

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

OCTOBER 20-21, 2021
SUMMARY MINUTES

TABLE OF CONTENTS

MEETING PURPOSE	3
Wednesday: October 20, 2021	3
WELCOME AND INTRODUCTIONS	3
Call to Order/Roll Call	3
Announcements	3
AGENCY UPDATES	5
Centers for Disease Control and Prevention	5
Centers for Medicare and Medicaid	6
Food and Drug Administration	6
Health Resources and Services Administration	7
Indian Health Service	7
National Institutes of Health	8
PNEUMOCOCCAL VACCINES	9
Session Introduction	9
Considerations for Age-Based and Risk-Based Use of PCV15/PCV20 among Adults and Proposed Policy Options	10
Vote #1: Pneumococcal Vaccines Age-Based Recommendation	22
Vote #2: Pneumococcal Vaccines Risk-Based Recommendation	24
ZOSTER VACCINES	27
Session Introduction	27
WG Interpretation of the EtR on Use of RZV in Immunocompromised Adults, Considerations for Use, and Proposed Policy Options	28
Vote: Zoster Vaccine	36
INFLUENZA VACCINES	37
Session Introduction	37
Phase II Safety and Immunogenicity Study of the Co-Administration of Fluzone® High-Dose Quadrivalent Influenza Vaccine and a Third Dose of Moderna mRNA-1273 COVID-19 Vaccine	37
Change in Age Indication for Flucelvax® Quadrivalent	43

PUBLIC COMMENT	45
Public Comments: October 20, 2021.....	45
Thursday: October 21, 2021	51
WELCOME AND INTRODUCTIONS	51
Call to Order / Roll Call	51
FDA Update	51
CDC Update	52
CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES	52
Session Introduction	52
Moderna Booster Dose Data.....	53
Janssen Booster Dose Data.....	59
National Institutes of Health, Mix and Match Booster Study	65
Public Comment: October 21, 2021	67
v-safe sm and VAERS: Third Dose and Simultaneous Vaccination	74
COVID-19 Vaccine Safety Updates.....	77
Myocarditis: VAERS.....	80
Myocarditis: VSD	81
VaST Assessment	84
COVID-19 Vaccine Effectiveness: Primary Series.....	88
EtR Framework.....	93
Clinical Considerations.....	98
Votes: COVID-19 Vaccine Booster Doses.....	102
Certification	105
ACIP Membership Roster	106
Acronyms Used in This document	115

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on October 20-21, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on pneumococcal, zoster, influenza, and COVID-19 vaccines.

WEDNESDAY: OCTOBER 20, 2021

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the first day of the October 20-21, 2021 ACIP meeting. She conducted a roll call, which established that a quorum was present. No potential or perceived conflicts of interest (COIs) were identified or declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. Dr. Lee acknowledged three transitions among the Liaison Representatives in 2021 and expressed great appreciation for the service that these longstanding members have provided to ACIP over the years:

- ❑ Dr. Paul McKinney, Association for Prevention Teaching and Research (APTR), who has served ACIP for decades as the APTR Liaison Representative. Dr. Richard Zimmerman will represent APTR moving forward.
- ❑ Dr. Caroline Quach, Canadian National Advisory Committee on Immunization (NACI). Dr. Shelley Deeks will represent NACI moving forward.
- ❑ Dr. Stephan Foster, American Pharmacist Association (APhA), who has served for 21 years as the Liaison Representative for APhA. Dr. Michael Hogue will represent APhA moving forward. Dr. Foster said that he smiled during the last meeting when it was announced that 70% of the COVID-19 vaccinations were administered by pharmacists. When he started at ACIP, he recalled being asked how to justify that pharmacists were even qualified to give vaccines.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, ACIP/CDC) noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 3:45 PM Eastern Time (ET) on the first day and approximately 12:00 PM ET on the second day. Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals who were not selected and any other individuals wishing to make written public comments may submit them through <https://www.regulations.gov> using Docket Number CDC-2021-0098. Further information on the written public comment process can be found on the ACIP website.

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

Dr. Grace Lee (ACIP Chair) announced that this would be Dr. Amanda Cohn's last meeting as the ACIP Executive Secretary. She recognized Dr. Cohn for her incredible service to the CDC and the ACIP as Executive Secretary over the past 6 years. Dr. Cohn received her medical degree from Emory University and completed her training in pediatrics at the Boston Combined Residency Program in Pediatrics (BCRP) before coming to CDC in 2004. Dr. Lee first met Dr. Cohn when they both were in training and their colleague and former ACIP member, Dr. Hank Bernstein, was one of their Clinic Attendings. There is a book that includes messages from ACIP members over the past 6 years, including former Chairs. While it did not make it to California in time for her trip, she will bring it the next time she comes to Atlanta. Dr. Lee read a few comments from the book:

- ❑ "Throughout your tenure as Executive Secretary of the ACIP, you have been grace under pressure."
- ❑ "You have been such a calm hand at the helm guiding the ACIP and the broader national public health community through so many challenges. Integrity, humility, intellect, trust in the people and the process—these qualities have been your North Star."
- ❑ "You have been a stupendous leader and importantly a wonderful person. Calm, knowledgeable, and always a guiding light through quite a year."
- ❑ "Amanda has been able to humbly lead people in making a real difference in public policy, especially during these unprecedented times of a pandemic, and this has earmarked you for greatness."
- ❑ "Your efforts now, as well as over the previous years, will safeguard the lives and the health of millions of persons for years to come. And beyond these meetings, you have created a sense of community for all of us. Even during these challenging times, we knew we were all in it together."

Fond memories include evening meals during the in-person meetings when they were able to get together, gathering for the group photographs on the CDC steps, lively committee discussions, Amanda's serious and concerned face and the forever engaging Amanda Cohn smile. Dr. Lee ended with a Dr. Seuss quote that someone brought up in the book, which is "You're off to great places, today is your day. Your mountain is waiting, get on your way." In addition to the book that is forthcoming, a framed picture of the ACIP version of Dr. Seuss was created for Amanda. Dr. Lee again thanked Dr. Cohn for her incredible service and dedication to the ACIP and to the country. They will be forever grateful for her time at ACIP.

Dr. Amanda Cohn (Departing ACIP Executive Secretary, ACIP/CDC) said that she was completely overwhelmed and that if they could see her face right then, it would be that smile with super, super redness all over it. She emphasized how much she going to miss all of the ACIP members, but noted that she would not be going that far away and would still attend all of the meetings. She stressed that she could not have done this without the support of all the amazing ACIP Members, *Ex Officios*, and Liaison Representatives who have been like family to her, as well as amazing mentors. She said she could not have asked for a better experience at this point in her career. She underscored the amazing support staff, Stephanie and Jessica, who secretly keep everything going when she cannot. She assured everyone that they would be in such good hands with Dr. Melinda Wharton, who has also been another mentor to her over her almost 18 years at CDC. She asked everyone to stay in touch and expressed her hope that they would be able to meet for dinner sometime in the near future and that she would be invited.

AGENCY UPDATES

Centers for Disease Control and Prevention

Dr. Amanda Cohn reported that the National Immunization Survey-Child (NIS)-Child for the years 2018-2020 that reports on children born in 2017 and 2018 was published on October 15, 2021. This report continues to demonstrate that there was lower coverage among those who are uninsured, Black, Hispanic, and living below the federal poverty line than among those who were privately insured, White, or living above the poverty line. This further demonstrates disparities in vaccine coverage, even with the amazing Vaccines for Children (VFC) Program. This report does not highlight what was seen over this past year and a half, which was decreased ordering from providers in FY-2020 and FY-2021 compared to FY-2019. There has been some rebounding of routine childhood immunizations in the private sector, but this continues to lag behind. Routine immunization remains a critical part of full recovery from the pandemic. While it remains uncertain what will happen this influenza season, CDC is preparing for resumption of seasonal influenza virus circulation. There are concerns that co-circulation of flu SARS-CoV-2 and other respiratory illnesses like respiratory syncytial virus (RSV) could place a high burden on the healthcare system. CDC is still raising awareness about the importance of influenza vaccination with its multi-year Fight Flu communications campaign. CDC is working with the Ad Council and is working to increase vaccine uptake overall, with a particular emphasis on reaching African American and Hispanic Latinx communities and those at increased risk for severe outcomes for influenza. Dr. Cohn highlighted a recent Call to Action by the National Adult and Influenza Immunization Summit (NAIIS) on August 23, 2021. This Call to Action discussed raising vaccine coverage among US adults, which was the focus of the agenda for this meeting. The NAIIS is co-led by CDC, HHS's Office of Infectious Disease and HIV/AIDS Policy (OIDP), and the Immunization Action Coalition (IAC). This highlights the tremendous benefits of vaccines, and how low levels of vaccination are made worse by the COVID-19 pandemic and ongoing disparities in immunization adult coverage in the US. The Call to Action included a series of concrete actions healthcare providers (HCP) can take to improve adult vaccination.¹

¹ <https://www.izsummitpartners.org/call-to-action-adult-immunizations/>

Centers for Medicare and Medicaid

Ms. Mary Beth Hance provided few updates on CMS activities around COVID-19 vaccines as well as routine vaccinations. Specific to COVID-19-related activities, CMS continues to provide materials as there are changes around COVID-19 vaccines. Examples include a press release that CMS issued in September reflecting the approval of the Pfizer-BioNTech booster doses and an informational bulletin that they issued in May around the expansion of the Pfizer-BioNTech vaccine to adolescents 12-15 years of age. They continue to update additional material, such as toolkits. On August 30, 2021, CMS released guidance relating to the American Rescue Plan's (ARP's) temporary 100% federal match for state expenditures for COVID-19 vaccines and vaccine administration for those enrolled in Medicaid and the Children's Health Insurance Program (CHIP). On September 9, 2021, CMS and CDC announced that emergency regulations requiring vaccinations for nursing home workers would be expanded to include hospitals, dialysis facilities, ambulatory surgical centers, and home health agencies as a condition for participating in the Medicare/Medicaid program. In addition, CMS greatly appreciates the support of its CDC colleagues. They have made many presentations to state Medicaid programs and other stakeholders on CDC's COVID-19 vaccination efforts, including efforts to get booster doses to those in congregate settings, efforts to reach adolescents, and efforts for planning for the vaccination of children 5-11 years of age. In addition, CDC and CMS continue to emphasize the importance of catching up on routine pediatric vaccinations. Again, CMS greatly appreciates this coordination. CMS continues to emphasize the importance of routine pediatric vaccinations. As Dr. Cohn just mentioned, that is clearly still an important issue. CMS has an InsureKidsNow.gov national campaign that has included a number of materials focusing on this that are available to stakeholders, states, and grantees. CMS is looking for additional opportunities to amplify this message, and continues to look forward to working with CDC on this as well.

Food and Drug Administration

Dr. Doran Fink announced that on October 14, 2021, the FDA approved an efficacy supplement to support use of Flucelvax[®] in a quadrivalent cell culture-derived seasonal influenza vaccine for use in infants and children 6 months to less than 2 years of age. This approval was based on a study of safety and immunogenicity of the Flucelvax[®] quadrivalent vaccine in comparison to a US licensed quadrivalent seasonal influenza vaccine comparator that was egg-derived. This now extends the approved use of Flucelvax[®] to all individuals 6 months of age and older. In COVID news, October continues to be an extremely busy month for the FDA. October 14-15, 2021, the FDA convened its Vaccines and Related Biological Products Advisory Committee (VRBPAC) to consider 2 Emergency Use Authorization (EUA) amendments for COVID-19 vaccines. On the first day, the committee heard presentations on data to support a booster dose of the Moderna COVID-19 vaccine for administration to certain individuals at least six months after completion of the primary series with the Moderna COVID-19 vaccine. The eligible populations requested by Moderna were the same as those that the FDA authorized in September for use of a Pfizer-BioNTech COVID-19 vaccine booster dose: individuals 65 years of age and older, individuals 18-64 years of age at increased risk of severe COVID-19 following primary vaccination, and individuals 18-64 years of age with frequent occupational or institutional exposure to the SARS-CoV-2 virus. The committee voted unanimously in favor of authorizing the EUA. There also was some discussion that began on the first day and continued into the second day about whether to lower the age range or use of a booster dose of the Pfizer and Moderna mRNA COVID vaccines to adult populations less than 65 years of age without additional risk factors for severe COVID disease or exposure to SARS-CoV-2. The committee was mixed in their discussion, with some members opining that a

lower age limit should be considered and others expressing that 65 years was the appropriate age cutoff at this time. The committee ultimately opined that the FDA should consider lowering the age cutoff as additional data on the need for a booster dose emerges. On the second day, the committee heard data to support use of a booster dose of the Janssen COVID-19 vaccine administered at least 2 months after a single dose primary vaccination with the same vaccine to individuals 18 years of age and older. VRBPAC voted unanimously in favor of the FDA authorizing that EUA amendment request. Finally, the committee heard a presentation on data from a study conducted by NIAID regarding safety and immunogenicity of heterologous or mix-and-match booster doses of COVID-19 vaccines and then engaged in a discussion of those data. VRBPAC members recognized that the study groups were relatively small in number and that the study was originally designed to be exploratory. Nonetheless, the committee members recognized the need for flexibility in implementation of COVID-19 vaccine programs. Comments provided by committee members were in favor of FDA considering these data to support EUA of heterologous booster doses to provide a regulatory allowance for mixing-and-matching. The FDA has been very busy since last Friday wrapping up its review and working toward authorization of the various EUA amendments. They expected to have some announcements later in the day. Finally, the FDA also has been reviewing an EUA amendment request from Pfizer-BioNTech for use of COVID-19 vaccine in children 5-11 years of age. The FDA will convene the VRBPAC on October 26, 2021 to present those data and FDA's review of the data.

Health Resources and Services Administration

Dr. Mary Rubin reported that the National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In fiscal year 2021, petitioners filed 22,047 claims within the program. \$210.4 million was awarded to petitioners and \$36.5 million was awarded to pay attorney's fees and costs for compensated and dismissed cases. As of October 4, 2021, HRSA had a backlog of 1477 claims alleging vaccine injury that are awaiting review. As of October 1, 2021, 3158 claims alleging injuries and death from COVID-19 countermeasures had been filed with the Countermeasures Injury Compensation Program (CICP), including 1357 claims alleging injuries from COVID-19 vaccines. About 82% of the claims are awaiting medical records for review, and about 77 claims are in medical review. More information can be found in the CICP website.²

Indian Health Service

Ms. Uzo Chukwuma provided an update on Indian Health Service (IHS) activities. IHS continues to maintain the COVID-19 vaccine effort that was initiated in September in response to agency-wide allocation, distribution, and administration of COVID vaccines within the IHS Tribal and Urban Indian Health facilities. As of October 19, 2021, the IHS data from the CDC COVID Tracker reported that 2,162,835 COVID vaccines were distributed within the IHS jurisdictions and 1,691,651 COVID vaccine doses were administered by the Office of Direct Service and Contracting Tribes (ODSCT) and other Indian organizations that chose IHS for vaccine distribution. The CDC Tracker also reported that 44.1% of the 2.1 million population has received at least 1 dose, while 36.6% are totally vaccinated. In early August, the IHS implemented a policy requiring COVID-19 immunizations for all personnel working in IHS facilities as an added strategy to minimize the risk of COVID-19 transmission to patients and among staff. The IHS Vaccines Task Force (IHS VTF) also promotes vaccine safety among American Indian and Alaskan Native (AI/AN) populations by reporting and monitoring through surveillance systems. The IHS VTF encourages the use of Vaccine Adverse Event Reporting

² <https://www.hrsa.gov/cicp/>

System (VAERS) and tracks AEs reported in the IHS Safety Tracking & Response (I-STAR) System. IHS collaborates with the CDC and engages tribal leaders and IHS on strategies to improve vaccine uptake among AI/AN populations. IHS routinely tracks pediatric immunization coverage. Long-term trends indicate a decline in immunization coverage for children 3 years of age. With the COVID-19 pandemic, a decrease in coverage was observed. Following onset of the COVID-19 pandemic, IHS immunization coverage for 3-year-old series was at 64.7%. IHS coverage fell to 57.8% by the end of the third quarter in fiscal year 2021. In response to declining childhood immunization coverage, the IHS implemented the Pediatric Immunization Improvement Project in May 2021 called “Safeguard our Future: Protect Tomorrow, Vaccinate Today.”³ Strategies included communication and a focus on media content such as blogs, quotes, provider and parents toolkits, and webinars to focus on and share best practices. The health informatics arm of the campaign concentrated on educating in the healthcare community by using data and information technology to identify and reach out to patients and recommend vaccines. HIS continues working with tribes, states, and CDC to promote childhood and adult immunization. The Influenza-like Illness Awareness System (IIAS) showed very low ILI activity over 2020-2021. In preparation of the upcoming influenza season, the IHS immunization program organized activities that included webinars with presentations from influenza experts, dissemination of information such as the ACIP recommendations, and discussions around influenza vaccine orders, and research action plans. Recently, the IHS collaborated with the CDC on incorporation of influenza vaccinations among AI/AN populations.

National Institutes of Health

Dr. John Beigel reported that the National Institute of Allergy and Infectious Diseases (NIAID) posted the preliminary findings for the homologous and heterologous booster vaccinations for those who have received an EUA COVID vaccine. As noted by Dr. Fink, the findings were presented during the VRBPAC meeting the previous week and would be presented during the second day of the ACIP meeting by Dr. Atmar. They also have been posted on the medRxiv server so that they will be available to the scientific community. NIAID also launched a Phase 2 trial for people with autoimmune disease who did not respond to the original COVID vaccine. This is unique and interesting because it uses not only an extra dose, but also is exploring how to modify or pause immunosuppressive therapy to improve the antibody response. NIAID also announced 3 large awards in September to conduct research and begin development of vaccines against multiple coronavirus types, including viral variants. This is an important step toward a pan-coronavirus vaccine. For non-COVID vaccine updates, NIAID announced the results of a human immunodeficiency virus (HIV) vaccine, the HVTN 705 study, that was conducted in sub-Saharan Africa that did not provide protection against HIV. HIV vaccine studies have been very difficult and NIAID continues to support multiple vaccine trials for that. NIAID also continues to advance influenza vaccines and just announced a new live attenuated influenza vaccine (LAIV) for intranasal administration. Dr. Beigel indicated that additional information would be provided in writing and would include links to each topic area.

³https://www.ihs.gov/sites/newsroom/themes/responsive2017/display_objects/documents/SafeguardOurFutureVaccineToolkitforParentsandFamilies.pdf

PNEUMOCOCCAL VACCINES

Session Introduction

Dr. Katherine Poehling (ACIP, WG Chair) welcomed everyone to the pneumococcal vaccine session on behalf of the Pneumococcal Vaccine Work Group (WG) and expressed the Pneumococcal Vaccine WG's sincere thanks to all of the contributors who provided important information to guide these discussions. As a reminder, the policy questions presented during the September 2021 ACIP meeting included the following:

PCV15 Age-based:

- Should PCV15 be routinely recommended to US adults ≥ 65 years in series with PPSV23?

PCV15 Risk-based:

- Should PCV15 in series with PPSV23 be recommended for U.S. adults aged 19–64 years with chronic medical conditions* or immunocompromising conditions**?

If age-based PCV20 recommendation at age ≥ 50 years:

- Should PCV20 be routinely recommended to US adults aged ≥ 50 years?
- Should PCV20 be recommended for U.S. adults aged 19–49 years with chronic medical conditions* or immunocompromising conditions**?

If age-based PCV20 recommendation at age ≥ 65 years:

- Should PCV20 be routinely recommended to US adults aged ≥ 65 years?
- Should PCV20 be recommended for U.S. adults aged 19–64 years with chronic medical conditions* or immunocompromising conditions**?

*Alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

**Chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant

The WG was very appreciative of the feedback provided during that meeting, which was very clear that it was confusing to have different age-based recommendations by vaccine. The request was to simplify the policy options for consideration for a vote. The WG took this feedback seriously and worked to figure out how to address this request. Early in the process, the WG created Guiding Principles which were that: 1) decisions on policy options should be supported by the best available evidence; 2) simplifying existing pneumococcal vaccine recommendations could help improve vaccine coverage among adults; 3) disparities in pneumococcal disease burden and vaccine coverage should be reduced; and 4) timely recommendations for each new vaccine should be made after FDA licensure.

With the feedback and these Guiding Principles, the WG had many discussions and wanted to share the rationale for harmonizing at age ≥ 65 years. As discussed during the last ACIP meeting in September, there are no data on the duration of pneumococcal conjugate vaccine immunity in adults. Due to the potential waning of immunity, vaccination at 65 years and older may be favorable when risk of disease may be higher. When the WG reviewed the data for the cost-effectiveness study at 65 years of age and older, there was consistent cost-savings (e.g., lower cost and better health outcomes compared to current recommendations) in all of the cost-effectiveness analyses. In addition, the proposed risk-based and age-based options still provide

an opportunity for higher pneumococcal conjugate vaccine (PCV) vaccine coverage, which may prevent more disease compared with current recommendations and may address health equity concerns.

The plan for this session was to present more data to explain the updated policy questions for consideration, which were:

- Should PCV20 alone **OR** PCV15 in series with PPSV23 be routinely recommended to US adults aged ≥ 65 years?
- Should PCV20 alone **OR** PCV15 in series with PPSV23 be recommended for U.S. adults aged 19–64 years with certain underlying medical conditions or other risk factors*?

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.

This led to a single risk-based and a single age-based recommendation for pneumococcal vaccine, with no recommendation for individuals without any of the identified conditions:

	19-64 Years	≥ 65 Years
None of the conditions listed below	No recommendation	Age-Based Recommendation
Chronic medical conditions† (CMC)	Risk-Based Recommendation	
Cochlear implant, CSF leak		
Immunocompromising conditions*		

†Examples include alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking *Chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies
<https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf>

During this session, Dr. Miwako Kobayashi presented considerations for age-based and risk-based use of PCV15/PCV20 among adults and proposed policy options.

Considerations for Age-Based and Risk-Based Use of PCV15/PCV20 among Adults and Proposed Policy Options

Dr. Miwako Kobayashi (CDC/NCIRD) presented the considerations for age-based and risk-based use of PCV15 and PCV20 among US adults and the proposed policy options. Currently, the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are recommended for use in US adults. As a reminder, PCV15 contains the 13 serotypes included in PCV13 and 2 additional serotypes (22F, 33F). These serotypes are referred to as PCV15 non-PCV13 serotypes. PCV20 contains the PCV20 serotypes, the 2 additional serotypes included in PCV15, and 5 additional serotypes (8, 10A, 11A, 12F, 15B). These 7 additional serotypes are referred to as PCV20 non-PCV13 types.

PPSV23 contains 4 additional serotypes that are not included in PCV20, referred to as PPSV23 non-PCV20 types (2, 9N, 17F, 20).

Pneumococcal disease can be divided into invasive pneumococcal disease (IPD) and non-invasive disease. IPD is a less frequent but severe form of illness such as meningitis, bacteremia, or bacteremic pneumonia. Non-invasive disease is a more frequent form of illness such as non-bacteremic pneumococcal pneumonia (NBP). Among US adults 19 years and older, more than 100,000 hospitalized pneumococcal pneumonia cases occurred in 2017.⁴ Approximately 30,000 IPD cases and about 3,000 IPD deaths occurred in 2019.⁵ Of the 30,000 IPD cases, 43% occurred in persons ≥ 65 years of age and about 48% occurred in persons 19-64 years of age with risk-based indications. This indicates that more than 90% of the adult IPD burden is in persons 19-64 years of age with risk-based indications and persons ≥ 65 years of age.

In this presentation, Dr. Kobayashi referred to adults 19-64 years of age who are currently recommended to receive PPSV23 only as those with chronic medical conditions (CMC) and those who are recommended to receive both PCV13 and PPSV23 as those with immunocompromising conditions (IC). Based on Active Bacterial Core Surveillance (ABCs) data for 2018-2019, 27% of remaining IPD burden was due to PCV13 types, 15% of all IPD was due to the 2 additional serotypes contained in PCV15, and approximately 30% was due to the 7 additional serotypes contained in PCV20. Adults with CMCs had a higher proportion of PCV13-type disease compared with adults with ICs. However, the proportions of additional serotypes contained in PCV15 and PCV20 were similar.

During the September 2021 ACIP meeting, the WG presented multiple policy questions on the use of new PCVs. That led to concerns that the new options would be confusing and would create more implementation challenges. After further review of data and discussions, the WG reframed the policy questions as:

- Should PCV20 alone **OR** PCV15 in series with PPSV23 be routinely recommended to US adults aged ≥ 65 years?
- Should PCV20 alone **OR** PCV15 in series with PPSV23 be recommended for U.S. adults aged 19–64 years with certain underlying medical conditions or other risk factors*?

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.

Dr. Kobayashi showed a table comparing the current and proposed options for an age-based recommendation, explaining that the proposed age-based option would apply to all adults ≥ 65 years of age. The proposed risk-based option would simplify the current risk-based recommendations. The majority of the WG members were in support of using either PCV20 alone or PCV15 in series with PPSV23 for adults ≥ 65 years of age and using either PCV20 alone or PCV15 in series with PPSV23 for adults 19-64 years of age with certain underlying medical conditions or other risk factors. A few members who were not in favor of these options did not agree mainly for 2 reasons. Some members preferred an age-based recommendation at ≥ 50 years of age since lowering the age-based recommendation may reduce disparity in pneumococcal disease burden in adults 50-64 years of age and may provide more opportunities to vaccinate adults before they develop underlying conditions or when a more robust immune

⁴ CDC SNiPP, 2017

⁵ CDC ABCs, 2018

response is expected. Some members had concerns with the PCV15 options given that it will need to be used in series with PPSV23. It is logistically more challenging to administer different vaccines and series. Providers need to know the vaccination history to correctly complete the vaccine series. If adults only receive PCV15 without returning for PPSV23, they will have lower serotype coverage.

Now to review the available data and WG considerations for an age-based recommendation at age 50 versus 65 years. The main reasons in favor of an age-based recommendation at ≥ 65 years of age for both vaccines are that: 1) due to potential waning of immunity, vaccination later in life may be favorable when risk of disease is higher for either PCV20 alone or PCV15 use in series with PPSV23; 2) an age-based option at ≥ 65 years of age was consistently cost-saving compared with current recommendations in cost-effectiveness analyses; and 3) the proposed risk-based and age-based options still provide an opportunity for higher PCV coverage, which may prevent more disease compared with current recommendations and may address some health equity concerns.

