go into the vote or would be part of the additional clinical guidance in which CDC would provide more details. The WG is also cognizant of the fact that they need to harmonize with how HepB is handled in this population for whom HepB vaccine is also already recommended. There is a combination product that contains both in a single injection that is an option. The WG will take these issues into consideration. She also pointed that that although economics is always very important to consider, it is very difficult to do with a disease that is outbreak-driven rather than being at a steady-state of exposure risk. While there is currently a large multi-state outbreak with certain communities at increased risk of exposure, that is why they presented outbreak costs as opposed to other general population costs the way that would be done with a disease that has a more steady state presentation.

Dr. Smith (ASTHO) noted that as the ATSHO representative and an HIV care provider, this would be very welcomed. Many HIV patients do have already defined risk factors, but because they are stigmatized conditions they oftentimes are not identified until much later. In the state HIV surveillance data for the most recent year, the largest category for risk factors is always “unknown” because it takes time to identify these risk factors. These individuals often have a payment source for their immunizations through the Ryan White Program. That is a way to get a relatively higher risk group for HepA immunized, because it is part of the system of care for them. In terms of timing and CD4 counts, this is an issue practitioners have to deal with for a



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number of immunizations (pneumococcal, meningococcal, HepB, et cetera). Oftentimes, there is a clinical judgment in terms of when to give those. If there are compelling reasons to give them right away when the CD4 count is low, they are sometimes given.

Dr. Talbot looked at the Adult Immunization Schedule to determine whether HIV had its own column, which would make sense. But it is already purple, which means it should be considered. She wondered whether that meant it should be considered but not paid for. HepB is yellow, which is indicated. It would be beneficial to know what the vaccination rate is for HIV+ individuals to determine whether changing the color from purple to yellow would move that bar in the intended direction.

Dr. Cohn clarified that the purple bar on the high risk table means that if they have another indication, it is not contraindicated. That is, they can get it if they have another indication, but it does not mean that they should be considered because of the indication that is in the column.

Dr. Messonnier indicated that for the next meeting, they would commit to finding out the specifics in terms of reimbursement for those covered by Ryan White. From an immunization standpoint, if it is on the schedule, it is a recommended vaccine.

Dr. Cohn added that the color Dr. Talbot was talking about on that table was not a recommendation.

Dr. Moore said that for the State of Tennessee, there are a lot of quality metrics related to that. Dr. Carolyn Wester, Dr. Moore's counterpart of Tennessee Department of Health, who is now the Director of CDC's Division of Viral Hepatitis, always insisted on a quality of care indicator that was monitored at the state level for all HIV patients. Therefore, HepB vaccine completion was very high among HIV patients because they are tracked and cared for somewhat better than others with other risk factors.

## Vaccine Supply

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

During this session, Dr. Santoli presented an update on the HepB vaccines supply. She reported that Merck is not currently distributing its adult HepB vaccine or dialysis formulation and will not be distributing vaccine through the end of 2019. Together, GlaxoSmithKline (GSK) and Dynavax have sufficient supplies of adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply during this period. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time. This has not changed since the last update in October 2018.

Merck's supplies of pediatric HepB vaccines have been constrained since mid-2017. Merck will continue to direct its limited supply to CDC to support utilization consistent with current clinical guidance. Merck expects to have a limited supply of monovalent HepB vaccine through 2019. This differs from the October 2018 update at which time a limited supply was predicted to be



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available through mid-2019. GSK is able to continue to cover the supply gap through 2019, with a combination of monovalent and combination vaccine. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time period. The expected monovalent supply remains more than sufficient to cover the birth dose for all children, as well as some second and third doses.

As a reminder, CDC has a vaccine supply page that is kept updated in sync with all of the updates made during ACIP meetings. The Vaccine Supply/Shortage Webpage can be found at: https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html.



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## Certification

Upon reviewing the foregoing version of the February 27-28, 2019 ACIP meeting minutes, Dr. Nancy Bennett, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.



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# ACIP Membership Roster

**Department of Health and Human Services**
**Centers for Disease Control and Prevention**
**Advisory Committee on Immunization Practices**
**November 2018 – June 30, 2019**

**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

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



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EZEANOLUE, Echezona, MD, MPH
Professor of Pediatrics and Public Health
Department of Epidemiology and Biostatistics
Director, Global Health and Implementation Research Initiatives
University of Nevada
Las Vegas, NV
Term: 07/01/2015-06/30/2019

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

GRAVENSTEIN, Stefan, MD, MPH
Professor of Medicine and Health Services Policy and Practice
Brown University
Associate Director, Center of Innovation for Long-Term Care Services and Supports
Providence Veterans Administration Hospital
Providence, RI
Term: 10/26/18 - 6/30/2022

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

MOORE, Kelly, MD, MPH,
Assistant Clinical Professor, Department of Health Policy
Vanderbilt University School of Medicine
Nashville, TN
Term: 07/01/2015-06/30/2019



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STEPHENS, David, MD
Professor of Medicine, Division of Infectious Diseases
Chair, Department of Medicine
Emory University School of Medicine
Emory University
Atlanta, GA
Term: 07/01/2015-06/30/2019

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

WALTER, Emmanuel (Chip), Jr., MD, MPH
Professor of Pediatrics
Duke University School of Medicine
Durham, NC
Term: 07/01/2015-06/30/2019

## 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

**Department of Defense (DoD)**
DEUSSING, ERIC, MD, MPH
Commander, Medical Corps, United States Navy
Department of Defense Liaison
Centers for Disease Control and Prevention
Atlanta, GA



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**Department of Veterans Affairs (DVA)**
KIM, Jane A., MD, MPH
Deputy Chief Consultant for Preventive Medicine
Office of Patient Care Services
National Center for Health Promotion and Disease Prevention
Durham, North Carolina

**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)**
NAIR, Narayan, MD
CAPT, USPHS
Division Director/Chief Medical Officer
Division of Injury Compensation Programs
Healthcare Systems Bureau
Rockville, MD

**Indian Health Service (IHS)**
WEISER, Thomas, MD, MPH
Medical Epidemiologist
Portland Area Indian Health Service
Portland, OR

**National Vaccine Program Office (NVPO)**
BECKHAM, Tammy
Acting Director

**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., D.O.
Associate Professor, Department of Family Medicine,
University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine
Ann Arbor, MI



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**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)**
EVEN, Susan, MD
Executive Director
Student Health Center
University of Missouri
Columbia, MO

**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)**
**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



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**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)**
NETOSKIE, Mark J., MD, MBA
Market Medical Executive, CIGNA
Houston, TX

**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)**
FINLEY, Christine, RN, MPH
Immunization Program Manager
Vermont Department of Health
Burlington, VT



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**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)**
SMITH, Nathaniel, MD, MPH
Director and State Health Officer
Arkansas Department of Health
Little Rock, AR

**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

**National Association of County and City Health Officials (NACCHO)**
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA



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**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 Immunization Council and Child Health Program, Mexico**
DURAN, Luis, MD
Director, Center for Children and Adolescent Health (CeNSIA)
Ministry of Health / Secretaría de Salud
Mexico

**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



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**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)**
WEBER, David, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology
University of North Carolina Schools of Medicine and Public Health
Medical Director, Hospital Epidemiology and Occupational Health, UNC Health Care
University of North Carolina
Chapel Hill, NC



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