With regard to potential waning of immunity, the risk of pneumococcal disease increases with increasing age. US adults ≥ 50 are expected to live about 30 more years and US adults ≥ 65 years are expected to live 19 more years. In the cost-effectiveness analyses, it was assumed that the duration of protection from PCV vaccination is about 15-20 years. If adults are vaccinated earlier in life, they may not benefit from vaccine protection later in life when their risk of disease is higher.⁶

As a reminder, cost saving means that the intervention yields higher health outcomes and lower costs than the current recommendations in cost-effectiveness analyses. During the September 2021 ACIP meeting, Dr. Leidner summarized the findings from cost-effectiveness analyses conducted by CDC and other groups. Looking at the different scenarios considered in the CDC model for age-based use of PCV20 at age 65 and at age 50 compared with current ACIP recommendations, use of PCV20 at age 65 years consistently showed that the intervention was cost-saving. Use of PCV20 at age 50 years resulted in worse health outcomes in some CDC scenarios. The results of cost-effectiveness analyses performed by other groups also showed that that PCV20 use at age 65 years was cost-saving in most scenarios. The CDC model showed that PCV15 in series with PPSV23 at age 50 resulted in lower health outcomes compared with current recommendations. The Merck model showed that the intervention prevented more disease than current recommendations, but the intervention was less cost-effective compared with use of the series at age 65 years. Therefore, the WG did not consider PCV15 use in series with PPSV23 for adults aged 50 years and older. In the CDC model, use of PCV15 in series with PPSV23 at age 65 was cost-saving in all scenarios considered.

In terms of higher PCV coverage and how that may address some health concerns, risk-based pneumococcal vaccine recommendations have yielded low vaccine coverage in the target population. According to the National Health Interview Survey (NHIS) data in 2018, approximately 23% of adults 19-65 years of age with risk-based indications had ever received any pneumococcal vaccinations. By race and ethnicity, the Hispanic population had significantly lower coverage compared with the white population. By simplifying a risk-based option, vaccine uptake may improve in adults with underlying conditions. Another difference in the new risk-based option is that more adults would be receiving conjugate vaccines since the 2 recently licensed vaccines are both conjugate vaccines. Conjugate vaccines have the capsular

⁶ ABCs Report: Streptococcus pneumoniae, 2018. <https://www.cdc.gov/abcs/reports-findings/survreports/spneu18.html>

polysaccharide antigens conjugated to a carrier protein and induce a T-cell dependent response, whereas the polysaccharide vaccine does not.

Based on available data, different assumptions were used for PCVs and PPSV23 for the duration of protection and vaccine effectiveness (VE) in the CDC cost-effectiveness analysis model as presented during the September 2021 ACIP meeting. It was assumed that PCV effectiveness does not decline for the first 5 years, whereas it was assumed that PPSV23 has linear decline after vaccination. It also was assumed that there is higher VE for PCVs compared to PPSV23. Approximately 90% of adults 19-64 years of age currently indicated for pneumococcal vaccinations are recommended to receive PPSV23 only. Under the new risk-based policy option, more adults would be recommended to receive one of the new PCVs, which may prevent more disease in this group. This also could help address disparity in pneumococcal disease burden to some extent. The proportion of CMCs in the Black population is higher in adults 50-64 years of age compared with the proportion in the non-Black population. Therefore, the new risk-based policy option may prevent more disease in populations with higher burden of CMCs before 65 years of age.

On the use of PCV15 in series with PPSV23, there are many reasons in favor of having an option of PCV15 use in series with PPSV23 and use of PCV20 alone: 1) use of PCV15 in series with PPSV23 provides broad serotype coverage; 2) use of PSV15 in series with PPSV23 at age 65 was cost-saving in CDC's cost-effectiveness analysis; and 3) a PCV13+PPSV23 series is currently recommended, so providers have experienced using PCV in series with PPSV23. As a reminder, PCV15 provides protection against 2 additional serotypes not contained in PCV13, and PPSV23 provides coverage against 9 additional serotypes that are not contained in PCV15.

Since 2012, adults 19 years of age and older with ICs have been recommended to receive PCV13 in series with PPSV23 and all adults 65 years of age and older were recommended to receive PCV13 in series with PPSV23 from 2014-2019. In 2019, the recommendation on PCV13 use was changed to shared clinical decision-making in adults 65 years of age and older without ICs, cochlear implant, or cerebrospinal fluid (CSF) leak. In terms of PCV13 and PPSV23 coverage in adults 65 years of age and older who are Medicare Part A or B beneficiaries, coverage of both PCV13 and PPSV23 increased gradually after the age-based recommendation in adults 65 years of age and older in 2014.⁷

The WG also discussed the possibility of a preferential recommendation for PCV20 over PCV15 in series with PPSV23. The main reasons in favor of a preferential recommendation were implementation challenges associated with use of PCV15 in series with PPSV23 and improved protection against the 5 serotypes included in PSV20 but not PCV15. The main reasons against a preferential recommendation were that there are no studies directly comparing PCV15 and PCV20 efficacy and safety. The potential impact of PCV20 use alone is unknown given lack of data on clinical outcomes. Licensure of PCV15 and PCV20 was based on immunogenicity and safety, and the clinical relevance of lower immunogenicity for PCV20 compared with PCV13 is unknown. There are no PCV20 data in immunocompromised adults. Use of PCV20 alone will lose protection against serotypes included in PPSV23, but not in PCV20.

⁷ Adapted from: Pneumococcal vaccination among U.S. Medicare beneficiaries aged ≥65 years, 2010 - 2019 | CDC

For Grading of Recommendation Assessment, Development and Evaluation (GRADE), the WG reviewed immunogenicity and safety data that compared the new vaccines to current vaccines. In 3 Phase 3 trials⁸ that compared the immunogenicity of PCV15 to PCV13, both given in series with PPSV23, the geometric mean titers (GMTs) and percentage of seroresponders after receipt of the series were higher in PCV15 recipients for some shared serotypes. In 1 Phase 2 and 2 Phase 3 PCV20 trials,⁹ PCV20 recipients had lower responses by GMTs and percent seroresponders in most shared serotypes. However, in the Phase 3 trials, PCV20 met non-inferiority criteria for all 13 shared serotypes by GMT ratio. In the GRADE assessment, the certainty of evidence on the benefits of PCV20 use alone in adults with CMCs or ICs was low.

Correlative protections are not established, so the impact of these findings against the critical outcomes are known. Also, the studies targeted generally healthy adults and did not include immunocompromised persons. Therefore, the studies are not representative of the populations considered for the risk-based policy option. In adults aged 19-64 years of age who currently have pneumococcal vaccine indications, the 4 serotypes included in PPSV23 but not in PCV20 comprised 12% to 15% of all IPD burden. In adults aged 65 years and older, these serotypes comprise 8% of IPD in adults aged 65 years and older when PPSV23 coverage was estimated to be around 50% to 60%. The impact of losing protection against these serotypes by use of PCV20 alone is unknown.

To summarize the WG's considerations for an age-based option for adults 50 years of age and older and 65 years of age and older, the main reasons in favor of an age-based option at age 50 were the possibility of reducing disparity and disease burden in adults aged 50-64 years and the possibility of providing more opportunities to vaccinate adults before they develop underlying conditions. The reasons in favor of an age-based option at age 65 years were that the potential for waning immunity makes it favorable to vaccinate later in life when risk of disease is higher. The age-based option at age 65 years was consistently cost-saving in cost-effectiveness analyses. The use of the new risk-based and age-based options still provides an opportunity for higher PCV coverage in adults compared with current recommendations, which may prevent more disease and address disparity issues.

In summary of the WG's considerations on PCV20 use alone and PCV15 use in series with PPSV23, the advantages of using PCV20 alone are that it is acceptable and feasible to implement a single vaccine option. In addition, the intervention was cost-saving in most cost-effectiveness analyses and it is expected to provide better protection for the serotypes that are covered by PPSV23 alone. The potential disadvantages of using PCV20 are that the clinical significance of lower immunogenicity compared with PCV13 is unknown, there are no data in immunocompromised adults, and use of PCV20 alone will lose protection against serotypes contained in PPSV23 but not in PCV20. The advantages of using PCV15 in series with PPSV23 are that the combination will provide broad serotype coverage and age-based use at age 65 years was cost-saving in CDC's cost-effectiveness analysis. The disadvantages of PCV15 use in series with PPSV23 are it is logistically more challenging to administer PCV15 in series with PPSV23, providers need to know the vaccination history to correctly complete the vaccine series, and the intervention can result in lower serotype coverage if the series is not completed.

⁸ V114-016, V114-017, V114-018 adapted from June 2021 ACIP presentation

⁹ B7471007 (Phase 3), Klein et al. 2021 (Phase 3), Hurley et al. 2021 (Phase 2) adapted from September 2021 ACIP presentation

Unlike PCV13, PCV15 and PCV20 were licensed for use in adults first. PCV15 licensure for use in children is expected to occur in early 2022 and in 2023 for PCV20. At this point, how the use of these vaccines in children might impact the disease burden in adults is unknown. Based on these considerations, the proposed language for the age-based recommendation is:

Adults 65 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.

Based on the considerations for risk-based recommendations, the proposed language for the risk-based recommendation is as follows:

Adults aged 19 years of age or older with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.*

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.

Discussion Summary

ACIP Member Comments

- Dr. Cohn acknowledged that the Pneumococcal WG's approach to the proposed recommendations had shifted since the last ACIP meeting in September 2021, which was demonstrated clearly in Dr. Kobayashi's presentation during this session. Dr. Cohn reiterated that implementation of the adult program is of critical importance right now. The discussions that occurred at CDC and among the WG were that having two different age-based recommendations would be more confusing, and that the need to simplify these recommendations to potentially improve coverage is critical. Given that this had shifted, CDC was open to ACIP members discussing persons 50 years of age. CDC's concern was related to program implementation and the adult program.
- Dr. Talbot, a Pneumococcal WG member, elaborated on the minority opinion among the WG. As an internist, she looked at this as an internist. The majority of physicians on the WG who care for adults were very interested in starting at 50 years of age. While they recognize that duration of protection is unknown if vaccination begins at 50 years of age, physicians are happy to evaluate a booster in the future because they hope their patients live long enough and have meaningful lives to require a booster. That would require the PCV15+ PPSV23 to be given at 50 years of age. While she would not like it, she would be willing to begin at the lower the age to capture people when they are most likely to respond to vaccine and to reduce the current disparities of disease that exist. She emphasized that internists could keep up with all of the "simple" recommendations if the majority of their patients did not have multiple comorbid conditions. While they would prefer to prevent, most of their adult patients are already in therapeutic mode by the time they present and there is not as much time for all of the necessary preventative measures that are expected of them. Having age-based recommendations greatly changes how they practice and does not require them to go through a list of 20 different health co-morbidities that are required for every single vaccine in addition to mammograms, colonoscopies, and everything else. She emphasized

that the younger age group would respond to vaccine and create a lasting vaccine response much better than someone 70 years of age.

- Dr. Daley emphasized the challenges of risk-based recommendations and inquired about whether the WG talked about other means to ensure that the risk-based recommendation for persons either 19-50 years of age or 19-64 years of age would be successfully implemented to the extent possible. While this is challenging, they would be having the same conversation about hepatitis B in a couple of weeks.
- Dr. Kobayashi indicated that the WG did not go into the details about the specifics of implementation, but the hope was that simplification of the recommendations would address the current challenges with the different tiers of risk-based recommendations. Having a single risk-based recommendation could address some of the challenges, though it is likely that more efforts likely will be needed in terms of implementation as well.
- Dr. Poehling commented that the WG reflected on what happened in children with influenza vaccine. For many years there was a recommendation for children at high-risk in terms of influenza, but there was very low uptake. When children 6-23 months of age began to have an age-based recommendation, there was a significant jump in the risk-based uptake. The thought was that a consistent, clear, age-based recommendation and a simplified risk condition across age groups would enable much clearer communication in that patients and physicians could advocate for better coverage.
- Dr. Bell pointed out that based on the COVID-19 Vaccines WG discussions, it became quite clear that the proportion of the population 50-65 years of age who have chronic medical conditions, broadly defined, is very large. While she recognized the concerns about implementation of risk-based recommendations, the recommendation would cover a huge part of the population of persons 50-65 years of age. Perhaps it could be made clear in communication to providers that “risk” in the context of pneumococcal vaccines encompasses close to 3/4 of their patient populations.
- Ms. Bahta expressed concern that many people under 50 years of age would be missed. While cost-effectiveness contributes a large component of these recommendations, consideration also should be given to a policy that is equitable. While it may cost more, it may actually reduce the mortality and morbidity in some diverse communities.
- Dr. Kotton highlighted the issues regarding possible clinician confusion between various vaccines and various definitions of medical conditions and immunocompromised hosts. There are different definitions for COVID-19 and pneumococcal disease, and they would soon hear and discuss more about the shingles vaccine and immunocompromised hosts. Therefore, she advocated for standardization of the definitions—especially for immunocompromised patients.
- Dr. Long agreed the pneumococcal recommendations are very difficult. She stressed that more than 45% of severe morbidity, hospitalizations, intensive care unit (ICU) admissions, and deaths due to pneumococcus occurred in persons over 65 years of age and more than 45% occurred in those with underlying conditions. Focusing on both of these groups would prevent the vast majority of vaccine-preventable pneumococcal disease. While there are many people with underlying conditions between 50-65 years of age, most of those are not going to compromise how they would respond to a vaccine. Unlike hepatitis B for risk is

based on behaviors, pneumococcal vaccine is not behavior-based. Physicians would have to recognize only that some of their patients have any of the CMC or IC diagnoses and need to be immunized earlier. Her concern about beginning the recommendation at 50 years of age would make it much more difficult to promulgate either PCV20 or PCV15 plus PPSV23 because if PPSV23 is used in many otherwise healthy Americans, it would raise the possibility of a blunted response to subsequent immunization that almost certainly would be required.

- Dr. Cineas commented that as a primary care physician (PCP), she also greatly appreciated the efforts toward simplifying the recommendations in order to facilitate implementation. Given that there are no data for PCV20 for immunocompromised individuals, she asked whether consideration had been given to using PCV20 for age-based recommendation either at 50 or 65 years of age and then using PCV15 in series with PPSV23 for those with immunocompromised or medical conditions.
- Dr. Kobayashi indicated that the WG had this discussion early on, but there are no data even for PCV15. The data are based on immunogenicity studies, so the potential clinical impact the series with either vaccine would have remains unclear. Therefore, the WG decided to propose the options presented during previous ACIP meetings.
- Dr. Brooks observed that among persons 65 years of age and older, the proportion of disease caused by the additional serotypes included in PPSV23 but not in PCV20 was 8%. The thought about using PCV20 in series with PSV15 and PPSV23 was not as strong because this would lose 8%. Compared to 30,000 deaths, 8% is a relatively small number. Therefore, he was leaning in favor of using PCV20 by itself for simplicity. The concern about those 50-64 years of age is the higher incidence of deaths and hospitalizations due to IPD among the African American population, a lot of which can be explained by underlying conditions. Regardless of the recommendation, there must be a very clear statement that patients with underlying conditions (e.g., 75% of patients) should be vaccinated. Vaccines do not work unless they are in someone's arm versus the refrigerator. By making the recommendation relatively simple, more lives will be saved ultimately. Dr. Brooks' one concern about PCV20 alone was that in terms of clinical effectiveness, the only data available are immunogenicity data and no actual data regarding the efficacy of PCV20.
- Dr. Lee agreed with Dr. Brooks that vaccines do not save lives—vaccinations do. The importance of getting vaccines into arms cannot be underestimated. Providers need flexibility and choice in what they stock in their offices, especially private providers who are often purchasing vaccines out of pocket and need to use them efficiently before they expire. Their choices may differ depending on the populations they serve, with an anticipated request for expansion of use in the pediatric population. She could imagine as a pediatric provider that it would be far easier for her to stock PCV15 if she was seeing both children and adults as a family practice provider. ACIP had discussions years ago that the most important and most effective intervention observed has been pneumococcal conjugate vaccines delivered in childhood, which has had the biggest impact on adult burden of disease more so than individual vaccines into adult arms. To address equity, she would argue that childhood vaccination programs perhaps are going to address equity at a population level more meaningfully than individual vaccines. ACIP is asked to make decisions that are challenging and difficult in terms of trying to maximize benefits, minimize risks to individuals in the population, and consider resource use. This posed a challenge since risk-based populations kept coming up. While she did not have an easy answer, it was

important to realize that every vaccine coming at them these days was targeting a risk-based population and it would become increasingly difficult to lean on a universal vaccine approach as a way to address equity or coverage.

- Dr. Loehr commented that if it was true that 75% of people 60-65 years of age have conditions that would make them eligible for the vaccine, he absolutely agreed with going down to age 50. However, this was not his experience and he would need to see some data about the 75%. If this is accurate, it would be much easier to cover everybody. His major concern with age 50 was two-fold. First, the decline that is probably going to occur over 15 years is likely to result in the need for a booster. While recognized that by then there would be more data, PCV15 and PPSV23 was not cost-effective at age 50. He would be hard-pressed to say that he wanted PCV20 at age 50, but did not really want PCV15 and PPSV23 until age 65. That would be too awkward for him. Though he did not have a strong feeling against going down to age 50, it was not his preferred option and he probably would err on the side of going to age 65.
- Dr. Sanchez said he tended to agree with 65 years of age, although he does not see adults over 50 years of age. Essentially, these recommendations would supplant the current ones in which PCV13 is given based on shared decision-making. The proposed recommendation would be for all persons 65 years of age and older or 50 years of age and older to receive the conjugate vaccine and there no longer would be an option for just PPSV23.
- Dr. Bell cautioned people not to assume that a risk-based recommendation focused on a behavioral risk factor like the one they would be considering with hepatitis B would necessarily be the least bit transferrable to the pneumococcal recommendation about health risk. At some point, she would like to hear actual data, not in the pediatric population for whom there also are school entry requirements, but showing that expanding a recommendation from a risk group through an age group makes a large difference in terms of coverage. Everyone thinks that that is the case, but it is not clear that it actually is the case. She was concerned about lumping when maybe lumping was not necessary or appropriate. She thought that the incremental benefit of going from age 50 with chronic conditions to all age 50 would be low. The incremental benefit may be particularly low in the context of having pediatric vaccination with the pneumococcal conjugate vaccines in the foreseeable future, which is likely going to change the epidemiology greatly. They might be looking at things in a completely different way at that time. While she supported the proposed recommendation on the table, she was not totally opposed to the idea of reducing the age group to 50 years and above, but would support the WG's final suggestion and would be happy with it.
- Dr. Kobayashi clarified that she was simply sharing the example of a vaccine that has an age-based recommendation that starts at a younger age. At the time of implementation in 2006, it was for all adults 60 years of age and older. As of 2018, the data on persons 60-64 years of aged showed slow coverage and disparities. While changing the option was one thing, ensuring that implementation actually follows this is probably the key.
- Dr. Long echoed Dr. Bell's sentiments and agreed with the 65 and older recommendation. She pointed out that they must remember that they were talking about serotype coverage. For instance, perhaps 8% of serious disease or lives would be lost from PCV20 without PPSV23. It is known that the polysaccharide vaccines perform very poorly, so the hope is to eliminate pure polysaccharide vaccines in the near future. Because of the miraculous

performance of conjugate vaccines in younger individuals, the PCV20 vaccine likely would perform and eliminate any potential 8% serotype loss from not giving the full PPSV23 vaccine. Because there is a lack of efficacy data for both of the new vaccines, she would prefer at this moment to deal with persons 65 years of age and older for whom there clearly would be a benefit and not to go down to an age-base of 50 years.

- Dr. Loehr's sense was that everyone agreed with an age-based recommendation for persons 65 years of age and older. However, he did not have a clear sense of the members for an age-based recommendation for persons 50 years of age and older. If he were voting, he would vote at this moment, he would vote for 65 years of age and above and not 50 years of age and above. He suggested that they vote first for 50 years of age and older to know whether that would pass, and then they would not have to vote for 65 years of age and above.
- To go on record, Dr. Lee said that she thought the 65 years of age and older recommendation as a cutoff made the most sense given the data in hand and taking into account the broader context of the pneumococcal conjugate vaccination program. She would not be in favor of lowering the age down to 50 years given they have immunogenicity but not efficacy data.
- Dr. Talbot indicated as an internist who treats adults, she wanted to go on record to support a reduction to 50 years of age and older for PCV15 + PPSV23 as well as PCV20, because she was not worried about the cost-effectiveness of the PCV15 followed by the PPSV23 as most practices would rather invest in 1 vaccine than 2. She also supported voting on 50 years of age before 65 years of age.
- Dr. Poehling thanked everyone for the robust discussion, which the WG had as well. Given the lack of effectiveness data, she was leaning strongly toward PCV15 and PCV20 knowing that childhood vaccinations would soon be expanded to include these vaccines in the near future. She also expressed favor for persons 65 years of age and older, with the proviso that it would be very important to review the effectiveness of the recommendations in 5 to 7 years based on real-world data versus best estimates.
- While Dr. Sanchez agreed with the comments about the age 65 cutoff and favored this recommendation, he wondered if perhaps in fairness to the internists there should be a separate vote for persons 50 years of age or over to at least go on the record for persons 50-64 years of age.

ACIP Ex Officio and Liaison Member Comments

- Dr. Fryhofer (AMA) said that speaking as a practicing physician, she agreed with Dr. Talbot that there are many adults over the age of 50 years who have multiple medical comorbidities, and that she greatly appreciated the WG's attempt to simplify the recommendation. She stressed that in terms of real-life implementation, vaccinations are not always recorded completely in registries. Therefore, tracking down which vaccine has been received is challenging and sometimes impossible. She requested further information about what the downside would be of a patient receiving PCV20 + PPSV23, additional clarification for the CSF leaks and the cochlear implants, and clarification about whether the recommendation would be for an additional PPSV23 dose at 65 years of age or 5 years after the previous PPSV23 dose.

- In terms of the downside of PCV20 + PPSV23, Dr. Kobayashi indicated that the assumptions for PCV15 and PCV20 were based on available immunogenicity and safety data. The WG initially discussed the option of PCV20 in series with PPSV23. However, the cost-effectiveness analysis showed that using PCV20 alone as an age-based recommendation already was cost-saving, meaning that this would prevent more disease and cost compared to the current recommendations. While adding PPSV23 would prevent additional disease, the incremental cost was much higher so the additional disease prevented was a lot more expensive. Because of that, the WG decided to propose the PCV20 option. Regarding the prior pneumococcal recommendation for those 19-64 years of age who had cochlear implants or CSF leaks, the recommendation was to give an additional PPSV23 dose 5 years after the last dose or after age 65, whichever was later. The WG is still discussing what kind of guidance to provide for people who previously received the recommended vaccination, including what to do with people who received the risk-based recommendation earlier in life. That will be addressed in the clinical guidance.
- Dr. Goldman (ACP) said that speaking as a private physician dealing with these patients every day, physicians are managing diabetes, hypertension, heart disease; explaining medications and convincing patients why they need them; recommending eye exams, foot exams, colonoscopies, mammograms, vaccines needed as adults; et cetera. As someone who teaches his colleagues the vaccine schedule during annual meetings in terms of what they should be doing, history has shown that risk-based recommendations are confusing, onerous, and actually are a barrier to access to care. A recommendation that is as simple as getting a certain vaccine at age 50 and above is easy to digest and understand, is safe for patients, and allows more patients to get adequately vaccinated. While he truly appreciated the work of the ACIP in terms of considering the population, his primary concern is the patient sitting in front of him in terms of what is going to reduce their risk. In his opinion, a simplified age-based recommendation at 50 years of age and above would dramatically improve access to vaccination, allow his colleagues to quickly and easily digest the new recommendations to ensure their patients get the vaccines they need, and prevent a lot more disease. With respect to equity, many minority patients are not living long enough to benefit from vaccines by age 65 because of social determinants of health (SDOH). This is another reason to go down to age 50. Regarding ease of use as a private physician, a single dose vaccine would be preferable, even if a booster must be given 15 years later, to having to deal with intervals for which patients do not always return for a second dose.
- Dr. Schmader (AGS) indicated that AGS wanted to go on record in support of the currently proposed age-based recommendation for adults 65 years of age as stated based on the evidence and advantage, extended beautifully by Dr. Kobayashi, and in agreement with the majority of the WG members. The AGS certainly was not opposed to an age-based recommendation of 50 and older if a booster is available and effective.
- Dr. Hayes (ANA) made a statement on behalf of the National Association of Hispanic Nurses (NAHN) who went on record as strongly urging the ACIP to consider expanding access of pneumococcal vaccines. The benefit of the pneumococcal vaccine is both to the recipient as well as to the indirect vaccine benefit for non-vaccinated populations. The NAHN supports the following recommendations that are specifically impacting Hispanic populations: 1) expansion of recommended age range to include those 50 years of age and over; 2) use of a single-dose vaccine regimen to ensure uptake and access to equitable preventative care; and 3) increase efforts to reduce health inequity related to vaccines. Dr. Hayes noted that

the NAHN comments were much longer and would be uploaded to the Public Comment section of the docket so that everyone could read the full document they submitted.

- Dr. Grogg (AOA) indicated that to AOA primary care practitioners, simplification would be the use of a single vaccine rather than two vaccines. However, they have not discussed the time period in terms of whether to give the PCV15 and polysaccharide at 8 weeks apart or 1 year apart. Either way is likely to decrease compliance.
- Dr. Zimmerman (University of Pittsburgh) shared an anecdote of a woman in his practice who had pneumococcal bacteremia with joint and tendon involvement at less than 65 years of age for whom an age-based 50 years and older recommendation might have provided protection. While they do not know what serotype she was infected with, there is some burden among people who are less than 65 years of age who do not have an identifiable risk factor who would benefit from an age-based recommendation. His practice is a Federally Qualified Health Center (FQHC).

Pfizer and Merck Comments

- Dr. Luis Jodar (Pfizer) thanked the members of the ACIP for the opportunity to speak to them and Dr. Kobayashi for a great presentation. On behalf of Pfizer, he provided three brief comments on the session's presentation as ACIP prepared for further discussions and a vote. First, it was mentioned earlier by Dr. Cohn that the updated policy options considered during this meeting constituted a drastic change of the policy options that were discussed during the June and September 2021 ACIP meetings. The policy options discussed in these meetings clearly separated the two proposed pneumococcal conjugate vaccinations discussed, PVC20 and PCV15. The conclusions of the EtR Framework presentations in June and September for PCV20 alone, 50-65 age-based, 19-49 age-based, and 19-64 risk-based recommendations were very favorable toward intervention and were either cost-effective or cost-saving. In contrast, the EtR Framework conclusions for the other proposed intervention given in series were more uncertain, with no clearly favorable conclusions. Pfizer requested that the ACIP vote on the remaining options equally. Pfizer does not believe that these options are equal as evidenced by the very different EtR Framework conclusions presented during previous meetings. For these reasons and regardless of what the ACIP decided during this meeting, Pfizer respectfully requested that the committee vote on each intervention separately based on their relevant merit. Second, the WG provided 3 points of the rationale for harmonizing to the 65 year old age group. These 3 points are complex as the discussion showed, and Pfizer believed that they merited further discussion by the WG and the ACIP. Of more concern to Pfizer is the potential downstream effects that age-based and risk-based recommendations are promoting or exacerbating in terms of health equity as pointed out in the previous EtR. Regarding the potential complexity of having 2 different age-based cutoffs, there is substance for ACIP making such recommendations. For example, the 60 plus recommendation for Zostavax[®] and the 60 plus recommendations for Shingrix. Pfizer respectfully requested that ACIP reconsider, either now or in the near future, the use of PCV20 at age 50 for the reasons outlined by the WG previously. Finally, Pfizer respectfully asked the committee to provide guidance for those people previously vaccinated with PCV13, PPSV23, or both to have the option to receive the additional protection provided by PCV20. Currently, people such as immunocompromised persons may have received PCV13 almost 9 years ago and could benefit from receiving a dose of PCV20. Dr. Jodar emphasized that Pfizer stands ready to work with CDC, the WG, and ACIP to provide any additional data to support such deliberations. On a personal note, he thanked Dr. Cohn for her partnership over the years and wished her the best.

- Dr. Rick Haupt (Merck) thanked ACIP for allowing Merck to make public comments regarding the deliberations and upcoming vote later in the day, and the Pneumococcal Vaccine WG for all of its efforts to ensure and simplify recommendations for adult pneumococcal vaccination. Merck agreed that the proposed language was consistent with the principles set forth by the WG at the beginning of the adult vaccination policy review in October of 2020. As a reminder, he made comments in September and provided information to the WG about PPSV hypo-responsiveness and stated unequivocally that scientific evidence does not support the hypothesis of PPSV-induced hypo-responsiveness when there is an adequate interval between doses. PPSV sequential regimens are not detrimental to booster immune responses in adults. As reviewed at the September 29, 2021 ACIP meeting, the final recommendation language proposed by the WG was economically favorable and consistently cost-saving across various scenarios. The language being proposed during this session would allow HCPs the option to choose between a sequential PCV15+PPSV22 regimen or a single dose of PCV20 regimen based on the risk profile of the individual being considered to be vaccinated. Pfizer also expects that the current risk-based recommendation would significantly address equity, especially in persons 50-64 years of age, which had been the subject of much discussion during these ACIP deliberations. In this age group, IC and individuals with CMCs account for 30% of the population, but contribute 70% of the pneumococcal disease burden. Therefore, it is reasonable to focus on this population using a risk-based approach. Merck already has begun taking orders for PCV15 and would begin distributing doses to customers in the coming weeks. They expect to have sufficient supply to meet the demand for recommendation of both the 65 year old age-based cohort as well as the 19-64 age cohort with underlying medical conditions or risk factors following the vote during this meeting. Finally, Dr. Haupt thanked the WG members and the ACIP members for all of their efforts and deliberations regarding the adult pneumococcal vaccine policy. Merck looks forward to working with the WG as they start deliberations regarding pediatric pneumococcal vaccine policy after the conclusion of the adult policy vote.

Vote #1: Pneumococcal Vaccines Age-Based Recommendation

Dr. Kobayashi (CDC/NCIRD) showed the first proposed age-based recommendation based on the majority of WG members having put this forward as what should be discussed and voted on by the ACIP:

Adults 65 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.

Discussion Summary

- Dr. Cohn reminded everybody that after the vote on the age-based recommendation, there was a second proposal on the table for the risk-based recommendation.
- Dr. Bell made a motion to approve the proposed age-based recommendation language as written, which Dr. Loehr seconded.

- Dr. Talbot made a motion to amend the proposed age-based recommendation from “Adults 65 years of age or older” to “Adults 50 years of age or older.” The remainder of the text would stay the same. Ms. Bahta seconded this amendment.
- After reviewing *Robert’s Rules of Order*, Dr. Lee indicated that the approach would be to vote first on the proposed amendment to “Adults 50 years of age or older” and whether the recommendation should be changed. They would then return to the main motion depending upon the results of the vote on the amended motion.

Amended Motion/Vote #1: Pneumococcal Vaccines (Age-Base)

Dr. Talbot made a motion to amend the proposed age-based recommendation to read as follows: *Adults 50 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.* Ms. Bahta seconded this motion to amend. No COIs were declared. With 4 affirmative votes, 11 negative votes, and 0 abstentions, the motion to amend did not carry. The disposition of the vote was as follows:

- 4 Favored:** Ault, Talbot, Bahta, Cineas
11 Opposed: Bell, Brooks, Chen, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez
0 Abstained: N/A

Initial Motion/Vote #1: Pneumococcal Vaccines (Age-Base)

Dr. Bell made a motion to approve the proposed age-based recommendation reading as follows: *Adults 65 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.* Dr. Loehr seconded this motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

- 15 Favored:** Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A

Vote #2: Pneumococcal Vaccines Risk-Based Recommendation

Dr. Kobayashi (CDC/NCIRD) showed the following proposed risk-based recommendation for pneumococcal vaccines:

Adults aged 19 years of age or older with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.*

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.

Discussion Summary

- Ms. McNally made a motion to approve the proposed risk-based recommendation language as presented. Dr. Daley seconded the motion.
- Dr. Kimberlin (AAP Red Book) asked for clarity with regard to whether the ACIP was voting in favor of both the age-based recommendation and the risk-based recommendation versus one or the other.
- Dr. Lee clarified that the age-based recommendation was for persons 65 years of age and older, while the risk-based recommendation pertained essentially to individuals 19-64 years of age with underlying medical conditions or other risk factors.
- Dr. Long pointed out that potentially, the vaccines could be split out. She suggested that the language for the proposed risk-based recommendation be changed from “Adults aged 19 years of age or older” to “Adults aged 19-64 years of age.”
- Dr. Kobayashi indicated that this clarification could be made.
- Dr. Brooks expressed concern that the list of underlying medical conditions did not include hypertension and obesity, which a large proportion of the population would have and who might benefit from getting vaccinated at a younger age.
- Dr. Kobayashi clarified that while there have been discussions about adding underlying conditions, those listed in the proposed recommendation were exactly the same as listed in the current risk-based recommendations. At this point, the WG focused on recommending the new vaccines. In the future, because suggestions have been received about adding other conditions, the WG will review those for consideration and would be happy to revisit hypertension and obesity as well.
- Dr. Long recalled that there were no data to suggest that obesity and hypertension posed increased risks for IPD.
- Dr. Kobayashi indicated that the WG started looking at the risk associated with obesity, but had not had time to take a deeper dive into whether certain conditions warrant consideration as part of the risk-based recommendation. If warranted, the WG will be happy to review those data in more depth.

- Ms. Bahta pointed out that practitioners would be seeing people who received pneumococcal conjugate vaccines in infancy and inquired as to whether there would be clinical guidance about those persons and whether they should receive vaccination from 19 years of age onward, given that this may be confusing.
- Dr. Kobayashi confirmed that the clinical guidance would be reviewed by the WG and presented to the ACIP during a future meeting. The clinical guidance will accompany the new recommendations.
- Dr. Hogue (APhA) recognized that the implementation recommendations from CDC would come with a publication. However, in the previous recommendation, the interval for the dosing of PPSV following conjugate vaccine was clearly stated in the recommendation. He asked whether there would be value in the last sentence by stating that, “If PCV15 is used, this should be followed by a dose of PPSV23 at least 1 year later” in order to help eliminate confusion.
- Dr. Kobayashi confirmed that the previous votes included the intervals. The WG discussed the possibility of harmonizing the recommended intervals to “at least 8 weeks” or “at least 1 year.” Based on the current discussion, the WG was leaning toward harmonizing to “at least 8 weeks” because that would give clinicians more flexibility and also would provide an opportunity for those with compromising conditions to receive the second dose sooner. However, there are data suggesting that waiting longer might induce a better immune response—especially in immunocompetent adults. Because of that, the WG’s hope was to include that as part of the clinical guidance with some clarity on who might benefit from certain intervals.

Motion/Vote #2: Pneumococcal Vaccines (Risk-Based)

Dr. Bell made a motion, which Dr. Loehr seconded, to approve the proposed age-based recommendation reading as follows:

Adults aged 19-64 years of age with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.*

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.

No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A

Member Statements

Subsequent to the votes, Dr. Lee invited ACIP members to make a statement about the rationale for their vote and/or to share any additional general comments.

- Dr. Brooks said that though he voted “yes,” he continued to have some concerns that the disparities in outcomes related to IPD may not be totally addressed by these recommendations. Although there seems to be evidence related to hypertension or obesity not being a higher risk for IPD, he would like to see the data and then theoretically revisit the underlying conditions at some time in the near future.
- Dr. Talbot pointed out that they voted on age ≥ 65 not for scientific reasons but because that was the age chosen for Social Security and Medicare. In 1935, the reason 65 years of age was chosen was that the average life expectancy of a man was about 60 years and a woman about 64 years. That is not a very scientific way for ACIP to move forward with adult immunization. It made sense at one time, but they really need to be more science-based going forward in terms of adult immunizations. They should reevaluate the correct age at which to vaccinate in order to improve healthcare in adults and older adults.
- Dr. Kotton emphasized the importance of ensuring that ACIP accumulates clinical data, because they are making a recommendation for immunocompromised and other at-risk patients largely on immunogenicity. This situation needs to be monitored to ensure that robust clinical protection continues and immunologic data are collected.
- Dr. Loehr thanked the Pneumococcal WG for all of their hard work and recognized that it was a very difficult process getting all of these data corralled and presented in a way that made sense for ACIP to vote on. He also emphasized the importance of revisiting this in 5 to 7 years after children have received the vaccinations to consider whether this recommendation is still necessary at that time.
- Dr. Long pointed out it would be increasingly important for those who take care of adults who will or will not be impacted by this decision, to submit isolates for serotyping if there is IPD. This is not a completely preventable disease and the likelihood is high that immunocompromised patients specifically have non-vaccine serotypes. Clinical observations will be very important.
- Dr. Daley thanked his colleagues on the ACIP, pointing out that he learns something new or gains a new perspective every time one of them speaks. He stressed that the work does not end once ACIP has made a vote or a decision. He agreed with everything his colleagues had mentioned in terms of things that need to be monitored very closely. Another of these would be coverage in persons 50-64 years of age with CMCs to see if these recommendations are achieving the intended goals.
- Dr. Lee agreed that they need to continue to review the data on effectiveness and not just immunogenicity, to monitor access and potential disparities carefully over time, and to remember that this is a dynamic decision-making process for which decisions need to be reconsidered when the time comes. At some point in the future, it may make sense to lower the age group. Given the data available at this point, she felt very comfortable with the decision ACIP made on the age-based and risk-based thresholds.

- Dr. Brooks underscored how impressive the work was from the WG. The last time this information was presented, it was all over the place. It was not the WG's fault, but instead was the complexity of the topic. Given that the WG was able to distill the information down to the 2 votes that were taken that were unanimous, he wanted them to understand how deeply he believed the whole committee appreciated what the WG and Dr. Kobayashi did, even if there remained some trepidation and concern.

ZOSTER VACCINES

Session Introduction

Dr. Camille Kotton (ACIP, WG Chair) reminded everyone of the zoster vaccine timeline. The recombinant zoster vaccine (RZV) was licensed by the FDA in 2017. CDC subsequently adopted the ACIP's recommendation in January 2018. The European Medicines Agency (EMA) approved an expanded RZV indication in August 2020 for adults 18 years of age and older at increased risk for zoster. A Supplemental Biologics License Application (sBLA) was submitted to the FDA in Fall 2020 to support RZV use in immunocompromised persons 18 years of age and older. ACIP began reviewing this earlier in 2021. The FDA approved the expanded RZV indication for use in immunocompromised adults 18 years of age and up in July 2021. With that in mind, the policy question now before ACIP is as follows:

- Should adults ≥ 19 years of age who are or will be immunodeficient or immunosuppressed due to disease or therapy be recommended to receive two doses of the recombinant zoster vaccine for the prevention of herpes zoster and its complications?
- Including but not limited to:
 1. Hematopoietic stem cell transplant (HSCT) recipients
 2. Patients with hematologic malignancies (HM)
 3. Renal or other solid organ transplant (SOT) recipients
 4. Patients with solid tumor malignancies (STM)
 5. People living with human immunodeficiency virus (HIV)
 6. Patients with primary immunodeficiencies, autoimmune conditions, and taking immunosuppressive medications/therapies

For the Evidence to Recommendation (EtR) Framework, the population is defined as immunocompromised adults at least 19 years of age. The intervention is 2 doses of RZV administered at least 4 weeks apart. The comparison group is no vaccine. Critical outcomes include herpes zoster (HZ) or serious adverse events (SAEs). Important outcomes include postherpetic neuralgia (PHN), HZ-related hospitalization, immune mediated disease (IMD), reactogenicity (Grade 3), graft versus host disease (HSCT), and graft rejection (SOT).

During the September 2021 ACIP meeting, the WG discussed the economics of vaccinating the IC population 19-49 years of age against HZ in the US and the preliminary EtR Framework regarding the use of RZV in IC adults ≥ 19 years of age. The WG subsequently convened 2 meetings during which they reviewed and discussed the feedback received during the September 2021 ACIP meeting, EtR Framework updates, considerations for use of RZV in IC adults, and proposed policy options. The presentations during the October 2021 Zoster Vaccine session focused on the WG's interpretation of the EtR Framework regarding use of RZV in IC adults, considerations for use, and policy options.

WG Interpretation of the EtR on Use of RZV in Immunocompromised Adults, Considerations for Use, and Proposed Policy Options

Dr. Tara Anderson (CDC/NCIRD) summarized the WG's interpretation of the EtR Framework for use of RZV in IC adults, considerations for use, and proposed policy options. She first recapped the policy question, 6 groups, and the PICO (Population, Intervention, Comparison, Outcomes) questions presented by Dr. Kotton and then summarized the available evidence and WG determination for each EtR domain: Public Health Problem, Benefits and Harms, Values, Acceptability, Resource Use, Equity, and Feasibility.

For the public health problem domain, the WG assessed whether HZ in IC adults is of public health importance. As previously discussed, millions of persons in the US are immunocompromised. In the 2013 NHIS, approximately 7 million adults self-reported immunosuppressed status. The prevalence varies by age ranging from 1.6% for those 18-39 years of age to 4.4% among those 50-years of age, with an overall total of 2.7%.¹⁰ There are an estimated 3 million among HSCT recipients, patients with HM, renal or SOT recipients, patients with STM, and people living with HIV. In addition to these groups, there are an estimated 22 million with more than 80 diverse autoimmune and/or inflammatory (AI/INF) conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD). These patients often have underlying immune defects but generally are not considered frankly IC unless they are on immunosuppressive treatments. Importantly, an increasing proportion of immunocompromised patients are likely to be treated with immunosuppressive medications and therapies.¹¹

The age-specific prevalence of these conditions is highly variable by condition. HZ is common in the general population. There were approximately 1 million cases of HZ per year in the US during the pre-HZ vaccine era.¹² HZ rates increase with age, with incidence rates ranging from about 2 to 9 per 1000 persons.¹³ As previously noted, the IC population at higher risk for HZ is substantial. A systematic literature review regarding the risk of HZ in groups 1-5 noted that the median HZ incidence estimates for these IC groups exceeded those reported for immunocompetent adults 50 years of age and older. The incidence rate of HZ ranged between 9 and 95 per 1000 person years. There was variation in study estimates for the cumulative incidence and the incidence of HZ within each group and between groups. In the systematic review, it was also noted that HZ complications and severe disease were increased in IC populations. However, the data were insufficient to assess risk by group.¹⁴

Regarding available data for PHN, approximately 6% to 10% of immunocompromised patients experienced PHN versus about 4% overall in administrative claims databases.¹⁵ Between 6% and 45% experience PHN across immunocompromising conditions and studies.¹⁶ Approximately 3% of IC patients experience disseminated HZ,¹⁷ but it is exceedingly uncommon in healthy persons. Between 10% and 17% mortality has been associated with disseminated HZ

¹⁰ Harpaz R, Dahl RM, Dooling KL. Prevalence of Immunosuppression Among US Adults, 2013, JAMA, 2016, 316(23):2547-8. Excerpt of Table; Self-reported Immunosuppressed Status

¹¹ See slide 75 in Dr. Anderson's presentation

¹² Harpaz et al. Prevention of Herpes Zoster, MMWR, June 6, 2008, Vol 57, #5

¹³ Figure: CDC, unpublished data; Updated from Harpaz et al. Clinical Infectious Diseases, Volume 69, Issue 2, 15 July 2019, Pages 341-344, <https://doi.org/10.1093/cid/ciy953>

¹⁴ McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125-34

¹⁵ Chen et al. Incidence of herpes zoster in patients with altered immune function. Infection 2014; 42(2): 325-34

¹⁶ McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125-34

¹⁷ McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125-34

among renal transplant recipients.¹⁸ Finally, 8% of HCT recipients with HZ are hospitalized¹⁹ versus less than about 1% of overall Medicare beneficiaries with HZ.²⁰

Regarding the risk of HZ in IC Group 6, the authors of one study evaluating the risk of HZ in autoimmune and inflammatory conditions determined that there is an approximately 2- to 4-fold higher risk of HZ in patients with autoimmune and inflammatory conditions than in healthy individuals.²¹ Another recent study identified similar results, with an approximately 1.5-fold higher risk of HZ for unvaccinated Medicare beneficiaries with autoimmune conditions versus those who are not IC.²² It was noted that the risks varied across conditions and by age groups. Age standardized HZ incidence rates varied with the highest rates in patients with SLE, IBD, and RA. Age-specific incidence rates among some persons 21-50 years of age can be comparable to, or substantially higher than, corresponding rates in healthy adults greater than 60 years of age—particularly patients with SLE, IBD, and RA.²³ The impact of immunosuppressive therapies is another consideration for these patients. The standard of care is for patients to be on one or more immunocompromising therapies, the duration of which can be months, years, or lifelong. In addition, it is not possible to define high risk subgroups based on anticipated therapies since treatments are very different from condition to condition and even over time for individual patients based on their response, tolerability, and other factors.

To summarize important points from WG discussions, IC populations are very heterogeneous, both across and within groups and among individuals over time. The risk of HZ and its complications is generally higher in IC populations, although there is variability across and within groups. It is not feasible to define every possible IC condition and medication/therapy combination. In addition, it is important to consider broad recommendations and provider guidance for IC populations. The WG extensively reviewed these and other findings and concluded that HZ and its complications in IC adults is of public health importance.

Now moving on to benefits and harms, Dr. Anderson reviewed the available evidence regarding how substantial the desirable and undesirable anticipated effects of RZV in IC adults are for each main outcome and summarized the WG's interpretation regarding whether the desirable effects outweigh the undesirable effects. A total of 19 studies were included in the evidence synthesis. Of these, 9 studies were included in the review of evidence and GRADE analysis since they included a comparative group. There were 7 randomized control trials (RCTs) and 2 cohort studies across several IC populations, including patients with HM, renal transplant recipients, solid tumor patients, autologous HSCT (aHSCT) recipients, patients living with HIV, patients with immune-mediated diseases (IMD), patients with IBD, and Medicare beneficiaries with autoimmune and IC conditions.

¹⁸ Rommelaere et al. Disseminated varicella zoster virus infection in adult renal transplant recipients: Outcome and risk factors. *Transplantation Proceedings*. 2012; 44(9): 2814-2817; and Kirnap et al. Prevalence and outcome of herpes zoster infection in renal transplant recipients. *Exp Clin Transplant*. 2015; Apr;13 Suppl 1:280-3

¹⁹ Winston et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, doubleblind, placebo-controlled trial. *Lancet (London, England)* 2018; 391(10135): 2116–27

²⁰ Izurieta et al. Effectiveness and duration of protection provided by the live-attenuated herpes zoster vaccine in the Medicare population ages 65 years and older. *CID* 2017;64(6):785–93.

²¹ Yun et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases. *Arthritis & Rheumatology* 2016;68(9):2328-2337

²² Izurieta et al. Recombinant Zoster Vaccine (Shingrix) real-world effectiveness in the first two years post-licensure. *Clinical Infectious Diseases*, 2021; ciab125, <https://doi.org/10.1093/cid/ciab125>

²³ Yun et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases. *Arthritis & Rheumatology* 2016;68(9):2328-2337. Excerpt of Table 2. Incidence rate of herpes zoster per 1000 person years by 10 year age group and auto-immune disease or comparator cohort.

The outcomes included in the overall GRADE analysis that were considered to be critical included HZ and SAEs, which were reviewed during this presentation. The important outcomes (PHN, HZ-related hospitalization, IMD, HCT, SOT, and reactogenicity Grade 3) were addressed in supplemental slides. For the first critical outcome of HZ, using the efficacy population based on 5 studies, the VE estimates ranged from 68% to 100%. Estimates were generally higher in young adults within a population and lower for aHSCT recipients. There are 2 peer-reviewed cohort studies, Izurieta 2021 and Khan 2021 with VE reported. Izurieta et al reported on Medicare beneficiaries, with VE among autoimmune patients of 68% and IC patients of 64.1%. Khan et al looked at VA patients with IBD and found adjusted hazard ratios of 0.41 for those over 60 years of age who were non-steroid users and 0.34 for those who were steroid users. The hazard ratio was zero for persons 50-60 years of age since no cases were reported.

Using the efficacy population for studies reporting immunogenicity and looking at the vaccine response rate for both humoral and cell-mediated immunity (CMI) across the 6 included RCTs, these studies show that there was a vaccine response. Starting with humoral immunity, response rates ranged from a low of 65.4% to a high of 96.2% at 1 month after the last dose. This somewhat decreased at the 12-month evaluation mark, with response rates ranging from a low of 51.5% to a high of 91.7%. For CMI, the response rates ranged from a low of 50% to a high of 93% at 1 month after the last dose, decreasing to a low of 17.6% and a high of 66.7% at 12 months after the last dose.

Looking at the GRADE Evidence Table for the first critical outcome of HZ, the evidence type began at Type 1 for the RCTs. There was no serious risk of bias identified and there were no concerns for inconsistency or imprecision. The body of evidence was downgraded for indirectness due to not comprising data on all relevant populations under the recommendation. The VE estimates ranged from 68.2% to 90.5%, with an overall certainty of Type 2 or moderate certainty. For RCTs containing immunogenicity data, the risk of bias was not serious and there were no concerns with inconsistency or imprecision. However, the body of evidence was doubly downgraded for indirectness due to both studies not comprising the range of populations under consideration for the outcome, and also because immunogenicity is a surrogate outcome. This evidence was graded Type 3 or low certainty. For the cohort data, the evidence started at Type 3. There were no serious concerns with risk of bias, inconsistency, or imprecision. However, the studies were downgraded due to indirectness and upgraded due to a strong association observed among those over 50 years of age. The evidence was graded Type 3 or low certainty.

For outcome 4, SAEs, 7 randomized studies evaluated multiple IC populations. Overall, SAEs were balanced between the vaccine and placebo groups. Using the harms population, or those who received at least 1 dose of RZV, there was a risk ratio of SAEs ranging from 0.79 to 1.99. It is important to note that this population is significantly ill and thus the high proportion of SAEs in both the vaccine and placebo groups are not unexpected. However, the SAEs related to vaccination were much less common, ranging from 0.33 to 1.6% in the vaccine group and 0.36 to 0.76 in the placebo group. For the GRADE Evidence Table for outcome 4, SAEs, the evidence type started at Type 1 and the body of evidence was downgraded only for indirectness. The proportions of RZV and placebo recipients experiencing any SAEs had risk ratios ranging from 0.79 to 1.99, but generally represented a similar proportion of SAEs in both groups. This body of evidence was graded with the certainty of Type 2, or moderate certainty.

To briefly summarize the GRADE results going through each outcome and major findings, the details for the important outcomes are available in the supplemental slides for reference. For benefits, the body of evidence showed relatively high VE across these heterogeneous IC populations, ranging from 68.2% to 90.5%. For PHN and HZ -related hospitalization, there was

little evidence with just one study that reported VE of 89% for PHN and 85% for HZ. For harms, SAEs were common and balanced in both vaccine and placebo groups, with risk ratios ranging from 0.79 to 1.99. SAEs attributed to vaccination were rare. IMDs were not shown to be increased for those in the RZV group. There was little data on HSCT and SOT, with one RCT each showing no increased risk of rejection. For reactogenicity, RZV was noted to be reactogenic with increased recorded local and systemic reactions in the RZV group. The limited data for some harms outcomes highlights the need for additional research as well as provider counseling, for example regarding appropriate timing of vaccination for some IC patients. Post-marketing surveillance will be critical to detect any rare SAEs, which were not identified in the clinical trials. Upon review of these data, the WG concluded that the desirable anticipated effects of RZV in IC adults are large and that the undesirable anticipated effects of RZV are small. Overall, the WG concluded that the desirable effects outweigh the undesirable effects which favors the intervention of RZV 2 doses at least 4 weeks apart.

Moving on to the values domain, the WG considered whether IC adults feel that the desirable effects of RSV are large relative to the undesirable effects and whether there is important uncertainty about or variability in how much IC adults value the main outcomes. There are limited data on knowledge, attitudes, and practices (KAP) among IC patients regarding potential use of RZV for the prevention of HZ and its complications. In general, HZ vaccination, including with zoster vaccine live (ZVL) and RZV is increasing,²⁴ and RZV series completion rates are high by 6 to 12 months after the first dose.²⁵ Although there is currently no ACIP recommendation, IC patients recognize the increased risk of HZ and many have already received RZV, as noted in a large study of Medicare data where nearly 1 million patients met the study definitions of autoimmune and IC and received RZV.²⁶ Concerns related to Grade 3 reactions may discourage some IC patients from getting RZV.

In summary, many IC patients desire the ability to receive RZV to prevent HZ and its complications. In fact, many are already pursuing vaccination with RSV as part of regular care, as shown in the Izurieta et al Medicare analysis. The ACIP HZ WG placed high value on the prevention of HZ and its complications in IC adults. Given the burden of HZ and its complications in these patients, it is anticipated that more IC patients would pursue vaccination with RZV if recommended by ACIP and their provider. Upon reviewing these data, the WG concluded that IC adults probably feel that the desirable effects of RZV vaccination are large relative to the undesirable effects and that there is probably not important uncertainty or variability in how much IC adults value the main outcomes.

Turning now to the acceptability domain, the WG considered whether vaccination with RZV is acceptable to key stakeholders working with IC adults.²⁷ Primary care physicians' perspectives were captured in a recent University of Colorado Denver KAP survey. The objectives of this survey were to assess among PCP serving adults: 1) current practices, attitudes, knowledge, and barriers to recommending RZV; and 2) the likelihood of recommending RZV to IC patients among the physicians who had not previously recommended RZV to these patients. Physicians

²⁴ Terlizzi EP and Black LI. Shingles Vaccination Among Adults Aged 60 and Over: United States, 2018. NCHS Data Brief, No. 370, July 2020; and Kawai K and Kawai AT. Racial/Ethnic and Socioeconomic Disparities in Adult Vaccination Coverage. *Am. J. Prev. Med.* 2021;000(000):1–9

²⁵ Izurieta et al. Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. *Clin. Infect. Dis.* 2021 Sep 15;73(6):941-948; and Patterson et al. Early examination of real-world uptake and second-dose completion of recombinant zoster vaccine in the United States from October 2017 to September 2019. *Hum. Vaccin. Immunother.* 2021 Aug 3;17(8):2482-2487

²⁶ Patterson et al. Early examination of real-world uptake and second-dose completion of recombinant zoster vaccine in the United States from October 2017 to September 2019. *Hum. Vaccin. Immunother.* 2021 Aug 3;17(8):2482-2487

²⁷ Hurlley et al., unpublished data

in existing Vaccine Policy Collaborative Initiative (VPCI) sentinel networks were surveyed. Family physician (FP) and general internist (GIM) results were combined, with any differences highlighted.

Regarding physician strength of recommendation for RZV and different types of patients 50 years of age and older, recommendations for healthy adults, adults anticipating a bone marrow or solid organ transplant who were not yet on immunosuppressive therapy, and adults on low dose methotrexate were consistent with current ACIP recommendations with 96%, 79%, and 70% respectively strongly recommending or recommending but not strongly RZV. Regarding patients without an ACIP recommendation, the strength of recommendation for RZV varied considerably by age and health status, with 67% strongly recommending or recommending but not strongly RZV for adults 50 years and older with HIV to 42% strongly recommending or recommending but not strongly RZV for adults 50 years and older receiving immunosuppressive therapy for a bone marrow or solid organ transplant. Of note, 27% to 42% of respondents noted that they defer to a sub-specialist for these IC populations 50 years and older.

For adults 18 to 49 years of age with an immunocompromising condition, 31% of respondents noted strongly recommending or recommending but not strongly RZV. Among physicians who had not recommended RSV to IC patients, the likelihood of recommending RSV to a range of IC patients 18 years of age and older was very likely for 40% to 48% of respondents and somewhat likely for 23% to 33% of respondents. Since these responses were based on how likely a respondent would be to recommend RZV to IC patient within the first 6 months of an approval and without input from a sub-specialist, these results highlight the importance of provider guidance for vaccination of IC patients.

In summary, given highly specialized care and the increased HZ risk among IC patients, the WG noted the vaccination is favored if there are no safety concerns. Although currently available evidence was considered acceptable by the WG, it was noted that additional safety data represent a research need. Importantly, despite the lack of recommendation from ACIP, many physicians are recommending RZV to patients with immunocompromising conditions. Of note, physicians need more direction on which patients are eligible for RZV, including a substantial minority who would be unlikely to recommend RZV to various IC patients even if it were licensed, recommended, and covered by insurance for them without input from a sub-specialist. In addition, many specialty organizations are recommending RCV for IC adults. Overall, the WG anticipates that acceptability would increase with FDA approval and an ACIP recommendation. Upon review of these data, the WG concluded that use of RZV in IC adults is acceptable to key stakeholders.

Moving on to the domain of resource use, the WG considered whether RZV in IC adults is a reasonable and efficient allocation of resources. As noted during the September 2021 ACIP meeting, 2 studies conducted by GSK and CDC assessed the economics of vaccinating IC adults 19-49 years of age against HZ in the US. Both studies compared vaccination with RZV to no vaccination and focused on individuals receiving HSCT as the base-case. In both models, the vaccination strategy was estimated to be cost-saving when compared to the no vaccination strategy. Both models included additional scenarios that focused on other immunocompromising conditions, including individuals with HM, SOT patients, patients living with HIV, breast cancer patients, and other autoimmune and inflammatory conditions. Most of these scenarios found that the vaccination strategy cost per quality-adjusted life-year (QALY) gained ranged from being cost-saving to \$99,000. In the CDC model scenario that focused on autoimmune and inflammatory conditions, the cost per QALY gained was estimated to be \$208,000. As noted in the base case of HSCT patients, the economic value of RZV appears to be favorable or cost-

saving. This is influenced by higher HZ incidence and HZ related health care cost and reasonable VE. For scenarios focused on other IC patient groups, the economic value of RZV vaccination was less favorable relative to stem cell transplant patients given their lower risk of HZ severe outcomes and lower healthcare costs. Of note, some autoimmune and inflammatory conditions may have the least favorable estimates of RZV use depending on the underlying risk of HZ, which was often lower for this group.

To summarize resource use, considering results across the base-case and scenarios from both models, the WG determined the estimated economic values to be generally favorable (i.e., cost-saving). Given the higher specialized care and resources typically invested for the base-case and other IC populations, the WG did not consider cost-effectiveness assessments to be a main driver for decision-making. Upon review of these data, the WG concluded that use of RZV in IC adults is a reasonable and efficient allocation of resources.

In terms of the equity domain, the WG considered what the impact would be of RZV use in IC adults on health equity. The NHIS captures HZ vaccination data,²⁸ including data for ZVL and RZV. Overall, in 2018, HZ vaccination coverage among adults 50 years and older and 60 years of age and older was 24.1% and 34.5%, respectively. White adults 50 years of age and older and 60 years of age and older had higher coverage compared with Blacks, Hispanics, and Asians. In an analysis using 2010 to 2019 NHIS data,²⁹ in general race, ethnicity, household income, education level, and health insurance type were significantly associated with receipt of HZ vaccination among adults 65 years of age and older. The WG anticipates an ACIP recommendation would increase access overall since recommendation increases the scope of the population eligible to be vaccinated and ensures coverage under the Affordable Care Act (ACA). However, there likely will still be challenges with uptake given the previously noted race, ethnicity, household income, education level, insurance disparities, variability in health insurance coverage, and lack of insurance that may result in out-of-pocket costs for some patients. It will be important to continue monitoring RZV vaccination through the NHIS, including stratifying by health status and race ethnicity. The WG also noted that equity potentially could be monitored at the local level during implementation. Upon review of these data, the WG concluded that health equity probably would be increased.

In terms of the feasibility domain, the WG considered whether RZV in IC adults is feasible to implement. RZV is a refrigerator-stable, 2-dose vaccine that can be co-administered with other adult vaccinations. The US healthcare system has experience delivering RSV to IC adults aged 50 years and older. However, very systemic factors challenge the adult vaccination program in the US (e.g., complicated reimbursement, lower prioritization of adult vaccines, and fragmentation of care). In the previously noted RZV KAP study³⁰ regarding physicians stocking and referring patterns, 47% of respondents indicated that they stock and refer for RZV while 42% indicated they only refer patients to receive the vaccine. Of 89% of respondents who referred patients to receive RZV at a location outside of their practice, 80% often were always referred to a pharmacy. Respondents indicated that it was easier to refer and identified cost, inadequate reimbursement, and not being able to bill Medicare Part D as barriers to stocking the vaccine.

²⁸ Lu P, Hung M, Srivastav A, et al. Surveillance of Vaccination Coverage Among Adult Populations — United States, 2018. *MMWR Surveill Summ* 2021;70(No. SS-3):1–26

²⁹ Kawai K and Kawai AT. Racial/Ethnic and Socioeconomic Disparities in Adult Vaccination Coverage. *Am. J. Prev. Med.* 2021;000(000):1–9.

³⁰ Hurley et al., unpublished data

Pharmacies have continued to expand vaccination programs, especially for adults, and are already a major provider of RZV. For the manufacturer, approximately 60% to 65% of RZV is distributed to and administered in pharmacies. It is anticipated that identification of IC patients (e.g., based on immunosuppressive medications, self-reported immunosuppression, and standing orders) will be concerns to the pharmacy setting. Additionally, some pharmacies may be out-of-network, potentially resulting in out-of-pocket costs for patients. Identification of IC patients may be challenging, especially since RZV is delivered in multiple settings. This highlights the need for provider and patient education materials and clinical decision support.

Of note, the majority of jurisdictions have lifelong immunization information systems (IISs), which can receive adult immunization information. However, many do not receive health status information. Therefore, the WG anticipates that this will increase reliance on other systems such as EHRs for decision support. The WG noted that clinical decision support guidance would be helpful and that it will be important to promote best practices and encourage providers to upload and update RZV vaccination information in jurisdiction IISs. Upon reviewing these data, the WG concluded that use of RZV in IC adults is feasible to implement.

For the overall EtR Framework summary, the WG determined that HZ in IC adults is of public health importance. The desirable anticipated effects of RZV use in IC adults are large and the undesirable effects are small, which favors the intervention. IC adults probably feel the desirable effects of vaccination with RSV are large relative to the undesirable effects. There is probably not important uncertainty or variability in how patients value these outcomes. Use of RZV in IC adults is acceptable to key stakeholders and is a reasonable and efficient allocation of resources. Health equity probably would be increased and the intervention would be feasible to implement. The WG therefore concluded that the desirable consequences of vaccinating IC adults with RZV clearly outweigh the undesirable consequences in most settings. A strong majority of the WG voted to recommend the intervention, with a minority opinion in favor of shared clinical decision-making.

With regard to considerations for use of RZV in IC adults, RZV may be used irrespective of prior receipt of varicella vaccine or ZVL. Regarding the dosing schedule, RZV is typically administered in 2 doses with the second dose given 2 to 6 months after the first dose. For individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule, the second dose can be administered 1 to 2 months after the first. As noted in CDC's *General Best Practices Guidelines for Immunization*,³¹ RZV can be co-administered with other adult vaccines at different anatomic sites. Providers should counsel patients about expected systemic and local reactogenicity before vaccination. As previously noted, timing of vaccination will be particularly important for some IC patients. If appropriate, patients should be vaccinated prior to immunosuppression. Otherwise, providers should consider timing vaccination when the immune response is likely to be most robust. Of note, RZV may be administered while patients are taking antivirals. Overall, the WG noted that providers do not want to miss the opportunity to vaccinate IC patients.

Regarding special populations, persons with a history of HZ should receive RZV. If an individual is experiencing an acute episode of HZ, vaccination should be delayed until symptoms abate. There is currently no ACIP recommendation for RZV use in pregnancy. Therefore, providers should consider delaying RZV until after pregnancy. However, there is no recommendation for pregnancy testing prior to vaccination. Regarding breastfeeding, CDC's *General Best Practices Guidelines for Immunization* advises that recombinant vaccines, such as RZV, pose no risk for

³¹ <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>

mothers who are breastfeeding or their infants. Therefore, clinicians may consider vaccination without regard to breastfeeding status if RZV is otherwise indicated. Regarding persons with no documented history of varicella or varicella vaccination, commercial immunoglobulin G (IgG) enzyme-linked immunosorbent assays (ELISAs) can be used to assess varicella-zoster virus (VZV) seroconversion after wild type infection. However, sensitivity and specificity can vary. Further, no commercially available assays are sensitive and specific enough to reliably detect vaccine seroconversion. It is important to note that RZV is not indicated for prevention of primary varicella infection and varicella vaccine is contraindicated for many IC patients. Persons born in the US prior to 1980 are considered immune to varicella. However, this criterion does not apply to IC persons. For persons born in the US after 1980 and IC persons, it is recommended to refer to the ACIP varicella vaccine recommendations. Finally, safety data are limited regarding use of RZV in VCV naïve persons.

Regarding policy options, Dr. Anderson presented the WG's proposed draft recommendation for discussion:

Two doses of recombinant zoster vaccine are recommended for adults aged ≥ 19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy for the prevention of herpes zoster and its complications.

Discussion Summary

- Ms. McNally inquired as to whether there is any clinical guidance on co-administration of RZV with adjuvanted influenza vaccine in IC adults.
- Dr. Anderson responded that CDC's Clinical Immunization Safety Assessment (CISA) Project colleagues indicated that there is an ongoing study to assess co-administration of SHINGRIX and FLUAD® and SHINGRIX and Fluzone® in individuals 65 years of age and older. The caveat is that it is not a study in IC patients, but there is some safety study activity. This is an ongoing study over the next couple of influenza seasons that is currently enrolling. CDC will continue to monitor any safety issues in the usual systems such as VAERS and VSD.
- Speaking from the primary care perspective, Dr. Goldman (ACP) expressed appreciation for this recommendation because there are still some specialists who are not recommending the vaccine in those who are IC—even after 50 years of age. This legitimizes and supports the use of this vaccine and should be very helpful. Regarding the fact that many patients do not have Medicare Part D, vaccinating at a younger age is important in terms of getting people covered after 65 years of age. Many physicians are not allowed to vaccinate their patients because of Congressional rules and Part D coverage, though he recognized this to be out of ACIP's scope. He asked what would happen if this recommendation passed in terms of persons who are laboratory-negative for varicella but meet the criteria for IC in terms of whether to go ahead and give them the RZV vaccine in that case since IC persons could not be given ZVL. He expressed his hope that the clinical guidance would provide clarification for these individuals.

- Dr. Anderson indicated that this topic has been discussed among the WG members. That is a challenging situation because as noted, the available commercial assays make this a challenging topic since they typically can detect wild-type infection. However, the sensitivity and specificity of those can vary. The reality is that none of the commercially available assays are sensitive and specific enough to detect vaccine seroconversion reliably. The other reality is that RZV is not indicated for prevention of primary varicella and the vaccine is going to be contraindicated for many IC patients. The WG will continue discussing this issue and it will be addressed in the Policy Note and fleshed out more in the clinical considerations. There are limited safety data regarding the use of the vaccine in people who are VCV naïve, and there is a challenge of confirming whether someone who is seronegative is truly naïve.
- Dr. Poehling emphasized that given the high percentage of RZV that is distributed through pharmacies, the clarity of information that flows between pharmacies and providers is imperative so that all are aware of vaccine status. This also highlights the importance of having a universal adult immunization registry so that everyone, including the patient, knows what vaccines they have received.
- Dr. Drees (SHEA) noted that the issue of persons who were born before 1980 arises frequently among health care workers (HCW). They are not considered immune because unlike the general population, they are HCW. Some HCW who may be 50 years of age or older and may test antibody negative, may report having a clinical history of chickenpox. With no documentation of that because it was so long ago, the current recommendation is to vaccinate them with varicella vaccine. While they also qualify for RZV, the interval is not clear. This is a common clinical dilemma for which it would be helpful to have some additional clarification.
- Dr. Anderson indicated that the intent is to address this in the clinical considerations.
- Dr. Kotton emphasized that the proposed recommendation would take a lot of education and robust clinical guidance so that clinicians in the field understand in whom this is best indicated. There is often confusion between varicella and zoster vaccines, so appropriate support must be provided. As someone who takes care of many IC patients and who has seen many patients use this vaccine off-label or pay for it out-of-pocket, she thought the proposed recommendation would enhance the protection of IC people against zoster.

Vote: Zoster Vaccine

Dr. Tara Anderson (CDC/NCIRD) presented the following proposed recommendation language for a vote, with a slight change to the order of the wording to ensure clarity:

Two doses of recombinant zoster vaccine are recommended for the prevention of herpes zoster and its complications in adults aged ≥ 19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy.

Motion/Vote: Zoster Vaccines

Dr. Ault made a motion, which Dr. Poehling seconded, to approve the proposed zoster vaccine recommendation as proposed: *Two doses of recombinant zoster vaccine are recommended for the prevention of herpes zoster and its complications in adults aged ≥19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy.* No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A

INFLUENZA VACCINES

Session Introduction

Dr. Keipp Talbot (ACIP, WG Chair) reported that the Influenza WG's activities since the June 2021 meeting included finalizing and publishing the 2021-2022 ACIP Influenza Statement in the *Morbidity and Mortality Weekly Report (MMWR)* on August 27, 2021.³² The WG's discussion topics have included the recent influenza activity in the Southern and Northern Hemispheres; a review of influenza vaccination for older adults; and data from the study of co-administration of Fluzone® High-Dose and Moderna mRNA-1273 COVID-19 vaccine. This session included presentations on the Phase 2 safety and immunogenicity study of the co-administration of Fluzone® High-Dose Quadrivalent influenza vaccine (QIV-HD) and a third dose of Moderna mRNA-1273 COVID-19 vaccine from Sanofi Pasteur and a CDC update regarding a change in the age indication for Flucelvax Quadrivalent vaccine.

Phase II Safety and Immunogenicity Study of the Co-Administration of Fluzone® High-Dose Quadrivalent Influenza Vaccine and a Third Dose of Moderna mRNA-1273 COVID-19 Vaccine

Dr. Ruvim Izikson (Sanofi Pasteur) presented the results of a Phase II open-label study to assess the safety and immunogenicity of Fluzone® QIV-HD. This study assessed the 2021-2022 formulation and a third dose of Moderna mRNA-1273 COVID-19 vaccine administered either concomitantly or singly in adults 65 years of age and older who were vaccinated previously with the 2-dose schedule of mRNA-1273 vaccine. The study code is QHD00028.³³ This study was conducted in partnership with the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response (ASPR) at the US Department of Health and Human Services and Moderna, Inc.

³² <https://www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm>

³³ Study Code: QHD00028 <https://clinicaltrials.gov/ct2/show/NCT04969276>

The rationale for the vaccine selection and study group was that adults 65 years of age and older are a critical priority for influenza and COVID-19 immunizations due to the risk of severe complications. Based on the COVID-19 vaccine primary series timing and strategy, older adults are most likely eligible for COVID-19 boosters and their annual influenza vaccine during the same window of time. This creates the risk that many will get vaccinated for either one or the other, with the priority being on COVID-19 vaccine. More than likely, influenza will be the missed vaccine. The QIV-HD vaccine was selected for this study as it is the most frequently administered vaccine among adults 65 years of age and older. The 100µg mRNA-1273 dose was selected based on projected regulatory expectations at the time of the protocol design. This represents more conservative scenarios by employing the highest dose projected for booster authorization.

This was a descriptive study with approximately 300 participants, 100 per group: Concomitant Administration (Group 1), Fluzone® High-Dose Quadrivalent alone (Group 2), and COVID-19 mRNA vaccine alone (Group 3). This randomized open-label study was conducted in the US at 6 sites. One inclusion criterion was that participants received 2 doses of their primary series of mRNA-1273 vaccine at least 5 months prior to enrollment. The mRNA-1273 vaccine booster dose was 100µg. Group 1, the co-administration group, received both vaccines during the same visit. Group 2 received the QIV-HD 2021-2022 240µg formulation alone. Group 3 received the COVID-19 mRNA vaccine alone. The visit schedule included a pre-immunization blood draw and vaccine treatment. At 8 days post-vaccination, safety information was solicited. At 21 days after immunization, another blood draw was done for immunogenicity. Dr. Izikson noted that the results he would be presenting truncated at day 21, but Sanofi is following these subjects through Day 181, which represents 6 months of safety follow-up. It is important to note that Group 3 participants who received only mRNA vaccines in the study were offered QIV-HD at Day 22 as part of routine medical care, which was voluntary.

Sanofi, BARDA, and Moderna recognized that the need for co-administration was emerging rapidly and was a major point of concern for patients and HCP. Therefore, a timeline with aggressive milestones was put in place in order to provide these study results early in the influenza season. In early May 2021, internal study endorsement was received within Sanofi Pasteur and the FDA protocol was submitted in early June 2021. FDA returned that protocol with approval and comment in a very short timeframe of 2 weeks. Institutional Review Board (IRB) approval was received on July 1, 2021 and the first subject was enrolled on July 16, 2021. The enrollment window was fairly short at just over 2 weeks. The first visit for the last subject was August 5, 2021 and the last visit (Day 21) for the last subject was August 31, 2021. September included a whirlwind of events. The database was locked on September 13th, the laboratory results were completed by September 20th, and the statistical analyses were conducted by September 28th in order to be able to provide the Interim Clinical Study Report at the beginning of October.

In terms of demographics by treatment group, ultimately there were more females than male participants in the study at 56% female compared to 44% male. The average age for the study was 72 years of age, with 76% of subjects between 65-75 years of age and about a quarter of participants at 75 years of age and older. The study fell short of the ambition of enrolling a more diverse and balanced sample population. There were a couple factors contributing to this, including the very short window of enrollment of just over 2 weeks. This led to the majority (95.3%) of the population being of white descent. The inclusion criteria required 5 months in-between primary series vaccinations and enrollment in the study. This meant that the pool of eligible enrollees would have had to have completed their primary COVID-19 series by February 2021, which substantially limited the cohort.

The study's safety objective was to describe the safety profile of QIV-HD and mRNA-1273 vaccines administered either concomitantly or singly. The endpoints captured included solicited injection site and systemic reactions occurring through 7 days after immunization; unsolicited systemic AEs through 21 days after immunization; and SAEs, AESI, and medically-attended adverse events (MAAEs) through 6 months after vaccination. As a reminder, the data point was truncated at Day 22 for this report.

To summarize solicited reactions through 7 days after immunization, the combined reactogenicity of QIV-HD vaccine and mRNA-1273 vaccine administered at the same visit was similar to that after administration of mRNA-1273 alone. About 94% of participants in the co-administration group and 96% of participants in the mRNA-1273 group administered alone reported at least one solicited reaction. The QIV-HD vaccine recipients receiving it alone had a lower reporting rate of 73%. As a reminder, a Grade 3 reaction is one that interrupts usual activities of daily living, significantly affects clinical status, or requires intensive therapeutic intervention. Injection site reactions that are measurable at a diameter of 100mm or more are recorded as a Grade 3 reaction. About 17% of the co-administration group and 18% of the mRNA-1273 vaccine alone group reported at least one Grade 3 solicited reaction. Only 3% of QIV-HD vaccine alone recipients experienced the Grade 3 solicited reaction.

These data can be further broken down into local injection site reactions and solicited systemic reactions. The 2 treatments that were received in the co-administration group were administered in separate limbs. That allowed an opportunity to compare injection site reactions among the cohorts receiving their respective vaccines singly. After injection of QIV-HD vaccines, the number of participants in the co-administration group experiencing at least one injection site reaction was 61%. This was similar to that of QIV-HD vaccine alone at about 62%. After injection of mRNA-1273 vaccine, 82% of participants in the co-administration group and 91% in the mRNA-1273 alone group experienced at least one event. Events meeting Grade 3 criteria were recorded at about 8% in both the co-administration group in the mRNA-1273 limb and in the mRNA-1273 group alone. Only 2 individuals reported a Grade 3 local injection site reaction after QIV-HD vaccine, and both were in Group 2. No participants in the co-administration group reported Grade 3 local injection site events following QIV-HD vaccine administration.

The co-administration group and the mRNA-1273 group had similar rates of participants experiencing at least one systemic reaction at 80% and 84%, respectively. Systemic reactogenicity was lower for QIV-HD vaccine at about 49%. Grade 3 systemic reactions were reported for the co-administration group and the mRNA-1273 alone group at about 13% each. Only 1 Grade 3 systemic reaction was captured in the QIV-HD vaccine alone group. Injection-site pain was the most frequently reported local reaction for both vaccines. The frequency of administration site pain was lower following QIV-HD vaccines. Overall, injection site reaction frequency was similar whether QIV-HD vaccine and/or mRNA-1273 vaccine was administered concomitantly or singly. Grade 3 reactions were reported less frequently following QIV-HD vaccine compared to that of mRNA-1273.

In terms of solicited systemic reactions captured through Day 8, fatigue was most frequently reported in all treatment groups. This was followed by headache, malaise, and myalgia. The overall pattern that emerges is that the co-administration group and the mRNA-1273 group alone had similar reporting rates. The frequency of Grade 3 systemic reactions was similar between the co-administration and the mRNA-1273 group alone. Grade 3 reactions were reported less frequently in the Fluzone[®] QIV-HD vaccine group. In terms of unsolicited AEs through 21 days, 1 participant in the co-administration group experienced 3 immediate unsolicited AEs of anxiety, dizziness, and hypertension. The anxiety and dizziness were both

considered Grade 1 events and resulted spontaneously in 1 day. Hypertension was recorded as Grade 3 and was considered resolved by Day 10. In Group 2, QIV-HD alone, 1 participant experienced 1 immediate unsolicited reaction of Grade 1 dizziness that resolved spontaneously in 1 day. Being that it was an adverse reaction, the investigator attributed this event to the treatment. Group 3, mRNA-1273 alone, did not have any immediate unsolicited AEs.

The frequency of unsolicited AEs was similar across treatment groups, though somewhat lower in the QIV-HD vaccine alone group. In the co-administration group, 2 subjects experienced unsolicited injection site adverse reactions and 1 subject experienced injection site pruritus at both injection sites on both limbs. Another participant experienced injection site pruritus in only the mRNA-1273 limb. There were 4 unsolicited systemic adverse reactions, including arm pain in the mRNA-1273 limb, cough, sinus congestion, and infection. In the QIV-HD vaccine alone group, 1 subject experienced unsolicited injection site adverse reactions of injection site and 3 subjects experienced 4 events, including unsolicited systemic adverse reactions of back pain, dizziness, cough, and nasal congestion. In the mRNA-1273 alone group, 1 subject experienced injection site pruritus as an unsolicited site adverse reaction and 6 subjects experienced unsolicited systemic adverse reactions. There were 9 events, including diarrhea, muscle spasms in the left calf on Days 6 through Day 8, neck pain, dizziness, nasal congestion, rhinorrhea, and pruritus. There were no Grade 3 unsolicited injection site adverse reactions or Grade 3 unsolicited systemic adverse reactions that were captured in any of the participants of the study. Additionally, no SAEs were captured through Day 22. The definition of an MAAE is “a new onset or a worsening of a condition that prompts to seek unplanned medical advice at a physician’s office or emergency department (ED).” It does not rise to the definition of an SAE, such as hospitalization, life-threatening event, or death. Through Day 22, there were 7 participants and 7 events captured. There was only 1 related MAAE in Group 3 mRNA-1273 alone group, which was the muscle spasms mentioned earlier that occurred on Day 6 in the lower left calf.

To summarize safety, injection site reaction frequency for QIV-HD vaccine or mRNA-1273 vaccine was similar regardless of whether the vaccine was administered concomitantly or singly. Injection site pain was the most frequently reported injection site reaction for both vaccines and tended to be lower following injection of QIV-HD vaccines. The frequency of Grade 3 injection site reactions tended to be lower following injection of QIV-HD vaccine compared to that of mRNA-1273. Fatigue was the most frequently reported systemic reaction in all treatment groups. The frequency was similar in the coadministration group compared to that of the mRNA-1273 group alone, but was lower in the QIV-HD vaccine group. Frequency of Grade 3 systemic reactions was similar in the coadministration and mRNA-1273 groups and lower in the QIV-HD vaccine group. There were no SAEs, no AESIs, and no deaths collected through Day 22. To date, no SAEs, AESIs, or deaths have been captured. There were no AEs leading to study discontinuation.

In terms of MAAEs, 1 participant in the mRNA-1273 group alone experienced 1 event that was related (e.g., muscle spasms). The frequency of unsolicited AEs and adverse reactions was similar across treatment groups, and most of them were systemic in nature. In the co-administration group and the QIV-HD vaccine group, 1 participant in each reported a Grade 3 unsolicited AE. Those were hypertension immediately following treatment in the co-administration group and a chemical burn to the eye in the QIV-HD vaccine group. There was 1 participant in the QIV-HD vaccine alone group who had an immediate unsolicited adverse reaction of dizziness that was Grade 1 in intensity.

The objectives for immunogenicity were to: 1) describe the immune response elicited by QIV-HD vaccine administered concomitantly or singly in each study group; and 2) describe the immune response elicited by mRNA-1273 vaccine administered concomitantly or singly in each study intervention group. The hemagglutination inhibition antibody responses to each influenza strain were conducted. At baseline, the geometric mean titers (GMTs) were similar across all groups. At Day 22, the co-administration group and the QIV-HD alone group demonstrated substantial and similar responses to treatment. The pre-vaccine titers for both Groups 1 and 2 were initially high. In H3N2, they were somewhat lower and in H1N1, even lower. For individuals exhibiting titers of $\geq 1:40$, based on the high GMTs from the previous slide, it would be expected that there would be high pre- and post-titers of 40 or greater, which was demonstrated. Because of the lower baseline GMTs in H3N2 and H1N1, it would be expected to see a lower proportion of individuals with greater than 40 at baseline. After immunization with QIV-HD vaccine, the majority of subjects reached titers of 40 or greater. Given the high baseline titers with both of the lineages, reaching a 4-fold rise of seroconversion is not as easily achieved. However, with baseline titers that are lower, such as H3N2 and H1N1 groups, a higher proportion of participants seroconvert as they are immunized. At baseline, the GMTs were similar across all groups. At Day 22, both groups who received the mRNA-1273 vaccine only demonstrated a 14-fold rise in antibody to SARS-CoV-2. In Group 2 who received only the QIV-HD vaccines, there was no substantial change from baseline.

To summarize the HAI immune response, all 3 treatment groups demonstrated similar GMTs at baseline. At Day 22, the co-administration group and the group that received QIV-HD vaccine alone demonstrated similar levels of GMT, proportions of participants with titers that were $\geq 1:40$, and seroconversion rates for each influenza strain. For the SARS-CoV-2 immune response, all 3 treatment groups demonstrated similar GMT levels at baseline. At Day 22, the co-administration group and the mRNA-1273 group alone demonstrated similar GMT concentration levels and proportions of participants with ≥ 2 - and ≥ 4 -fold-rise of antibody titers.

In terms of the overall interpretation, the hope is that results provide patients and providers with confidence that co-administration guidance is supported by these data. The study results demonstrate that QIV-HD vaccine and mRNA-1273 vaccine (100 μ g) can be administered safely together without evidence of immunogenicity interference, supporting existing co-administration recommendations of COVID-19 and influenza vaccines.

Discussion Summary

- Ms. Bahta inquired as to whether there was any explanation for pre-vaccination titers being higher.
- Dr. Izikson pointed out that they immunized these participants early in the season and the previous year's influenza immunization rates were fairly high at about 94%. It is fairly likely that the immunogenicity did carry over, especially after years of exposure to these and other vaccines as well.
- Dr. Chen asked whether there was an attempt to blind recipients to the vaccine they were being given and the likelihood of any bias from reporting of subjective symptoms. Noting that the current clinical considerations allow administration in the same site, he also asked whether there was a possibility that there could have been more reactogenicity if delivered at the same site versus in this study where vaccines were administered in different arms, and/or if this could have changed the immunogenicity.

- Dr. Izikson indicated that the subjects did know what was being received where. He recalled that the guidance recommends some distance in time between both vaccine administrations when co-administration is offered in a clinic. The concerns are well-received in that there are some open questions regarding immunogenicity and safety. While a lot of those questions are outside of the scope of the protocol for this study, he agreed that there is potential for bias in an open-label study.
- Dr. Sanchez noted that there were only 1 or 2 individuals over 85 years of age. He also asked whether the study participants had been vaccinated only with the Moderna vaccine and if any of them had previous COVID infection.
- Dr. Izikson indicated that the inclusion criteria required that all subjects had been previously immunized with the full 2-dose series of the Moderna mRNA-1273 vaccine. Those were the only vaccines every subject had received 5 months prior to enrollment. Serostatus and confirmation of prior COVID infection was not part of the inclusion/exclusion criteria, so that information is not available for stratification of individuals in the study.
- Dr. Long recalled that Dr. Izikson mentioned that of the 300 participants in the study, close to 100 received both vaccines concurrently on the same day, about 100 received influenza vaccine alone, and about 100 received mRNA alone. She wondered whether the latter 2 groups chose that or if they could have gotten one vaccine one day and another vaccine a month or two later.
- Dr. Izikson clarified that this was a prospectively enrolled clinical study in which all participants signed an informed consent and were randomized to one of those 3 groups so that the investigators could actively compare the co-administration group to either a group of individuals who received the QIV-HD vaccine alone or the mRNA-1273 vaccine alone. This was to help determine whether there was increased reactogenicity in the co-administration group compared to each of these vaccines administered singularly. They all received something—either both vaccines at the same visit or QIV-HD vaccine alone or mRNA-1273 vaccine alone. The Group 3 participants were offered a QIV-HD vaccine after completion of their Day 22 activities as part of their routine medical care, which was in regard to the ACIP recommendations that older adults receive an influenza vaccine prior to the influenza season. However, no additional information was captured regarding the QIV-HD vaccine after Day 22.
- Dr. Long emphasized the importance of being able to answer important public health questions, support trust and confidence in vaccination programs, and continue to emphasize avoiding missed opportunities for vaccination. While this study was small, she thought it was very important and expressed appreciation for the collaboration across companies in order to get this done. She also requested further information about the 1 individual who had hypertension in Group 1.
- Dr. Izikson indicated that this participant was being treated for hypertension on a beta blocker and presented initially with the 2 other immediate unsolicited AEs of anxiety and dizziness. The clinical staff took this participant's blood pressure, which had reached a threshold of 176/78. The person was then observed until they felt better and were advised to seek medical care after leaving the office. The person's blood pressure was taken again the next day and was down to 118/69.

Change in Age Indication for Flucelvax® Quadrivalent

Dr. Lisa Grohskopf (CDC/NCIRD) provided an update on a change in the age indication for Flucelvax® Quadrivalent, which was discussed during the June 2021 ACIP meeting. Flucelvax® Quadrivalent is one of the US's inactivated influenza vaccines, all of which are quadrivalent this season. This is a cell culture-based vaccine rather than an egg-based vaccine. The age indication for Flucelvax® Quadrivalent changed from $m \geq 4$ years to ≥ 2 years. This was cited in the most recent ACIP Influenza Statement that was published in August after this age change was approved by FDA in March 2021.

The FDA approved an age indication for ≥ 6 months on October 14, 2021. That change in indication was presented during the June 2021 ACIP meeting. This was approved based on a randomized trial of immunogenicity and safety of the Flucelvax® Quadrivalent compared to a licensed egg-based IIV4, Fluarix® Quadrivalent that has been licensed for a number of years. The study was conducted among 2,402 children ages 6 months through 47 months of age. Flucelvax® Quadrivalent was given in a 0.5 mL per dose, which is the same dose at which it had been licensed previously to be given to children ≥ 4 years of age. Fluarix® Quadrivalent was given at its own approved dose volume of 0.5 mL per dose for children 6 months through 35 months of age and 0.5 mL per dose for children 36 months through 47 months of age. To summarize the results presented during the last meeting, the pre-specified non-inferiority criteria for immunogenicity in terms of GMT ratios and difference in seroconversion rates were met for all 4 viruses, and rates of solicited and unsolicited AEs were similar between groups.

To put this approval into the context of what is available for influenza vaccines this season in the US, there are 9 influenza vaccines. Inactivated influenza vaccines comprise the largest group of these, of which there are 5 standard doses unadjuvanted. Of these, 4 are egg-based (Afluria® Quadrivalent, Fluarix® Quadrivalent, FluLaval® Quadrivalent, Fluzone® Quadrivalent) and one is cell-culture based (Flucelvax® Quadrivalent). The additional vaccines are approved for somewhat narrower age ranges. Fluad® Quadrivalent and Fluzone® High-Dose Quadrivalent are for persons ≥ 65 years of age, Flublok® Quadrivalent (RIV) is approved for persons 18 years of age and older. FluMist® Quadrivalent for persons 2-49 years of age.

Historically, children ages 6 through 35 months of age were approved generally to get a lower dose of influenza vaccine at 0.25 mL rather than 0.5 mL for inactivated vaccines that was approved for those 3 years of age and older. Beginning several years ago with the expansion of the approved age indications for Fluarix® and FluLaval® from 3 years down to 6 months, there began to be licensures for 0.5 mL per dose for children 6 through 35 months of age. There are still some differences with regard to approved dosing among the 5 vaccines that are now approved for children 6 through 53 months of age. Fluarix® and FluLaval® are 0.5 mL per dose, Flucelvax® is now also 0.5 mL per dose, Afluria® Quadrivalent 0.25 mL per dose and Fluzone® Quadrivalent is approved for either dose volume.

ACIP has not historically had specific votes for expansions in age indications for vaccines that are already licensed and are just expanding into an age that is already recommended to receive influenza vaccine. The plan is for this change to be reflected in the online version of the table of available vaccines for the 2021-2022 season.³⁴ The table will be included in the *MMWR Recommendations and Reports* and also will be included in the brief summary of the ACIP Recommendations, which is a 4-page summary of the recommendations that has been produced since the 2017-2018 season.

³⁴ <https://www.cdc.gov/flu/professionals/acip/2021-2022/acip-table.htm>

Given the low influenza activity last season, one common question regards what has been occurring in the Southern Hemisphere for the past summer as their season starts in the Spring and runs through around October. For the 3 Southern Hemisphere sentinel countries (Argentina, South Africa, and Australia) through Week 40 of the surveillance year, Australia and Argentina were well below the epidemic threshold and have not risen. South Africa was somewhat different in that they recently had a week that just peaked above the epidemic threshold. It is not clear whether that might represent a move toward returning baseline activity and will have to be followed over time. However, the activity overall has been well below the average activity for the 2011-2019 seasons. For the Northern Hemisphere sentinel countries (Canada, South Korea, and Denmark) through surveillance through Epi Week 40, the data were similar. There has not been much of a peak to date. Based on specimens submitted by sentinel surveillance laboratories, activity has remained fairly low.³⁵

Looking at US virologic surveillance, FluView is a report that is produced weekly by CDC's Influenza Division surveillance staff based on data from US clinical laboratories and US public health laboratories. Numbers of positive tests are broken down by type, Influenza A and Influenza B, and by subtypes in some instances. Normally, there is a rather large peak in the percent positives. However, activity was relatively level for last season. The percent positive specimens shown by the clinical laboratories was approximately 0.1% between May 23, 2021 and October 9, 2021. Since midsummer, the public health laboratories were beginning to see more consistent reporting week-to-week of specimens that are positive. It is too early to call any kind of predominance. At this point, there is a mix of H1N1, H3N2, and Bs. Therefore, it is not yet possible to make a call on what kind of season this is going to be. As Dr. Cohn pointed out at the beginning of the meeting, CDC is preparing for influenza to make a comeback, particularly as mitigation efforts are lessened in some places.

Discussion Summary

- Dr. Lee inquired as to whether a VCF vote would be required for the change in the age indication for Flucelvax® Quadrivalent.
- Dr. Grohskopf confirmed that a VFC vote would not be required.
- Dr. Daley asked whether vaccine administration errors are tracked in terms of a child receiving twice the dose they are supposed to.
- Dr. Grohskopf indicated that vaccine administration errors are reportable to VAERS and that is a category that is followed. VAERS occasionally publishes papers about certain types of errors, several of which have been reported. The frequency with which that occurs and with which it is reported probably varies depending upon the type of error, such as giving an incorrect dose volume. Errors that sometimes occur in which someone receives a vaccine that is not indicated for their specific age. While it was difficult to comment on how frequently that occurs off of the top of her head, she offered to supply references to the papers reporting errors.
- Thinking about pandemic preparedness, Dr. Maldonado (AAP) asked whether there would be any upcoming updates on highly pathogenic avian influenza (HPAI) in order to get a sense of the potential for vaccine platforms being developed in response to those.

³⁵ WHO FluNet <https://who.int/tools/fluNet>

- Dr. Grohskopf said that while there is not currently an HPAI WG, she will present this request for an update for an ACIP meeting in the near future.

PUBLIC COMMENT

Public Comments: October 20, 2021

The floor was opened for public comment on October 20, 2021 at 3:45 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC–2021–0098. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received. The public comment session was conducted prior to the votes. However, the votes were included with their respective sessions for ease of reading.

Mr. Steve Kirsch
Executive Director
COVID-19 Early Treatment Fund

My name is Steve Kirsch. I'm Executive Director of the COVID-19 Early Treatment Fund. I have no conflicts. Today I want to talk about the two "elephants in the room" that the ACIP committee members all refuse to acknowledge. The first is the correct values of the VAERS underreporting factor, and the second one is the missing of dozens of serious adverse events, including deaths. The recognition of either of these "elephants" should cause the committee members to demand an immediate halt to the COVID vaccination program. Our first "elephant in the room" is a very serious error committed by CDC staff member [bleep] who is the VAERS expert. The ACIP committee has relied on [bleep] for interpretation of the VAERS data, but he has misled the committee on a critically important issue, the underreporting factor for VAERS this year, otherwise known as the URF.

Dr. Lee requested that the timer be paused and stated the following: Thank you for your comment. You know, our committee does appreciate diverse viewpoints that are respectful in nature and that are not personally directed at individuals. I will ask that you not name individuals. Otherwise, I will need to cut your time short and ask that we move on to the next public comment speaker. But we will go ahead and resume the timer, Mr. Kirsch.

Okay. The committee has been led to believe that VAERS is 100% reported. That is preposterous. The VAERS URF is at least 41 for serious adverse events this year. It was calculated using methodology outlined in a paper published by five CDC authors published last year. I used the anaphylaxis data from the Blumenthal study, a study done at Mass General Brigham published on March 8 in *JAMA*. Those rates, the rates determined in that study, largely agree with those found in the Hashimoto study published on June 14 in the *Journal of Travel Medicine*. If you cannot challenge the methodology or the data, the Precautionary Principle demands that you accept the result, which is the URF is 41. Now, this has profound implications. The myocarditis incidence rate is now 1 in 317 fully vaccinated 16-year-old boys for the Pfizer vaccine based on slides presented at the August 30 ACIP meeting. But much more important is the death count. There are 7674 deaths reported in VAERS as of today. Let's remove the total of all deaths reported in an average year considering all those background

deaths, so minus 200; 7474 times 41 is 306,000 excess deaths this year. We should have stopped the vaccines at 50 deaths. We even used 7 independent methods to validate our estimate is correct. None of those other methods use VAERS. I even offered a \$1 million prize to anyone who can find a material error in either the data or the methodology. Nobody's claimed that price. Contrary to CDC's claims, we can show causality of all of these deaths because all the Bradford Hill criteria are satisfied. So if the vaccines didn't cause those excess deaths, then what did? The committee must answer that question or I believe they should resign. There is a second "elephant in the room," which is the missing safety signals. How can you miss 300,000 dead Americans as a safety signal? How can you possibly miss pulmonary embolism? It's elevated by over 800 times this year versus previous years. There are dozens more examples like these. The committee should either call for an immediate halt to the vaccination program or they should resign. Thank you.

Dr. Robert Edmonds, PhD
Concerned Individual

Dear committee, my name is Robert Edmonds. I have no financial conflict of interest to disclose. While my remarks are more attuned to tomorrow's agenda, today I will speak about tinnitus and the Johnson & Johnson vaccine. COVID-19 vaccines including Johnson & Johnson's vaccine have saved many lives. Identification, though, of low frequency adverse events connected to vaccination are important, not to discourage vaccination but to encourage patient education to seek timely care and for provider education to apply the appropriate treatment should the low frequency events occur. Peer-reviewed case studies of tinnitus following vaccination potentially suggest a small window of time for treatment of tinnitus after onset utilizing corticosteroids. After this limited window, though, management is often the only remaining option available. Last week, Johnson & Johnson presented data that indicates a combined imbalance from all Phase 3 trials of 24 versus 9 for tinnitus. Without information about the distribution of preconditions in both the vaccine and placebo group, they can only surmise the chance of a coincidental signal is 1 in 143 for this scenario. And if the case from Phase 1 is included, 1 in 156 for consideration of all phases of development. Note last week's update increased confidence in tinnitus as a real signal. Additionally, the 95% confidence lower bound to the signal already above zero increase away from zero with this update as well. Note the confidence intervals and confidence estimates have not been provided for these adverse events in any documentation. The Food and Drug Administration at this time, unlike the European Medicines Agency, has not recognized tinnitus as a related low frequency event. Therefore, I urge an investigation beyond passive monitoring. Investigation of this nature would probably first indicate what tinnitus background to compare to, like whether comparisons should be conducted against what would include an assumed non-bothersome tinnitus background or only a smaller, more severe, extremely bothersome tinnitus background. Without an investigation of this nature, it'd be difficult to detect a tens of percent rise in an assumed large background without unique consideration of severity. Additionally, more careful examination may or may not identify unique nature to the cases, exclude or include other potential causes, and could identify unique cases hard to explain without a causal relationship. I'd be happy to expand upon any of these points after these remarks. In closing, I return to the trial data, and I will repeat [that] Combined trial data presently indicates that 1 in 156 chance of there being a coincidental signal. If you agree these events are unlikely to be coincidental as the trial data suggests, I urge further investigations with federal and private partners to further investigate this matter and communicate those results back to the Food and Drug Administration and, if real, meaningfully communicate this to patients and providers as well. Thank you for your time.

Erin Costello
EKCPeopleSuck.com

I hope you're all having a fine afternoon. I have two purposes for my statement being made here today. First and foremost, I want to thank every committee member for your work and your efforts given to helping every member of the public avoid unnecessary and sometimes detrimental sickness and disease. I especially want to thank you for agreeing to be a part of this committee over the past few years, given the rise in misinformation, which has then caused some people to misplace their anger that they feel and place it on you and other members of the medical and scientific community. I can imagine how unnerving that can be at times. Myself and other parents, and even those of us without kids, have devoted our free time to hopefully reversing some of this anger and ignorance. I am even hopeful on some days, though not often enough. My last purpose here for speaking today is to express my hope that the recommended age for the shingles vaccine be lowered from 50 years of age to 45 years of age. I know myself, I would be very much relieved, but mostly I just want to say thank you very much for all of your time and your efforts dedicated to this cause.

Dr. Danyu Lin, PhD
University of North Carolina

Hi. This is Danyu Lin from the University of North Carolina at Chapel Hill. Our group has been estimating the durability of protection for the COVID vaccine from both Phase 3 trials and the surveillance data. So today, I'd like to share some of our results. So, first of all, we analyzed the Phase 3 trial data published in *New England Journal of Medicine* for the Pfizer and the Moderna trial. And we find that the vaccine efficacy in reducing the risk of symptomatic COVID-19 is about 75% at 6 months of Dose 2 of the Pfizer vaccine, and for the Moderna vaccine it's about 90% 6 months after Dose 2. So this suggests that there's not as much need to give booster to the Moderna vaccine recipients as compared to the Pfizer vaccine recipients. Our group has also been analyzing the surveillance data from the State of North Carolina. And, I mean, some of these results—first of all, we estimated the efficacy in reducing the risk of COVID-19 over a 9-month period, and we find that both mRNA vaccines are highly effective in reducing the risk of hospitalization and death with vaccine effectiveness in the lower 90%, even after 7 or 8 months. And Moderna vaccine is more durable than the Pfizer vaccine in reducing the risk of COVID-19 deaths in the case of the Phase 3 trial. And the durability of protection is similar across demographic groups and also are similar for people who are vaccinated at a different time, suggesting that waning vaccine efficacy is likely due to the declining immunity rather than the emergence of a new variant. And also, we find that the effectiveness of the Johnson vaccine drops after 1 month, which suggests that it will be worthwhile to investigate the effectiveness of Johnson but as a 2-dose regimen given approximately 1 month apart. And that's the end of my comment.

Ms. Patricia Barber
Retired Banker & Non-Profit Executive

I am Patricia Barber, a retired banker and a non-profit executive. Thank you for this opportunity to speak and for the diligent work this committee and staff has done over this difficult and lengthy period of crisis in the health of our country. As a senior, I am particularly aware of the value that vaccines play in keeping me in good health. From personal experience, and from health education, I know that pneumonia is one of the health threats facing older adults and that it causes thousands of hospitalizations and deaths each year. Any increase in the effectiveness

of preventing this dangerous infection is an important step in the right direction for all of us. One of the things that I and so many others have learned more about through the COVID pandemic has been the degree to which our body changes and becomes more susceptible to illness as we age. We are now so much more aware that our immune systems declined significantly as we age, and we know that the degree and the rapidity with which that occurs seems to vary for a number of reasons, but that the decline is inevitable. I hope the committee will factor the full impact of this into its deliberations. We know that there are many predictable biological events which serve as hallmarks for the body reaching various stages of seniority, from graying hair to wrinkles to slow metabolism. We also know that these occurrences don't all happen at the same time in each one of us. Thus, it is important to recognize that aging begins and advances at different times and at different paces. We need to keep this in mind so that the changes in our immune system, which may not be apparent to the eye, can and will be addressed appropriately. Protection from pneumonia is a prime example. While we know that the oldest among us are the most at risk, so-called younger cohorts of seniors, those in their 50s and 60s, also are experiencing in varying ways and measures—changes that mark the advance of age. The old adage “an ounce of prevention is worth a pound of cure” comes to mind. Restated for this situation, a broad definition of seniority will protect and save a multitude of seniors.

Dr. Litjen (L.J) Tan, MS, PhD
Chief Policy & Partnerships Officer/Immunization Action Coalition (IAC)
Co-Chair, National Adult and Influenza Immunization Summit (NAIS)

Good afternoon, members of the ACIP. I am L.J. Tan, Chief Policy and Partnerships Officer for the Immunization Action Coalition or immunize.org, and also Co-Chair for the National Adult and Influenza Immunization Summit. I'm also honored to have served as a Voting Member of the NVAC, the National Vaccine Advisory Committee, and as a liaison member of the ACIP for 12 years. Just a few comments regarding the vote of the committee to not amend the age-based pneumococcal policy statement down to 50 years of age. While harmonizing an age-based recommendation is commendable, it shouldn't have been done at the expense of improved health outcomes for a large population of vulnerable persons. Indeed, this seems unreasonable when the alternative was another age-based cost-effective, even cost-saving recommendation. I'm concerned that the current policy statement appears to show more considerations for the vaccine options than the benefits of vaccine recipients. Why? As we all know, there remains a large burden of preventable pneumococcal disease today, and we know from the implementation of other adult immunization programs that with an age-based recommendation down to 50 years of age, we will capture a significant number of persons who may go on to become diagnosed with high-risk conditions. Indeed, our current pneumococcal high-risk recommendation for adults 19-64 years of age has been in place for many years, and we are sitting on low coverage rates hovering at 23.6%. There is no reason to think that simply changing the vaccine options will change these low numbers. We have tried and tried with various vaccines, and the evidence is clear. Risk-based recommendations in adults are poorly implemented. And the data has shown that, indeed, age-based recommendations in adults do work. An age-based 50-64 year old recommendation would have provided immediate benefit to a high-risk population, rather than keeping them at risk while waiting for some future program to catch up and reach effectiveness. We would also have captured a significant number of vulnerable persons of racial and ethnic minority and also of lower social economic status who may otherwise miss vaccination with a risk-based recommendation. This is an issue of equity. And, finally, waning immunity does not seem a good reason to not seize the opportunity to reduce a lot of burden of disease today. It seems inappropriate to not implement a cost-effective solution that will save more lives and improve equity based on the assumption that immunity

might wane 15 to 20 years in the future, regardless of boosters. That said, with the policy statement now under consideration, immunization advocates stand ready to work with you to address the challenge of implementing a risk-based pneumococcal recommendation and, indeed, all other adult risk-based recommendations. On the broader issue of adult immunizations, the negative impact of COVID-19 on immunization coverage rates in the US has been well-documented. We are aware coverage rates in the adults with very low pre-COVID, and we all know that when coverage rates are low, disparities are exacerbated. The pandemic devastated already low adult immunization coverage rates. And we were delighted that Dr. Cohn mentioned the Call to Action that was developed at a National Adult and Influenza Immunization Summit. I urge all of us to consider these standards for care going forward. I would like to thank this amazing committee for the incredible body of work that you all have done to protect the health of the country and, in particular, over the past 2 years as you continue to engage in getting out of the pandemic and back to life. We stand ready to work to implement your important recommendations.

**Mrs. Jeanette Contreras, MPP
National Consumers League (NCL)**

My name is Jeanette Contreras and today I am representing the National Consumers League which, for over 120 years, has championed the safety and efficacy of vaccines as life-saving medical interventions. We extend our gratitude to this committee for the opportunity to present public comments. Our founder, renowned social reformer Florence Kelley, supported vaccines as a key factor in mitigating a smallpox outbreak near the end of the 19th Century. Her stalwart advocacy for immunizations has informed our bedrock principles for increased access to and vaccine confidence among consumers. In the US, nearly 50,000 people die each year from pneumonia, and Americans living with underlying health conditions are at a higher risk of acquiring the illness. Given the prediction of a more active flu and pneumonia season this year, the threat to older Americans and those living at greater risk of infection is especially high. Coupled with the ongoing threat of COVID-19, a rising number of Americans who recover from the coronavirus will find themselves susceptible to respiratory infections. We are pleased that the FDA has approved 2 new pneumococcal vaccines that offer broader protection than existing options. Consumers rely on the scientific expertise of the FDA and CDC to make recommendations based upon the best available evidence. We are encouraged that ACIP is considering recommending the pneumococcal vaccine for young adults with underlying health conditions and adults over age 50. Providing clear age-based recommendations can help to increase the rate of vaccine uptake. Providing risk-based recommendations for young adults with underlying conditions increases equitable access to immunizations. These recommendations would be particularly significant for vaccine uptake in communities of color who suffer disproportionately from chronic medical conditions at younger ages. As we work to reduce the risk of serious illness and death this winter, a vaccine to prevent against pneumococcal disease is more relevant than ever. Ensuring our most vulnerable Americans have access to these important preventative tools must be our priority. The National Consumers League will continue to instill vaccine confidence in consumers and look forward to swift recommendations by this committee on the use of these new and improved pneumonia vaccines. We appreciate your consideration of our views on this important public health topic.

Joanna Colbourne
Deputy Executive Director
National Foundation Infectious Diseases (NFID)

Good afternoon. I am Joanna Colbourne, Deputy Executive Director of the National Foundation for Infectious Diseases, or NFID. On behalf of NFID, thank you for the opportunity to address the ACIP, which plays an important role in guiding US immunization policy and protecting public health. COVID, flu, and pneumococcal disease are vaccine preventable diseases that together caused millions of illnesses and thousands of hospitalizations and deaths among vulnerable populations, which include older adults and those with chronic health conditions. Although there are safe and effective vaccines available to prevent these diseases, research shows a lack of awareness on the part of many individuals who are at higher risk for serious complications. Given that fewer than half of US adults typically receive an annual flu vaccine, NFID commissioned a survey in August 2021 to better understand beliefs about flu and pneumococcal disease, as well as attitudes and practices around vaccination during the COVID-19 pandemic. The survey found that 44% of US adults are unsure or do not plan to get vaccinated against flu this season. Of further concern, the survey found that nearly 1 in 4 who are at higher risk for flu-related complications said they were not planning to get vaccinated. Although last flu season saw historically low flu activity, we could see flu surge in the US this season with relaxed COVID-19 mitigation strategies, increased travel and the reopening of schools and businesses. Now more than ever, it is essential that everyone aged 6 months and older receive an annual flu vaccine. Even in cases when flu vaccination does not completely prevent infection, it can reduce the duration and severity of illness and can help prevent serious complications, including hospitalization and death. The survey also revealed an alarming lack of knowledge about pneumococcal disease. Among adults who are at higher risk for the disease, 51% are not familiar with pneumococcal disease and only about a third reported that they have been advised to get vaccinated. Healthcare professionals play a critical role in protecting their patients from vaccine-preventable diseases. Both healthcare professionals and the public must understand immunization recommendations for all vaccine-preventable diseases. This fall, millions of people will be rolling up their sleeves for additional doses of COVID-19 vaccines. Although COVID and flu vaccines can be given at the same time, there continues to be confusion as well as practical concerns about implementation. Clear, consistent guidance from CDC is essential to eliminate confusion. At the recent NFID news conference to kick off flu season, CDC Director Rochelle Walensky urged everyone to get vaccinated against influenza each year. NFID stands ready and willing to continue working with CDC throughout flu season to educate the public and healthcare professionals about recommended vaccines. Thank you for your time and attention and hard work.

Ms. Meredith Whitmire
National Association of Nutrition and Aging Services Programs (NANASP)

Thank you and thank you for the opportunity to present to you. My name is Meredith Whitmire, representing the National Association of Nutrition and Aging Services Program. We commend you for the extraordinary work you continue to do throughout the COVID-19 pandemic—work that certainly has saved lives. I have one simple request today. Please immediately reconsider your decision not to vote on extending coverage of newly approved and updated pneumococcal vaccines to all those aged 50 and older. As an organization which has been advocating on behalf of pneumococcal vaccines for older adults since 2014, we do appreciate that you are considering coverage for all those 65 and older. However, after reviewing the evidence from the Pneumococcal Working Group, it seems evident that these vaccines would benefit a broader aged community, particularly as we begin the flu pneumonia season that is expected to be a

very active one. Further, many younger adults with chronic conditions are susceptible to pneumococcal disease, as discussed by the Working Group. These conditions disproportionately are found in populations of color and often go undiagnosed, meaning that these adults would be missed via the risk-based recommendations. Additionally, as was discussed earlier, the Working Group highlighted that one of the approved vaccines only requires one shot, another potential way to increase equity among vaccine recipients. As we stated in oral testimony in September, another compelling reason to recommend approval now is CDC's own guidance that pneumonia vaccines can be administered along with COVID-19 vaccines. As more Americans, especially older Americans and those with chronic conditions either get their first or second doses of COVID-19 vaccines or their boosters, it would be such a convenience to have both done on the same visit. Just as you have moved swiftly and decisively at different junctures on COVID-19 vaccine recommendations, we believe the same urgency is needed with respect to these pneumococcal vaccines for all adults 50 and older. Older adults have been disproportionately impacted by the pandemic, and so have younger adults with chronic conditions. We should avert the same situation with pneumonia. Finally, we also commit to doing all necessary education to inform the older adults we work with and others who would be eligible about the need for and availability of these new vaccines.

THURSDAY: OCTOBER 21, 2021

WELCOME AND INTRODUCTIONS

Call to Order / Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the meeting. She conducted the roll call during which no conflicts were identified or declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

FDA Update

Dr. Doran Fink (FDA/CBER) made a brief statement regarding the FDA regulatory actions the previous day. He announced that during the previous afternoon, FDA authorized the Moderna COVID-19 vaccine for use as a single booster dose at least 6 months following completion of a primary series of the Moderna COVID-19 vaccine in individuals 65 years of age and older and individuals 18 through 64 years of age who either are at increased risk of severe COVID-19 following primary vaccination or who have frequent institutional or occupational exposure to the SARS-CoV-2 virus. Additionally, FDA authorized the Janssen COVID-19 vaccine for use as a single booster dose at least 2 months after the single dose primary vaccination in individuals 18 years of age and older. Finally, FDA authorized use of all 3 of the available COVID-19 vaccines for use as heterologous booster doses following completion of a primary vaccination with any of the 3 authorized COVID-19 vaccines. Because need for a booster dose is determined by the immunity elicited by the primary vaccination or primary vaccination series, the populations eligible for heterologous booster dose and the appropriate interval between completion of the primary vaccination or primary vaccination series and the booster dose is the same as those populations who are eligible for the booster dose of the primary series. The dosing interval is also the same as the dosing interval authorized for the vaccine used for the primary vaccination. All of these authorizations followed discussion/recommendations of the FDA VRBPAC the previous week.

CDC Update

Dr. Rochelle Walensky (CDC Director) said that she was delighted to say a few words, especially during yet another busy two days of meetings and the discussions. She began by simply saying “thank you.” For over a year, this committee has met to discuss COVID-19 vaccines, analyze the studies and ever-evolving data, establish a framework for equitable delivery, analyze the safety data, and make recommendations that keep people safe and protected against disease. Despite the enormity of the task, the ACIP did not waver in their commitment to the work in front of them. She emphasized how grateful she was to have them to provide insight, guidance, and recommendations. As always, the ACIP had a tremendous amount of work ahead of them throughout the day. Each presentation would be evidence-packed, and she stressed how appreciative she was for the heavy lift they were about to undertake, from a discussion on the benefits and safety of a booster dose of Moderna for those at greatest risks, to the best way to protect those who have received the Janssen vaccine, to a conversation about heterologous vaccine series and what could be extrapolated from the clinical trials and laboratory studies to real-world data. ACIP’s votes are important, and of equal importance is how the committee approaches each type of data and frames their recommendations. She reminded everyone that when she spoke with ACIP in September, she made 3 commitments to ACIP to: 1) never lose sight of their collective goal to protect as many people as possible from COVID-19; 2) stand with them moving forward and facing new decisions and new twists and turns in this pandemic; and 3) listen to them and learn not just from their votes, but from their discussion and deliberation. These past 20 months have taught them many things, but mostly to have humility. Everyone is constantly learning about this virus, growing the evidence base, and accumulating more data. None of them individually can predict what may happen next, and none of them individually can know exactly what to do, but together they can be prepared and make the best recommendations to protect the greatest number of people. She emphasized that she was listening and eager to learn from ACIP’s perspectives. Over the coming days, CDC will release clinical considerations and public health guidance that will turn these decisions into practice. CDC’s recommendations will address not only who should receive a booster dose, but also include what vaccine they should receive, how, and when. It would be through ACIP’s conversations that CDC would explore the nuances of this guidance and then communicate it to the public. In closing, Dr. Walensky shared her deep thanks to the ACIP team at CDC. They have spent countless hours preparing for these meetings, responding to data requested from the WG and full committees, presenting the evidence, and establishing the framework for ACIP’s recommendations. They are an incredible, dedicated, tireless, and committed team. She thanked everyone for giving her the chance to speak with them and for the hard work they were about to do and reiterated that she would be there listening and looking forward to hearing the discussions.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) provided the session introduction on behalf of the ACIP COVID-19 Vaccines WG. There have been over 45 million cases of COVID-19 in the US over the course of pandemic. Even though the epidemiologic curve looks somewhat better than it did the previous month, there were still about 75,000 new cases per day on average in the US. Currently, there are approximately 1000 deaths in the US every day. This is an important place to make the point that for most individuals in most circumstances, deaths from COVID-19 is vaccine-preventable.

Over the last 6 weeks, the COVID-19 Vaccines WG considered booster doses for COVID-19 vaccines. This included review of real-world VE studies from the US and abroad, RCT safety and immunogenicity data regarding booster doses, NIH heterologous or mix-and-match study results, GRADE of the evidence regarding boosters, and the EtR Framework regarding implementation, values acceptability, resource use, and equity in the consideration of the use of booster doses in the US. In addition, the WG pivoted to prepare for critical decisions coming up around the use of COVID-19 vaccines in a younger pediatric age group 5-11 years of age. This has included a review of SARS-CoV-2 seropositivity in children and a much closer look at the current pediatric COVID-19 infection epidemiology.

As Dr. Fink just announced, the FDA expanded the Moderna COVID-19 vaccine EUA to include a single booster dose to be administered at least 6 months after completion of the primary series in the following groups: 1) individuals 65 years of age and older; 2) individuals 18 through 64 years of age at high risk of severe COVID-19; and 3) individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The FDA also expanded the Janssen COVID-19 EUA to include a single booster dose to be administered at least 2 months after completion of the primary series for individuals ≥ 18 years of age. In addition, the FDA amended the EUAs to allow for each available vaccine to be given as a heterologous or mix-and-match booster dose in eligible individuals following completion of primary vaccination with a different COVID-19 vaccine.³⁶

This session included presentations on Moderna booster dose data, Janssen booster dose data, the NIH mix-and-match booster dose study, v-safesm and VAERS data on third dose and simultaneous vaccination, vaccine safety updates, myocarditis updates from VAERS, myocarditis updates from VSD, a Vaccine Safety Technical Work Group (VaST) summary, COVID-19 VE for the primary series, EtR Framework, clinical considerations, policy questions, and a vote on Moderna and Janssen booster doses.

Moderna Booster Dose Data

Dr. Jacqueline Miller (Moderna) reviewed the updated Phase 3 efficacy data from the post-marketing study, discussed how that informed Moderna's decision to submit a booster dose application, and presented safety and immunogenicity data on the booster dose. The EUA for Moderna's COVID-19 vaccine is for a 50 μg booster and is particularly authorized for patients at increased risk of severe complications, including those over 65, those over 18 but younger than 65 at high risk for severe COVID-19, and those with frequent institutional or occupational exposure. Additionally, the fact sheet will reference the ability to use the Moderna booster dose as a booster for other vaccines' primary series.

First to review the booster dose in terms of how it is different from the 100 μg 3-dose primary series that was authorized for certain populations, it was noted in August that patients with SOTs or who were otherwise immunocompromised did not always develop neutralizing antibodies to any of the authorized vaccines. Therefore, Moderna submitted and had authorized a 100 μg dose to be given at least 1 month after the second dose. This is really a 3-dose primary series for patients with compromised immune systems and was not the indication being discussed during this session. The focus of this discussion was other populations who received the 2-dose 100 μg primary series and the administration of a third dose at least 6 months after

³⁶ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-additional-actions-use-booster-dose-covid-19-vaccines>

completion of the 2-dose series with a 50 µg booster. At this point, approximately 1.6 million Americans in the immunocompromised population had received a third dose of 100 µg, for whom the safety data would inform part of the discussion later in the afternoon.

To review an update from Moderna's Phase 3 efficacy trial and the incidence of COVID-19 disease being seen among subjects through their follow-up period, a follow-up was completed of the blinded efficacy analysis through March 2021. After the EUA authorizations of Moderna's vaccines, the subjects in the placebo group who were all at increased risk for COVID-19 were offered crossover vaccinations in order to continue to follow them and learn from this study. After these subjects received crossover vaccinations, Moderna continued to compare incidence rates. There was a final blinded efficacy analysis comparing the vaccine group versus the placebo group through March of 2021. At that time, up to 5.3 months of median follow-up showed that efficacy remained at 93.2%. Efficacy against severe disease throughout the same period remained at 98.2%,³⁷ which was very similar to the results discussed in December 2020. Importantly, cases reported in the trial during the time of this follow-up were sequenced and it was noted that the original strain with the D614G mutation and the Alpha variant were by far the most commonly circulating strains during this period of follow-up.

An exploratory analysis of antibody persistence and boosting was performed during the same period of February through March 2021 (Study 201B),³⁸ during which other strains began to emerge in the US. As variants began to emerge in other parts of the world, the Beta variant in Africa and Gamma variant in South America were being tested for throughout Moderna's program using serum from recipients of mRNA-1273 to assess how well it was able to neutralize antibodies against those variants and whether a 50 µg booster could increase the breadth of coverage in terms of neutralizing antibody responses. At 1 month after Dose 2, all subjects developed neutralizing antibody titers to the original strain and most subjects developed neutralizing antibody titers against the 2 variants that were tested. At 6 to 8 months, all but 1 subject had neutralizing antibody titers to the original Wuhan strain. Approximately half of subjects lost the ability to neutralize the Beta, Gamma, and Delta variants by 6 to 8 months later. This was probably due to a combination of lower neutralizing antibody titers to begin with and the known waning of antibody persistence that happens with all vaccines over time. Those subjects were given a 50 µg booster and all were above the lower limit of quantification of the assay for all 4 of the strains. The fold rises between 23- and 44-fold in an exploratory research grade assay.

Phase 3 Study 301 assessed the incidence rates of COVID-19 disease in vaccinated individuals from July to August 2021 when Delta began to become the most commonly reported variant. As mentioned earlier, there was an original group of subjects who were vaccinated with mRNA-1273 in the Phase 3 study between July and October 2020. Then there was an originally randomized placebo group who received the placebo between July and October, but who ultimately were crossed over to receive mRNA-1273 in January to March 2021. While a true efficacy trial no longer could be conducted with the placebo group, there were still 2 groups for whom relative incidence rates could be compared. One group included subjects who were vaccinated about a year ago and the other group of subjects who were vaccinated about 6 to 8 months ago at this point. Meanwhile, Moderna is closely following the reported cases of COVID-19, which are still being assessed and confirmed by the adjudication committee as the subjects progress through efficacy follow-up. The most cases reported until July 2021 included 23 in January 2021. In July, 81 cases were observed and 169 cases were observed in August. This

³⁷ El Sahly, NEJM, 2021

³⁸ Research VSV pseudoneutralization assay used; Adapted from Choi et al., Nature Medicine 2021

was nearly a difference between what had been observed previously, which prompted Moderna to take additional action and perform additional analyses.

In a comparison of incidence rates overall and by age groups (18-64 years and ≥ 65 years), the overall incidence rate in the earlier-vaccinated group was 77.1 per 1000 person years compared to 49 per 1000 person years in the later-vaccinated group, for a relative difference of 36.4%. That was statistically significant in that the 95% confidence interval ruled out the value zero. The same was true in both of the age strata. In the oldest age group for severe disease, the group difference was even larger.³⁹

In terms of why a 50 μg dose was chosen, the primary goal was to use the dose that could be most optimally effective for boosting. The principle was to expose subjects to the dose that they needed, but not expose them to more than they needed. Lower booster doses than those used in primary series of other vaccinations have been shown to reactivate immune memory. A key example is Tdap. Lowering the dose also increases the ability to supply mRNA-1273 in the US and worldwide. In terms of the study design, this was an extension of the same Phase 2 studies discussed in December 2020. The placebo group in the Phase 2 study also were crossed over to receive mRNA-1273 primary vaccination and they did not participate further in this study. There were 2 additional groups. One group was primed to 50 μg of mRNA-1273 and the other was primed to 100 μg of mRNA-1273. The reason the Phase 2 study was chosen even though it had a smaller sample size was because the Phase 3 studies had just finished their vaccinations, so they had not progressed long enough in the study to receive a booster dose. The sample size for the immunogenicity set was 146 and 149 subjects, respectively. That rose to 173 and 171 subjects with safety, resulting in a total of 344 subjects as the total safety database who received the 50 μg dose. Immunogenicity of this booster dose was compared with a subset in both studies, so a total of 1000 subjects provided the immunogenicity data.

In terms of demographics, the mean age was 52 years. The majority of subjects were female and most subjects were white. Moderna is increasing the sample size of the subjects they will boost, which is ongoing in the Phase 3 study in order to evaluate a larger and more diverse population for the safety, immunogenicity, and effectiveness of the booster dose. To review the safety data, similar to the Phase 3 study, solicited adverse reactions were collected in the diary cards for 7 days after the booster dose; unsolicited AEs were for 28 days post-booster; and SAEs, MAAEs, deaths, and AEs leading to discontinuation were collected through the end of the study. The local solicited symptoms were the same as those presented to ACIP in December 2020 (e.g., pain, erythema, swelling, and axillary swelling or tenderness).

In terms of solicited adverse reactions with 7 days post-booster from the 50 μg booster after the 100 μg primary series compared to the pivotal Phase 3 study because those are the data included in the fact sheet, the reported rates were approximately comparable for the booster dose compared to Dose 2 of the primary series overall. For all of the solicited adverse reactions, the only reaction that was reported more commonly after the booster dose than the second dose was axillary swelling and tenderness. Most events remained mild to moderate in severity, and their median duration was less than 3 days. For solicited systemic symptoms, overall reports tended to be lower than after the second dose of the primary series. Once again, most events were mild to moderate in severity and the median duration was less than 2 days. The rates of unsolicited AEs were approximately equal to what was observed previously. There have been no vaccine-related SAEs or deaths in Study 201B to date.

³⁹ Baden et al., MedRxiv, 2021

Moving to the immunogenicity data for the 50 µg booster dose in terms of the original strain and the Delta variant, the strategy for demonstrating the effectiveness of the booster dose was to conduct immunobridging to the subset of the Phase 3 study. That was because the Phase 3 study was linked to the original 94% efficacy and 93% efficacy which was durable for 5 months. In addition, demonstrating immunobridging offers confidence that immunogenicity will be restored to the level it was post-Dose 2. This study aligns with FDA guidance pertaining to licensure of COVID-19 vaccines. The 2 co-primary endpoints were in terms of GMT ratios or GMR and 1 in terms of seroresponse rates. Dr. Miller presented 2 analyses for each. The first one was pre-specified in the protocol and the second was an additional analysis that was requested upon filing. GMR was from the original specified hypothesis and aligned with the guidance for a statistical criterion in which the lower limit of the GMR had to be above 0.67 and the point estimate had to be above 1.0. For the group who received the 50 µg dose (pooled for 50 µg prime and 100 µg prime group) the GMR was 1.7 with a lower limit of 1.5, which met the point estimate criterion of ≥ 1.0 . The criterion also was met if only the group who received the 100 µg primary series was considered, in which case the point estimate was 1.8 with a lower limit of 1.5.

There was a second pre-specified hypothesis based on seroresponse rates. Seroresponse in this case was predefined as a 3.3-fold rise in titers. In the case of the pivotal Phase 3 study, it was compared to pre-Dose 1 titers. The 3.3-fold increase was selected because the characteristics of the assay when subjected to statistical analysis suggested that the inherent variability of the assay supports discrimination at the 3.3 pooled level. In the case of the pooled primary series group, the seroresponse rate was 94%. The lower limit was above $\geq -10\%$. The statistical criterion was $\geq -10\%$, so the criterion was met. Based on a 4-fold rise from pre-booster titers, as requested by the agency and limited only to the group who received the 100 µg primary series, the seroresponse rate was 88%. The lower limit was -16, so the criterion was not met.

To evaluate that criterion a little bit further to understand why it was not met, the pre-booster titers remained quite high, particularly with respect to the Wuhan strain on which this hypothesis was based. Subjects who did not meet 4-fold rise had 4 times higher pre-booster titers compared to those who did meet 4-fold rise. Pre-booster titers were 108 among those who met the ≥ 4 -fold rise and 492 among those who did not. Nonetheless, both groups achieved post-vaccination GMTs well above the level of 1000. In terms of the correlate of protection analysis that was performed by the NIH, the threshold of 1000 was associated with protection that was approximately 96%. Although a correlative of protection has not been established, there has been an association of increasing neutralizing antibody titers, particularly above 1000 with protection against infection.

Now turning to individual fold rises overall and then by age group. Overall for the Wuhan strain, there was an approximately 12-fold increase pre-booster to post-booster among persons 18-64 years of age that rose to about 18-fold in subjects ≥ 65 years. The older adults, who are at greater risk of complications of COVID-19, achieved a 17.9-fold GMFR to Wuhan-1 D614G. In terms of cross-protection with the Delta variant, there was an overall fold rise of approximately 16-fold among persons 18-64 years that rose to 22-fold in those ≥ 65 years of age.

To summarize safety, rates of adverse reactions after the 50 µg booster dose were comparable to those observed after Dose 2. Pain remains the most common solicited local adverse reaction in both groups. Headaches, fatigue, and myalgia were the most common systemic adverse reactions both groups. The majority were mild to moderate in severity. Axillary swelling or tenderness was the only adverse reaction more frequently reported after the booster as

compared to Dose 2 in Study 301. No vaccine-related SAEs or deaths were observed in Study 201B. Currently, there is a mean of 3 months of follow-up after the booster dose administration. Regarding immunogenicity, the pre-specified co-primary hypotheses were met on the pooled dataset. These were not met in the additional analysis on seroresponse. The 50 µg booster dose following the 100 µg primary series resulted in higher antibody titers to the original virus (D614G) than post-Dose 2, and this was statistically significant with the GMR of 1.8 and a lower limit on the 95% confidence interval of 1.5. There was a 13-fold increase from pre-booster titers for the original virus and a 17-fold rise from pre-booster titers for the Delta variants. Consistently high antibody titers were seen in those 18-64 years of age and those ≥65 years of age.

Discussion Summary

- Additional information was requested by Dr. Poehling on the 2 vaccine-related MAAEs and by Dr. Sanchez on the SAEs—even if they were not thought to be vaccine-related and whether any thrombotic events were seen at all.
 - Dr. Miller indicated that the 2 vaccine-related MAAEs were cases of headache and rash. What led to their assessment as being vaccine-related was the timing at which they occurred. They were comparable to the data being collected as part of routine solicited adverse reactions. In terms of the SAEs, she noted that in the 100 µg primary series group and there was 1 tendon rupture, 1 spontaneous abortion. In the 50 µg primary series group, there was 1 older gentleman who had a DVT and pulmonary embolism and 1 female 89 years of age who had bradycardia and a pacemaker placed, and post-operatively had a case of pericarditis. These were assessed as serious, but not vaccine-related. The older gentleman had was 71 years of age, had a past medical history of hypertension, and developed his DVT and pulmonary embolism 79 days after receipt of the booster dose. The time period, age, and risk factors contributed to the investigators' assessment.
- Dr. Long asked whether Moderna's intent was to use the exact same packaging for the primary series and booster and merely instruct administrators to withdraw a different volume.
 - Dr. Miller confirmed that this is the plan. Administration of the booster dose will be a .25 mL volume. Moderna is going to pro-actively conduct education to make sure that it is understood how this should be given. There will be a "Dear Healthcare Provider" letter, the information is updated on Moderna's Fact Sheet, Moderna's medical teams will present webinars, free training will be provided, there will be a 24/7 hotline, and information will be posted on Moderna's website about how to administer the booster dose.
 - Dr. Loehr referred to Dr. Coyle's comment as part of the docket for this meeting that the American Immunization Registry Association (AIM) expressed concerns about the process of drawing half of the dose (.25 mL) being confusing for the American registries and in terms of keeping track of vaccines. He asked whether Moderna could make it easier for public health to order and manage their vaccine.
 - Dr. Cohn added that the context of AIM's concern was related to the same vial being used for both a primary series dose and a booster dose in that using the same National Drug Code (NDC) does not allow for the inventory and product management and tracking of individuals who received doses.

- Dr. Miller said that while she understood the concern with regard to the code, she would have to take this question back to the group as it was outside of her area of expertise, which is development.
- Dr. Lee added that not only are the billing codes important from a tracking and administration standpoint, but also there is concern about administration errors that could occur if people are asked to draw different doses from the same vial. It also is important to be able to track this in terms of vaccine safety surveillance systems, and it is helpful to have a specific code for pediatrics for this reason. While she recognized that this is a broader question, she emphasized that she wanted to make sure they were clear on this publicly because it will help post-market safety surveillance systems as well as our post-market effectiveness data systems to make sure that people got the right dose and to have a good understanding of safety that does not require assumptions.
- Dr. Cohn expressed appreciation for all of the companies making an effort in the initial trials to include diverse populations. While that level of attention to enrolling diverse populations has become more difficult for all of the companies, it is important to continue to maintain an emphasis on that to ensure that they do not go backwards with regard to the progress that has been made on inclusive enrollment in clinical trials.
 - Dr. Miller stressed that Moderna agrees and underscored that this trial was conducted at a time before they instituted the Inclusion and Diversity Board and all of efforts put into place in the Phase 3 study. That is a major reason that Moderna thinks it is important to continue to capture data—not only to have a larger safety database from the study with the 50 µg per dose, but also to continue to ensure that the results are generalizable. She explained that the reason she focused on the immunobridging study was because in the COVID study, they saw no differences in efficacy between various racial groups.
- Dr. Long observed that the age groups were lumped together as 18-64 years and 65 years and older and asked whether more definition could be provided within the large age range of 18-64 years.
 - Dr. Miller pointed out that while the question was relevant, it was difficult to break the age group down further in the Phase 2 study due to the small sample size overall. The Phase 3 study did not have age groups above 65 years. The analysis was adjusted for various stratification factors. They assessed age as a confounding factor as well as for comorbid medical conditions, and then looked at whether subjects were healthcare workers and not assuming that they had higher exposure rates. The difference was the same about 36% difference regardless of how they adjusted for the potentially confounding factor. So I don't have more age stratification than that.
- If the geometric mean antibody was compared in individuals pre-Dose 2 of the 2-dose series with pre-booster GMT, Dr. Long wondered what could be learned about the relative risk for myopericarditis in people with high antibody titers when they get their second dose for instance.
 - Dr. Miller indicated that while she would not be able to provide a very precise answer as she did not have the pre-Dose 2 titer data in mind for this presentation, this was

- discussed at length during the December meeting. After the first dose, about half of the subjects had neutralizing antibody titers, but a good percentage of subjects needed the second primary series to achieve neutralizing antibody titers. While there are probably differences in titers between pre-Dose 2 and pre-booster, they are not the same population. What is important is that the antibody titers have waned substantially and would be a lot lower pre-booster than they were post-Dose 2.
- Dr. Hogue (APhA) reported that pharmacists are concerned about the booster dose in terms of the sterility of the product, given that now the number of entries into a vial with a needle potentially could be doubled. He asked whether Moderna had conducted any studies to assess continued product stability, sterility, and integrity of the rubber stopper. This is a very concerning issue and perhaps might make the case that it would be helpful if Moderna had a separate product that was designed just for boosters with a smaller volume.
 - Dr. Miller indicated that Moderna has conducted multiple studies and that this was part of the overall submission. What will be in the labeling information is that 20 entries into the vial are the maximum that can be used, and that is supported by data. There are also sterility data to support all of the storage and handling information in the filing. In the context of the pandemic, this is the way the 50 µg booster dose is being managed. This is consistent with how other pandemics have been managed with different doses for potentially different populations, such as the 2009 H1N1 pandemic. Moving forward, Moderna is considering packaging the product differently. That also is relevant to the pediatric vaccination program that Moderna has ongoing in which they will be pressing forward with lower doses in the primary series.

Janssen Booster Dose Data

Dr. Penny Heaton (Janssen) presented booster dose data for Janssen's Ad26.COVS2.S COVID-19 vaccine. More than 14 million adults in the US have received Janssen's vaccine. While the single dose has provided durable efficacy against COVID-19, the data shared during this session was intended to highlight the opportunity to further increase protection with a booster dose. As a reminder, the Ad26.COVS2.S vaccine and development strategy were different. First, the initial Phase 3 study evaluated the safety and efficacy of a single dose regimen for efficient pandemic response globally. Second, the data from this study showed that protection is durable. The efficacy of a single dose has persisted for at least 6 months. Third is the unique immunoprofile with antibody titers that peak later and persist for at least 8 to 9 months. Cell-mediated immunity (CMI) is especially strong with CD4 and CD8 T-cell responses that are likewise durable.

Although durability is very clear, it is also evident that there is room to boost protection, particularly against symptomatic infection. Janssen believes that a homologous booster dose aligns with the US priority to optimally protect individuals against any COVID infection. Data from Janssen's booster studies show how the Ad26 vaccine can support this goal. The data show that a booster dose is safe and increases protection, including against symptomatic COVID-19. More than 9000 individuals have received a booster dose of the Ad26 vaccine in Janssen's blinded RCTs. Janssen's second large, randomized Phase 3 study evaluated 2 doses of Ad26, and a single dose with a booster that was given 2 months later. Efficacy against symptomatic disease was 94% in the US and 74% globally, and there was complete protection against severe COVID. This study also found a similar reactogenicity profile after each dose. Antibody titers increased rapidly, consistent with an anamnestic response. In a separate study,

a booster was given at 6 months to induce even higher titers, with a 12-fold increase. While there were not enough cases caused by Delta in Janssen's RCTs to evaluate efficacy against this variant, they do have 2 lines of evidence that give Janssen confidence in its efficacy against the strain. The first is a large real-world evidence study in the US that was conducted when Delta became dominant showed similar efficacy as in Janssen's RCTs. Further, the booster at 6 months showed an increased breadth of immune response with neutralizing antibody titers against variants of concern, including Delta.

Regarding data from the final analysis of Janssen's pivotal single-dose trial in the US, the efficacy of the Ad26 vaccine was 70% against symptomatic disease. Plotted over time, the efficacy did not wane for at least 6 months. A similar level of protection was seen in a real-world evidence cohort study showing that Ad26 remained effective in the US even as the Delta variant surged and remained stable for at least 6 months. That was through the end of August. The primary endpoint of the single dose study was also met. Globally, efficacy was 75% against severe COVID-19 after a single dose, and efficacy likewise persisted. In addition, protection against severe disease caused by emerging variants remained strong. However, looking globally at VE against symptomatic disease, a trend was observed that decreased over time. An interrogation of the data show that the reduction in global VE for symptomatic COVID appeared to be driven by the emergence of variants rather than declining immune responses. Three variants with VE below 50% (Gamma, Lambda, and Mu) became prevalent in regions in countries outside of the US during the period of analysis.

The vaccine's durability is also reflected in the persistent humoral and CMI. Recall that while antibodies are needed to prevent SARS-CoV-2 infection and to confine the virus to the upper respiratory tract, CD8-positive T-cells are important for preventing spread down the respiratory tree and severe disease. It is the totality of the immune response that protects against COVID-19; that is, the combination of persistent antibodies and a strong and persistent CD8-positive T-cell response. The latter is the hallmark of the adenoviral vector-based vaccines. That is why strong protection is seen against severe COVID-19 hospitalizations and deaths despite the lower antibody levels elicited by Ad26 as compared to the antibody titers reported for the mRNA vaccines.

With regard to Study COV3009 that evaluated the booster dose at 2 months after the single dose, Janssen refers to the second dose as a booster dose for two reasons. First, essentially all participants had the antibody after the single dose. Second, the rise in antibody after Dose 2 had the profile of an anamnestic response. This second Phase 3 study was a large global randomized placebo-controlled trial conducted in 9 different countries across 3 continents. Once the Janssen vaccine was authorized for emergency use, the study allowed unblinding and offered any participants on placebo to receive the Janssen vaccine. Of the more than 31,000 participants who received the single dose, 53% received the booster before the crossover was completed. Therefore, they were part of the double-blind analyses presented during this session. Among the participants evaluated for efficacy, 25% were at least 60 years of age. Here we show the efficacy of the single dose and booster studies. In the US, VE against symptomatic COVID reached 94% after the booster dose. Globally, VE against symptomatic infection improved to 75% post-booster. There was complete protection against severe outcomes. However, due to the limited follow-up time after the booster for the unblinding, the number of cases that occurred during the observation period and the double-blind part of this study were limited.

Janssen also has additional immunogenicity data from other studies that evaluated boosters at different time points. Booster doses have been given at 2 and 3 months after the single dose in younger and older adults and 6 months after initial vaccination in younger adults. Responses were evaluated looking at binding antibody and also wild-type and pseudovirus neutralization assays, and the neutralizing responses correlated strongly. A booster administered at each of the time intervals resulted in increased antibody levels for those 18-55 years of age. Similar increases were observed in those 65 years of age and older. Importantly, when the booster was given at 6 months after the primary dose, it resulted in a 12-fold increase. Overall, these studies showed that a booster dose of Ad26 enhances immune responses, and the benefit may be greater when given at 6 months or later. This finding and the durable efficacy profile are reassuring for those in the US who received the Janssen vaccine more than 2 months ago.

Dr. Macaya Douoguih (Janssen) presented Janssen's safety experience with the Ad26 booster dose. Cumulative exposure to a booster dose of Ad26 includes 9220 participants across 5 clinical studies Janssen has performed. The preponderance of data on the booster dose comes from Study COV3009, Janssen's Phase 3 pivotal 2-dose study in which the second dose was administered 2 months after the primary vaccination. To review the reactogenicity for the booster dose administered at a 2-month interval in Study 3009, since local reactogenicity was similar between the primary and booster dose, Dr. Douoguih reviewed only the systemic reactogenicity during this presentation. In terms of systemic reactogenicity for individuals 18-59 years of age and ≥ 60 years, the data showed that solicited and systemic AEs were less common and generally of lower severity with the booster dose compared to the primary dose in both age cohorts. Notably, the frequency of fever following the booster dose was approximately half of what it was after the primary regimen in the younger cohort. The frequency of events was lower in the cohort of older adults, and Grade 3 events were low overall. There were no Grade 3 fevers in the older adults after either the primary or booster dose.

Looking at the 6-month reactogenicity profile from Study COV1001, which was Janssen's first in-human study and preliminary blinded data from Study COV2008, which is ongoing, a subset of participants in Study COV1001 was boosted at 6 months following the primary dose. The frequency of solicited and systemic AEs was lower with the 6-month booster than the primary dose. While the numbers were limited, the systemic events were also milder in severity. Study COV2008 is an ongoing randomized double-blind trial of participants originally enrolled in Janssen's single-dose pivotal trial, Study 3001. This study is evaluating 3 different dose levels of an Ad26.COV2.S booster at least 6 months after the primary vaccination. There are 127 participants who are estimated to have received the dose level being considered as a booster, and blinded safety data are available on a total of 83 participants to date. While the dose level data remains blinded, it is reassuring to note that no Grade 3 systemic reactogenicity events have been reported. Overall, giving a booster at 2 or 6 months did not result in any increase in solicited reactogenicity compared to the primary dose and in some cases showed a trend toward decreased reactogenicity.

Regarding unsolicited AEs from the safety subset of Study COV3009, diversity was very good demographically in the Phase 3 study and was very closely matched in the safety subset as well. Overall, the frequency of unsolicited AEs was similar between groups and similar to the single-dose pivotal study. The rate of unsolicited adverse events was 15% in the Ad26 group compared to 10.9% in the placebo group after the first dose. This imbalance was driven by vaccine-associated events such as fatigue, injection site reactions, and headaches that were captured outside of the safety subset. The rate of unsolicited AEs also was similar between the groups after the second dose. Rates were balanced in the full analysis set as well for any MAAEs, any SAE, any SAE not due to COVID, and deaths. The number of deaths was

numerically higher in the placebo group at 13 versus 4. Among those who died, none in the Ad26 group were considered related to the vaccine and none were due to COVID. Of the 13 deaths, 6 in the placebo group were attributable to COVID-19.

In terms of Study COV3009 data on AEs and AESI, following the identification of a safety signal for the very rare events of thrombosis with thrombocytopenia syndrome (TTS) in the post-authorization data, TTS was considered an AESI in Janssen's clinical studies. In Study COV3001, 1 case of TTS occurred in each group. The participant in the Ad26 group experienced thrombocytopenia at 86 days following vaccination, followed by cellulitis and deep vein thrombosis (DVT) approximately 100 days post-vaccination, and also was diagnosed with COVID-19 during this event. Anti-platelet factor 4 (anti-PF4) results were not reported. In the placebo group, 1 participant had a DVT on day 27 during the double-blind phase and subsequently developed a pulmonary embolism 2 days later in combination with thrombocytopenia. Neither case met CDC criteria for definitive TTS.

Because there were no confirmed TTS cases in the study and because these events are extremely rare, Janssen looked into post-marketing data collected by the government in the United Kingdom (UK) for the AstraZeneca (AZ) 2-dose vaccine since it is more sensitive than other viral vectored COVID-19 vaccines. With 24.9 million first doses and 24 million second doses administered, the estimated rate of blood clots with concurrent low platelets was 15.1 cases per million following the first dose and 1.9 cases per million with the second dose. The overall case fatality was 17%, with 66 deaths occurring after the first dose and 6 deaths occurring after the second dose. The government's interpretation was that there was no indication of an increased risk of these events after the second dose in any age group.⁴⁰

Regarding some AEs for Study COV3009, there were 3 selected due to imbalances observed in the single-dose pivotal study (embolic and thrombotic events, convulsions or seizures, and tinnitus). No imbalance was seen in Study COV3009 from thrombotic events to seizures. Although the numbers are small, an imbalance was observed of tinnitus following the first dose and then no difference after the booster. Guillain-Barre Syndrome (GBS) and facial paralysis are events of interest for all COVID-19 vaccines, for which no imbalance was seen in Study COV3009. A numerical imbalance between the Ad26 and placebo group was observed for arthritis, which was not observed in Janssen's single-dose pivotal study of 40,000 participants. In Study COV3009, imbalances were observed due to events that occurred 28 days after the primary dose. There were no clear patterns of differences between the Ad26 and placebo groups, and a large proportion of cases were apparent exacerbations of existing conditions. The majority of these events were non-serious, and there was no imbalance in the 28-day period in terms of events following a booster dose.

In the context of greater VE with the booster dose, this study showed that the reactogenicity and safety profile of booster at 2 or 6 months was similar to the single-dose primary regimen. The incidence and severity of local AEs was also similar regardless of the timing of the booster. Systemic AEs appeared to be lower and of milder severity at 6 months relative to 2 months. The large, randomized placebo-controlled Study COV3009 did not identify any new safety signals for AEs, SAEs, or AESIs at the booster dose. Global post-marketing surveillance of the 2-dose AZ COVID-19 vaccine suggests that rare TTS events are much less frequent after the second dose than after the first. No TTS cases following the booster dose have been observed for Ad26. Janssen will revise its ongoing and planned post-authorization studies to incorporate follow-up

⁴⁰ <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>

of booster doses in addition to the primary doses.

Dr. Heaton (Janssen) concluded that Janssen's randomized placebo-controlled trial provides strong evidence of the safety and efficacy of a homologous boost of Ad26 vaccine. The Ad26 vaccine immunoprofile is unique and a strong and persistent CD8-positive T-cell response is a hallmark of the platform. CMI, including CD8-positive and CD4-positive T-cell responses with maturation of potent neutralizing antibody are all important contributors to protection, and that protection is higher with the booster dose. As shown in Study COV3009, the point estimate of accuracy was 94% against all symptomatic disease in the US, matching the peak efficacy reported for the mRNA COVID vaccines. Further, the magnitude of the safety information from an RCT is also unique to the Janssen program. More than 9000 participants have received a homologous Ad26 boost that provides a large safety database showing that the booster dose is safe and well-tolerated. Janssen believes this robust data package supports the administration of a homologous booster dose for Janssen-vaccinated individuals. The data show how the Janssen COVID-19 vaccine can help further protect individuals from COVID-19. As such, Janssen strongly supports the VRBPAC recommendation, which provides flexibility for administering a booster dose of Ad26. More than 14 million persons who received their COVID-19 vaccination with Ad26 have the information needed to determine the timing of the booster dose, at least 2 months following the first dose or at 6 months or later to maximize durable protection. Any person who may get a booster in the future will likewise have the right data for scheduling their booster.

Discussion Summary

- Dr. Talbot pointed out that the last safety slide regarding TTS following the second dose was the AstraZeneca vaccine that was used in the UK, but they had stopped using that vaccine in young, healthy women prior to most of them getting a second dose. It was not clear to her that these data were helpful since the main risk group for that syndrome was removed from the group getting the vaccine, making it difficult to determine the impact of a second dose because of the change in the denominator.
 - Dr. Douoguih emphasized that the difference was still fairly substantial and striking in terms of the denominator. However, it is not replacing any data that Janssen would generate with its vaccine and they do think it is important to monitor this.
- Referring to Slide 12, Dr. Daley requested additional details regarding the difference in symptomatic COVID efficacy against symptomatic COVID-19 in the US (95%) compared to globally (75%) in terms of what explained the difference.
 - Dr. Heaton pointed out that the Alpha variant was the predominant strain in the US at the time they upped efficacy to 94%. The efficacy against new variants was 63%. There were no Delta cases at the time of the study. Following real-world evidence on a month-to-month basis, a single dose has been 70% to 80% efficacious depending on the severity of the disease. They also continue to assess neutralizing antibody titers. Those data also show good neutralization of the Delta strain currently circulating, which they are continuing to monitor as well.

- Dr. Grogg inquired about whether there were any additional data on immunocompromised patients in terms of booster efficacy.
 - Dr. Heaton indicated that there were not very many immunocompromised patients in the randomized controlled studies. In their real-world evidence study, there were 29,000 individuals who met the definition of immunocompromised. That includes active cancer, a history of organ or stem cell transplant, primary immunodeficiencies or HIV in the first year, or being on immunosuppressive therapies. The effectiveness of the vaccine was 67% against hospitalizations in those individuals. Janssen is continuing to follow this over time, as well as safety, pharmacovigilance, and the effectiveness data. They do have efficacy on individuals with comorbidities, which was 77.9% against all symptomatic disease. The numbers become increasingly smaller in terms of severe immunocompromise, making it difficult to draw any conclusions.
- Dr. Sanchez asked whether any pregnant women were included in the study and if so, whether there were any AEs or other data on pregnant women and the vaccine.
 - Dr. Douoguih responded that while they did not include pregnant women in their efficacy studies, they do have a separate clinical study that will enroll approximately 400 pregnant women in the second and third trimester and that began in September and is ongoing.
 - Dr. Maree, Janssen's Chief Medical Officer, added that they do have limited information on pregnancy outcomes following vaccination. There are 54 reports from clinical trial data and 320 pregnancy reports from post-authorization spontaneous and solicited data sources, including 58 cases reporting breastfeeding. No safety signals have been identified. A pregnancy registry is ongoing, and it would be modified to encompass the evaluation of the booster dose as authorized.
 - Dr. Ault reminded everyone that during one of the first times the Janssen vaccine was discussed, mention was made that the Ebola vaccine had the same vector and there was a lot of experience with pregnancy and that vaccine.
- Dr. Lee asked whether Janssen is doing any post-Dose 1 and post-Booster assessments in terms of anti-PF4 antibody measurement, which she asked because a lot of what efforts are centered on are trying to mitigate risk as much as possible both from disease and vaccination. That might actually provide some information about whether a different boost would be appropriate, such as in young women for example.
 - Dr. Douoguih confirmed that Janssen is looking at anti-PF4. They started by looking at participants who had and did not have thromboembolic events in both the vaccine and placebo groups within the COVID program. They also are evaluating people who are in Ad26-based vaccine studies with non-COVID vaccines for comparison. Preliminarily, they are seeing PF4 positivity in both the placebo and vaccine groups, so the numbers are fairly small. There probably will be more to report on this in the coming months as they continue this analysis.
 - Dr. Lee added that to broaden the question to other manufacturers as a discussion point, it could be incredibly helpful to similarly assess cardiac enzymes post-booster dose or post-Dose 2, even in asymptomatic individuals,

who are enrolled in clinical trials in terms of understanding whether there are any patterns and whether risk can be further mitigated with ACIP recommendations.

National Institutes of Health, Mix and Match Booster Study

Dr. Robert Atmar (Baylor College of Medicine) reported that the Mix and Match Study was an open label, non-randomized, adaptive design, multicenter study to evaluate the safety, reactogenicity, and immunogenicity of COVID-19 booster vaccines in persons who completed an EUA vaccine regimen at least 12 weeks earlier. Participants were 18 years of age and older, healthy or with stable underlying disease, not immunocompromised, not pregnant, and with no history of SARS-CoV-2 infection by history and consented to participate in the study. Approximately 50 persons per EUA vaccine group, with approximately even numbers of persons 18-55 years of age and 56 years of age and older, were enrolled sequentially in 3 stages. The first stage began in early June. Participants received 100 µg dose of Moderna vaccine. Participants received the Janssen vaccine in the second stage, and the Pfizer vaccine was administered in the third stage. There were 9 groups total. A safety call was made at Study Day 8, and the participants were returned or will return on Study Days 15 and 29 and at 3, 6, and 12 months for blood draws and safety evaluations.

In terms of the characteristics of the study participants, approximately 50 persons per group were enrolled. The mean age per group ranged from 48-57 years. The distribution of the study population by race and ethnicity did not fully represent that of the US population. The average time from completion of the EUA regimen to boost progressively increased across the stages due to the sequential enrollment set forth in the study design. It also tended to be shorter for those who received the Janssen EUA vaccine regimen versus those who received an mRNA vaccine under EUA. There were 2 persons (1 in Group 4 and 1 in Group 6) who had evidence of prior SARS-CoV-2 infection based upon a high antibody level to the N protein at baseline. When other participants in Group 5 developed COVID-19 on Study Day 27, none of these individuals were excluded from the analyses Dr. Atmar presented.

Regarding the antibody assays being evaluated in the study, pseudovirus neutralization assays are being performed in the laboratory of Dr. David Montefiore at Duke University. IgG binding antibody assays are being performed in Dr. Adrian McDermott's laboratory at the Vaccine Research Center (VRC) at the NIH. The virus strains of focus for this presentation included D614G N from the Montefiori Lab and 4-plex for Wa-1 and 10-plex Fit for Purpose (FFP) for Alpha, Delta, and Wa-1.

In terms of the immunogenicity results for day 15 and where available Day 29, the lowest antibody titers at baseline tended to be in those who received the Janssen vaccine initially and was followed by those who received the Pfizer and then Moderna vaccine. All groups showed a boost by Study Day 15. For those boosted with Moderna, antibody levels were level or decreasing slightly by Day 29, while those boosted with the Janssen vaccine had slightly higher antibody levels on average by Day 29. Data are not yet available for Day 29 for the Pfizer vaccine recipients. The lowest post-boost titers were in those who received the Janssen vaccine initially and then were boosted with the Janssen vaccine. The magnitude of responses in the younger and older age strata were similar, so only the pooled data were presented for each group. Looking at the IgG binding antibody responses as measured in a non-validated 10-plex ELISA to the Wa-1 strain, Alpha variant, and Delta variant, all groups had increases in antibody levels after boost. The highest levels achieved were to the Wa-1 strain, followed by antibody levels to those for the Alpha, and with Delta variants being progressively somewhat lower. The

patterns of responses in the different vaccine groups were similar to those seen earlier. Notably, the range of antibody levels decreases after boosting.

With respect to safety, there were 2 unrelated SAEs. The first was acute renal failure due to rhabdomyolysis from a fall that occurred 30 days after a Moderna boost. The second was an episode of acute cholecystitis that occurred 24 days after Janssen boost. No pre-specified study-halting rules were met. No new onset chronic medical conditions occurred through Study Day 29. There was one related AESI based on it being a medically-attended visit for a person who developed severe vomiting, which was determined to be related to their Janssen boost. The frequency of unsolicited AEs deemed related to the booster vaccine was similar across the booster groups and most were Grade 1 or 2 in severity. There were 4 unsolicited AEs deemed to be related and severe. In addition to the vomiting for the Janssen-boosted individual mentioned previously, severe vomiting occurred in 1 person boosted with the Moderna vaccine. In the Ad26.COV2.S booster group, 1 individual experienced severe fatigue and 1 experienced solicited AEs, including both injection site and systemic reactogenicity, and were basically as expected based on what has been reported in prior clinical trials. The most common events were injection site tenderness, followed by malaise, myalgias, and headaches. Most reactions were mild or moderate in severity.

Some of the limitations of this study are that it was non-randomized, open-label, and subjects were enrolled sequentially for the different stages. The study was not designed to compare between boosts. For example, intervals between primary vaccines and boost were not controlled for. Correlates of protection are not completely elucidated, and they are even less well-understood for severe disease and death. While only antibody data were presented during this session, cellular immune response data also are being analyzed but are not yet available. These data also only represent early time points from the trial, though the vaccines may differ in time to reaching peak responses and they have different durability of those responses.

In conclusion, use of the Moderna, Janssen, and Pfizer vaccines as boosters led to anamnestic serologic responses in all 3 EUA-dose vaccine groups. When given primary EUA COVID-19 vaccine, heterologous boosts elicited similar or higher serologic responses as compared to their respective homologous booster responses. mRNA vaccines resulted in higher antibody levels in the first 28 days after the boost, and no safety concerns were identified. More information related to the study results are available in the preprint.⁴¹

Discussion Summary

- Dr. Brooks asked whether the smallest boost occurring after a Janssen primary series was related to the interval between the primary vaccine and the boost, given that the data showed that the response was much better after 6 months as opposed to 2 or 3 months.
- Dr. Atmar clarified that he reported on the magnitude of the level achieved post-boost. The antibody responses seen after Janssen vaccine is known not to achieve the same levels as after an mRNA vaccine. Therefore, those who received the Janssen vaccine did not achieve as high a level after a boost. That is not particularly surprising and is consistent with what has been reported after the primary vaccine regimen with the Janssen vaccine. In terms of antibody levels peaking, the Day 29 levels were somewhat higher for the Janssen vaccine. With the Moderna vaccine, a peak was observed at Day 15.

⁴¹ Preprint: <https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v2>

- Dr. Poehling inquired as to whether there were any cases of exacerbation among people with stable chronic conditions.
- Dr. Atmar indicated that there were isolated cases of high blood pressure. However, there was nothing persistent that was considered to be an exacerbation of anyone's underlying condition.
- Given that the risk of serious illness is highest in people over 75-80 years of age, Dr. Schmader (AGS) asked how many subjects in this study were over 75 years of age.
- Dr. Atmar indicated that there were 2 to 3 individuals. In the Janssen group boosted with Pfizer, there were no participants in that age range.

Public Comment: October 21, 2021

The floor was opened for public comment on October 21, 2021 at 12:16 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2021-0098. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received. The public comment session was conducted prior to the votes. However, the votes were included with their respective sessions for ease of reading.

Mrs. Erica DeWald Director, Strategic Communications & Partnerships Vaccinate Your Family

I'm Erica DeWald, Director of Strategic Communications and Partnerships with Vaccinate Your Family. Thank you so much for the opportunity to speak today. As the committee continues to evaluate the COVID-19 vaccine for children, I wanted to share our board's thoughts around requiring the vaccine for school entry. As you may know, our Co-Founders Rosalynn Carter and Betty Bumpers were instrumental in the passage of laws requiring vaccination for school entry back in the 1980s. Vaccinate Your Family continues to support school vaccine requirements that keep our children safe from deadly, infectious diseases. While that primary series of vaccines ought to be completed by age 2, school requirements ensure that no children fall through the cracks of the healthcare system and could be caught up on needed vaccines prior to entering kindergarten. Traditionally, vaccines are not added to the requirements for daycare and school attendance until they have been on the market for an extended period of time. Childhood safety data for each vaccine on the recommended schedule helps ensure parental acceptance of vaccines. School and daycare requirements should be in place as the final mile to ensure that children remain safe from deadly infectious diseases in their place of learning. There are several parameters that should be in place prior to considering vaccine requirements for school/daycare attendance: 1) parental acceptance; 2) broad availability of the vaccine; 3) physician or provider support for the vaccine; 4) full licensure of the vaccine; 5) stable and adequate vaccine supply; 6) addition of the vaccine to immunization information systems, also known as registries; 7) adequate data to assure vaccine safety; 8) significant uptick in the recommended population, in this case children, to reduce the compliance burden on both schools and childcare systems; 9) coverage for the vaccine and delivery in private health insurance plans; and 10) for vaccines that are not federally-funded

already, sufficient funding to purchase the vaccine through the VFC Program, Section 317 Program, or a state program. While data supporting the overall safety of COVID vaccines is well-established, the multiple criteria typically in place prior to considering the school-based requirement have not yet been met. Therefore, Vaccinate Your Family is urging State Legislators, Governors, and Health Commissioners to first ensure that necessary parameters have been met prior to considering the addition of COVID-19 vaccinations for children to the list of requirements for school attendance. As for our full statement, please visit our website at vaccineyourfamily.org. Thank you so much for your time today.

Karyne Jones, MPA
President & CEO
National Caucus and Center on Black Aging (NCBA)

My name is Karyne Jones and I'm the President and CEO of the National Caucus and Center on Black Aging. NCBA has a 52-year history of working to improve the quality of life and health and well-being for older African Americans and other communities of color. I know this committee has many different and competing factors to consider when making the tough decision on the use of vaccines, but I cannot help but use my time to express my disappointment in the committee's decision not to expand the age-based recommendation for pneumococcal vaccines to age 50 and older. CDC data has shown that previous meetings confirmed that the recommendation for those over the age of 50 would not only be cost-effective but help to bring equity to populations that historically have low immunization rates, namely the population my organization represents. I submitted a joint written comment for this meeting with Dr. Yanira Cruz, who's the President of the National Hispanic Council on Aging (NHCA), and we titled that comment "When America Gets a Cold, Communities of Color Get Pneumonia." Yesterday's vote was an important opportunity to work towards ending the reality of this committee's missed chance, as several voting and liaison members of this committee noted yesterday. Individuals aged 50-64 will respond to the vaccine much better than someone over 65 who has experienced advanced decline of the immune system. Further, it was noted that while we certainly need to take cost-effectiveness into account, we also must support policies that are equitable and will ultimately reduce mortality and morbidity in diverse communities. The last point I will raise with you for yesterday's discussion, which I think was worth repeating, is the very real fact that while it is a nice idea that people in their 50s could live another 30 years and thus require a booster shot, many patients from black and brown communities will not live to 65 due to chronic conditions, environmental factors outside of their control, and the effects of a lifetime of inequitable care. Why wouldn't we offer them protection earlier in their life span when we will have a greater chance of strengthening their immune system before chronic conditions set in? ACIP's reluctance to make these vaccines available to as many Americans as possible is shortsighted and it sends a confusing message to the American public. Unfortunately, what's clear to me and to many of my counterparts who represent diverse communities is that this decision does very little to improve health communities of color and addressing health disparities. Thank you very much.

Mrs. Linda Rehkopf
Patient

My name is Linda Rehkopf and I have a primary immune deficiency (PID) along with a predisposition to developing ARDS (acute respiratory distress syndrome), which I've survived 5 times prior to the COVID years. So, when the whole world inhaled in March 2020 because of a pandemic, I thought "Welcome to my very scary world." My family goes to extraordinary lengths to keep me safe. I would like to know as you deliberate vaccine protocols where is the data on

patients with primary immune deficiencies? I've been able to find just one study on vaccine response in patients with PID. I tried to enroll, but it was full and I was denied participation. So, because I'm not in a study group at NIH or John's Hopkins, or other places, I've only ever gotten a "yes" or "no" answer on my lab tests for antibodies to COVID. But I know from my own research that these tests exist. I know of multiple studies to determine numeric antibody levels in solid organ transplant patients. I know that NCI has a study on B- and T-cell response to COVID. Without minimizing those patient groups, I would like to know when the ACIP will have similar data for patients with PID. When will the test for the numeric level of antibody production after vaccination be widely available to the patient population I represent? And will our family members, those in our bubble, will they be able to get antibody levels tested? It seems that we can but only if we know how or who to ask or where to look. Others in the autoimmune and PID community still have to argue with their pharmacists, doctors, and public health personnel just to get a third dose, not a booster, which this committee recommended in late July and August. The language from this committee matters. How it is communicated to the public and the patient advocacy groups matters. I urge you to develop antibody testing guidance for those of us in the primary immune deficiency community and for our families. I urge you to allow our family members to get third shots and booster shots outside of your guidelines presently. I encourage routine testing for the numbers, not just positive or negative emojis, because knowing the numeric level of antibodies I produce along with B- and T-cell response will help me decide when it's safe to go outside my house and exhale. Thank you for your time.

**Dr. David Wiseman
Synechion**

Thank you. I was a senior J&J scientist and have since received research fees outside of vaccines. I received funding from Steve Kirsch and [unclear]. Please see our written comments. Thank you ACIP and VRBPAC for diligently wrestling difficult issues, but you are only as effective as the data presented to you and your understanding of how your words will be used to shape policy. FDA's Dr. Krause was charged with Pfizer's withholding data from FDA. We suggested that waning immunity data were withheld from ACIP. While their advisory committee decisions are not binding, FDA and CDC have stretched recommendations on boosters. The distinctions between the Pfizer EUA and the Comirnaty® BLA vaccines do not appear to have been explained to you and are increasingly blurred, including by CDC. The discussion of flu with the EUA Moderna vaccine yesterday opens a regulatory back door. A non-voting ACIP discussion about vaccines in pregnancy preceded a CDC Health Advisory, despite Comirnaty® saying that data are sufficient to inform pregnancy risks. Do pregnant women know that CDC has two studies where there is a quote "urgent need to monitor the safety of these vaccines," or do they know these studies requested informed consent or parental permission waivers? Pregnant women are effectively mandated to unknowingly participate in a medical experiment. Do you endorse this? The smaller limited mix-and-match study labeled "preliminary" in its medRxiv pre-print version, was a subject to a VRBPAC non-voting discussion, but we now see FDA's ruling, but not VRBAC's intent, creating therapeutic chaos and a safety tracking nightmare. You appear unaware that these vaccines are classified by FDA's gene therapy products and what that means long-term and that Comirnaty® has not been evaluated for carcinogenicity, genotoxicity, or male fertility. Safety signals remain unaddressed. They show VAERS signals greater than myocarditis, deaths 200 to 300 times higher compared with flu vaccines, coagulopathy 400 to 500 times the Pfizer or Moderna and 1400 for Janssen, myocardial infarction 300 to 400 times. The case for boosting is largely based on small immunobridging studies, with no established immune correlates of protection. It relies on Israeli data for efficacy where there was significant statistical concern, and where following primary or booster vaccination increasing severe cases precedes that for unvaccinated people, suggesting

transmission issues. You are being asked to evaluate Janssen's safety and efficacy data because the FDA has admitted it is not verified. It seems every regulatory safeguard is being tossed out. America trusts you to follow the science and transcend politics. Your decisions have much broader consequences, such as mandates. Don't base decisions on extrapolations and extrapolations of improperly reviewed data. We urge you to challenge CDC and FDA and to demand answers. Thank you for your work.

Candace K. Johnson
Kidney Transplant Patient
Participant in the Johns Hopkins Study for Antibodies
Transplant Recipient and Immunocompromised Patient Advocacy Group (TRAIPAG)

Good afternoon. My name is Candace Johnson. I'm a kidney transplant patient, a participant in the Johns Hopkins study for antibodies and T- and B-cell, and a member of the TRAIPAG advocacy group. My message today is to strongly encourage the FDA and CDC to reconsider their guidance on antibody testing. Current data is based on information through July or earlier. Dr. Dorry Segev, Associate Vice Chair for Research and Professor of Surgery and Epidemiology at Johns Hopkins, wrote an article in *The Hill* this weekend that we have much better antibody tests now. In listening this morning, vaccine studies on efficacy are based on antibody response. Labs are run on a routine basis to gauge health status. Why not add quantitative antibodies to the list? Without testing and collecting this data, especially on breakthrough infections, we'll never know how effective actual levels are. Dr. Segev's research has indicated that higher antibody levels neutralize more COVID than lower levels. So, these tests clearly prove something. To quote his words, "It's time to check antibodies and take the guess work out of this pandemic." This is particularly critical for immunocompromised people. Quoting Dr. Segev again, "Vaccination does not necessarily mean strong immunity." I am a perfect example of that. With 3 doses of the Moderna vaccine, on the Roche scale my antibodies are less than 0.4%. I know I must double mask and social distance to keep myself and others as safe as possible, but what about others who may not have produced antibodies and don't know it? Using antibody test levels will give us an understanding of where we stand in terms of protection. Thus, as this panel is doing today, please consider regular testing so that we can make informed decisions. Not measuring antibodies is flying blind. On yet another very important note, our family members and caretakers continue to suffer along with us as we quarantine and do everything in our power to protect ourselves. I urge the FDA and CDC to include these individuals in the group of those eligible for booster shots so that they can not only protect themselves, but also protect us if they get COVID. Thank you for the opportunity to make these comments and for listening. Your diligence and your compassion is greatly appreciated.

Laura Burns
Double Transplant Recipient
Participant in Johns Hopkins Studies on Vaccine Efficacy in Lung Transplant Recipients
Transplant Recipient and Immunocompromised Patient Advocacy Group (TRAIPAG)

My name is Laura Burns. I'm a double transplant recipient and a participant in 4 of the Johns Hopkins studies on vaccine efficacy in lung transplant recipients, led by Dr. Dorry Segev. I am also a member of TRAIPAG. We urge you to adopt the Moderna and Janssen EUA changes announced by the FDA yesterday and to allow the mixing-and-matching of vaccines. At the last ACIP meeting, I asked you to specifically authorize boosters for our close contacts who form our bubble. Our members implore you to include them this time around and to address this issue in your discussion. As Dr. Walensky said, our job is to protect as many people as possible. We're

also concerned by the use of the term “booster” for a second dose following the J&J. The FDA panel universally opined last week that this was in actuality a second priming dose, not a booster, because it brings vaccine efficacy from around 70% to over 90%, making it closer to the mRNAs. So, they authorized it for everyone 18 and older and after just two months, but what about the immunocompromised who have no response to the first J&J? We cannot assume they won't need 3 doses to be primed. And how are they to know whether they respond to a second dose? As a doctor, wouldn't you order an antibody test? In your decision-making, you have relied extensively on studies which measure antibodies as a proxy for vaccine efficacy. Shouldn't we? The written comment submitted to the op-ed in *The Hill* by Dr. Segev is called “It's Time to Check Antibodies and Take the Guess Work Out of This Pandemic.” I urge you to read it. When you have a medical issue, doctors want labs, which inform them as to your status. Not measuring antibodies is flying blind. We can no longer say we don't know what antibody levels mean. That might have been somewhat true in July, but it's not true now. We have a very good sense of what antibodies mean and that they correlate with neutralization and actual clinical protection. More and more studies are showing this. They're not perfect, but many tests done in clinical medicine aren't perfect. The way to use antibodies is to test them and incorporate them into the bigger picture of individualized patient counseling. Dr. Sanchez, you have often raised the question in past meetings, “If we don't test for antibodies, how will we ever find the correlate of protection?” Indeed, how will we? So, please approve the Moderna and Janssen boosters. Allow the immunocompromised who got J&J to get a third dose as you did for the mRNA. It's a question of equity in allowing for mix-and-match. I thank you very much for all of your hard work and for your kind attention.

Ms. Sarah Barry
Independent Vaccine Advocate

Thank you to all of the ACIP for continuing to do critical work during this time. My name is Sarah Barry. I am independent pro-vaccine advocate and I am grateful for the opportunity to speak today. First, I would like to update you all on the status of anti-vaccine legislation in Ohio. I'm happy to report that HB-248, which was written and supported by Ohio's anti-vaccine lobbyists, is officially dead. As a reminder, HB-248 would have made it illegal for anybody to require any vaccine, not just the COVID vaccine. Attempts were made to create a new, more watered down version of HB-248 called HB-435, but at this time, it appears that both bills are dead in the water. I would caution that although this is good news, anti-vaccine activists in Ohio still have a tight grip on the legislature. I strongly believe that a heightened awareness of the political lobbying anti-vaxxers do all over the country is necessary to combat vaccine hesitancy and this information. Most recently, I obtained and provided to the *Ohio Capital Journal* footage of Ohio Senator Andrew Brenner speaking to a group of anti-vaccination advocates about alternative treatments for COVID-19, one of whom suggested gargling diluted bleach as a preventative. Senator Brenner then shared that he will be introducing a bill that will prohibit discrimination “against people or information that deals with alternative therapies, such as what you've been discussing today.” I've talked before during ACIP public comment about how prior to the pandemic, the anti-vax community has allowed and sometimes explicitly endorsed abusive treatments and cures for autism, such as using bleach enemas or chelation. I strongly believe that if a forceful campaign against such abuse had been implemented prior to the pandemic that we would not be in as bad of a position as we are in today. It is incumbent on all of us to recognize the outside influence anti-vaxxers have on our political landscape and to realize that the trickle down effects of ignoring that influence will lead to worse health outcomes for all people in this country. Yes, I have most certainly worked hard on my own to expose the anti-science and anti-vax sentiments within the Ohio legislature by working directly with reporters and journalists who will take me seriously, but there is nothing stopping you all as individuals

from doing the same in your own communities. And I think that your position as being on ACIP will help lend credibility and not make it as hard for you to be taken seriously as it sometimes is for me, and if you need help with this, I do invite you to message me on Twitter at my handle 42believer. I will close my statement by sharing with you all the mental toll my advocacy has taken on me. As a visible pro-vaccine advocate, I have been subjected to online abuse by extremists, such as the Proud Boys, and also what I worry are intentional efforts to intimidate me at my home. For many months now, there have been regular anti-vax protests across the street from where I live. Some days, the anxiety literally makes me throw up. I will not stop because we all know that this issue is that important. I know that such abuse might make it hard to do this advocacy on your own, but I urge you. It is so important to take it seriously and to not let people strike you down and discontinue your advocacy. And please, continue having these important conversations. Thank you for your time.

Mr. Mark Gibbons
President, RetireSafe

Thank you for the opportunity to speak today. My name is Mark Gibbons. I'm a husband, a father, a veteran, and a man who has passed the demarcation line of mid-Century birthday. I'm also the President of RetireSafe, a non-profit advocacy organization giving voice to the concerns of older Americans. Health and healthcare, while always of major importance, now rank at the top list of concerns of virtually all adults, but especially those of us who are approaching Medicare and Social Security eligibility or are already enrolled. And it is through that reality I wrote my remarks. First, thank you for your tireless work that you have done this year. Surely, no year in history has been as complex or as important. I had hoped to be given a time slot to speak yesterday before your vote on the new pneumonia vaccine, but our point remains the same. Those of us over 50 know we are vulnerable to flu, and that's why we get vaccinated each year. Please know our concern about how vulnerable we are to pneumonia as well. While it is true that the older one is, the higher rate of pneumonia among our age group. People my age, 58, over 50 but under 65, are unfortunately well-represented among millions of people who receive hospitalization for pneumonia in any given year and sadly among the 50k who die from it. We are vulnerable because many of us are beginning to have chronic illnesses that are not yet diagnosed or don't have health insurance or are genetically predisposed. Maybe that is because over 40% of us are overweight—a factor that many recent studies have linked to susceptibility to pneumonia or because we smoke and we don't tell our doctor that we do. Whatever the reason, 65 is not a magic moment when we go from low risk to high. It's a continuum that advances. I'm not looking forward to telling our community of supporters that they may not yet be eligible for vaccines which can protect them from this dangerous disease, but on their behalf, I want to respectfully suggest that ACIP consider widening the margins of protection—not in several years but much, much sooner. We need your help. Thank you.

Mr. Burton Eller
National Grange

My name is Burton Eller. I'm from the National Grange, the nation's oldest organization representing agricultural, rural, and small town life in America. Allow me to begin this with some harsh facts. In urban areas, most people live about 4 miles away from a hospital, but the distance is twice that in rural America. Lack of access to healthcare where we live accounts for 55% of what could be preventable hospitalizations or death. Rural life expectancy is 2 years shorter. Since 2015, 181 rural hospitals have shut their doors and 1 out of every 4 that remain are struggling. Fewer healthcare providers and facilities, longer distances to obtain care or receive community services, lower wages, fewer employment opportunities, and less access

to technology—these factors result in very serious healthcare concerns for rural Americans. We all had a very hard winter last winter, but the situation in rural America was already operating with significant disadvantages. No one solution will solve all these problems, but you can depend on Grange members and all rural Americans to do their part in climbing out. We do understand that prevention is a key factor in health security, and that is the major point we want to make today. Rural life has risk factors that may not show up in clinical studies but, nevertheless, are very real. For example, just before COVID, the National Center for Health Statistics reported that the age adjusted rates for influenza and pneumonia were higher in rural counties than in urban. We are worried as we enter this pneumonia and flu season this year. Hopefully, COVID will continue to decline, but will there be significant twindemics of these other two dangerous diseases? If so, we already know that we will be playing catch up from the start unless action is taken now. We thank ACIP for its work on new pneumonia vaccines, but we had hoped that age 50 would have been the designation point to help get us on a jump start basis. We will do everything we can to make certain rural America knows what's available to them and why it is so important to protect themselves and their families. We will work with you in every way to our common goal. Thank you.

Dorit Reiss, PhD
Professor of Law
University of California
Hastings College of The Law

My name is Dorit Reiss. I'm a Professor of Law in the University of California Hastings College of The Law. Thank you again to the committee for all your hard, intensive work in these trying times. Today I want to talk to you as someone who teaches administrative law and emphasize the need for explanation and transparency. I want to touch on four things. First, after your previous meeting, the CDC Director changed from the committee's fourth recommendation. It's the job of the CDC Director to decide, and she does not need to be a "rubber stamp." But even when she deviated from the committee's recommendation, the public deserved to know why. I would urge the CDC Director in the future to clearly and openly state the reasons for deviating from any committee recommendation. She may have more public-oriented point of view through the committee, more policy-oriented, but as in other administrative contexts, the public desires to know the basis on which decisions are made, including why this director decided to deviate. The committee's deliberations are public. We heard several explanations from members. We need similar from the director. Second, the committee does not post an explanation, but when you make recommendations about boosters and mix-and-match, the public will have questions. We are already hearing following the FDA meeting questions on if the data is not there about mix-and-match, why recommend the preference for the same vaccine? You have to make recommendation even in uncertainty, but the people implementing them are going to have to explain. Every year you put out immunization schedules and in them you give explanations. If your committee could consider adding a short explanation to recommendations where the stance is uncertain, I think it will be very helpful for people who have to put their recommendations into practice. Third, as mentioned by the previous speaker, we still have strong disparities in vaccine access. That's not your area. You do not control access, but the message from the committee is that these priorities need to be made—prioritizing bringing vaccines to people who have not received them. For example, vaccine clinics are going to be where people are providing support to people who need time to get a vaccine could be useful, and the statement that in providing that additional resources, prioritizing neighborhoods and groups badly hit by the pandemic would also be helpful. And finally, I want to remind you, and I'm saying this because many oral comments are really helpful, but you do not have to legally provide oral comments and that they have been used and will be used to create anti-vaccine

propaganda and legitimize it as coming from the CDC. If you have staff members summarize the major issues in recent comments submitted 72 hours before emitting, you may achieve more meaningful public participation by providing issues across commenters and maybe giving the committee a chance to consider them carefully. Thank you for your time.

Kelly Moore, MD, MPH
Chief Executive Officer (CEO)
Immunization Action Coalition

Thank you, Dr. Lee. I'm Dr. Kelly Moore, the CEO of Immunize.org, also known as the Immunization Action Coalition. I'm a former ACIP member and the former Chair and current member of the Viral Hepatitis Work Group. My comments relate to your upcoming hepatitis B policy consideration. There's been a lot of discussion about the relative merits of risk-based versus age-based adult vaccine recommendations. Some have asked for evidence that age-based recommendations work better. There's quite a bit of it. As my colleague LJ Tan noted yesterday, our risk-based pneumococcal vaccine recommendations are poorly implemented, with just over 23% of high-risk individuals vaccinated, while 69% of those subject to an age-based pneumococcal recommendation are vaccinated. We can also point to similar low coverage rates under the old influenza risk-based recommendations years ago set aside in favor of age-based recommendations, and the current risk-based adult hepB and hepA vaccine recommendations. Programmatically, unless risks are easily defined and obvious, risk-based recommendations for preventive interventions are weak solutions to population-wide problems. The current risk-based hepB and pneumococcal recommendations favor those who are more highly educated, with advanced health literacy, who have no problems accessing medical care and advocating for their needs, and who have healthcare providers who find ways to incorporate vaccine risk screening in their practices. That is no way to deploy vaccines to address health disparities. Every person is at some degree of risk of hepatitis B infection that rises and falls over their lifetime. Of all the acute hepB cases reported to CDC, only 1 in 3 reports a known risk factor and 2 out of 3 acute hepB cases reported leave risk factor blank or indicate no risk factor present. HepB vaccination provides lifelong protection. Whether you choose to travel, or develop diabetes, or share a home with a person with hepatitis B, you're protected. That's why our age-based childhood vaccination program has been such a phenomenal success. We have set national hepatitis B elimination goals, but rates are rising in middle aged adults. We cannot eliminate hepatitis B in the United States without a new approach. To make no change is the definition of insanity if you define insanity as "doing the same thing repeatedly and expecting a different result." You will hear that the Work Group discussed an age-based adult recommendation with an upper age limit, with risk-based above that age, as well as a simple universal adult recommendation. I can support either choice, but we cannot continue, and all of the Work Group agrees, in more of the same.

v-safesm and VAERS: Third Dose and Simultaneous Vaccination

Dr. Anne Hause (CDC/NCEZID) reminded everyone that the COVID-19 vaccines are being administered under the most intensive vaccine safety monitoring efforts in US history. CDC is monitoring the safety of these vaccines through 4 complimentary systems: v-safesm, VAERS, VSD, and CISA. There are also additional systems in place managed by government partners. This presentation focused on data from VAERS and v-safesm.⁴²

⁴² Full list of U.S. COVID-19 vaccine safety monitoring systems: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety.html>

As a reminder, VAERS⁴³ serves as an early warning system for vaccine safety. It is co-managed by CDC and FDA. Anyone can submit a VAERS report, regardless of the possibility of the vaccine causing the event or the clinical seriousness of the event. The key strengths of VAERS include rapid detection of safety issues and detection of AEs. Limitations of VAERS include that it is a passive surveillance system that relies on voluntary reporting, has inconsistent quality and completeness of information, reporting biases, and cannot determine causality of AEs. As of October 10, 2021, there were 4,990 reports to VAERS following Dose 2 of Janssen or Dose 3 of mRNA COVID-19 vaccines. The median age was 64 years and 63% of the reports were from women. Race or ethnicity was unknown or incomplete for 49% of the report, and 39% were from persons who identified as white, non-Hispanic.⁴⁴

Overall, 94% of the 4,990 VAERS reports following Dose 2 of Janssen and Dose 3 of mRNA COVID-19 vaccinations were non-serious. This varied slightly by vaccine manufacturer, but is similar to what has been observed for COVID-19 vaccines overall and other vaccines in general. Among serious reports, the most common AE according to VAERS was extra dose administered. Among non-serious reports, the most common AE was interchange of vaccine products. This may mean that the additional dose was given in error or given outside of recommendations at the time. Per federal law, VAERS reports include reports of hospitalizations, prolongation of existing hospitalization, life-threatening conditions, permanent disability, congenital deformity, or birth defects or death. Also, please note that these AEs are not mutually exclusive and a report may include more than one AE.

Among the millions of persons who have received a third dose of mRNA or second dose of Janssen COVID-19 vaccine, there were 30 reports of deaths to VAERS. There were no reports of death following Dose 2 of Janssen. The median age was 79 years. The median time elapsed from a third dose to death was 2 days. A CDC physician reviewed the available documentation including death certificates to determine a preliminary impression of cause of death (COD). It was not possible to determine the COD for 8 reports due to insufficient data. VAERS also is monitoring reports of AEs following co-administration of COVID-19 vaccines and other vaccines. Most reports to VAERS did not specify the vaccine type administered with the COVID-19 vaccine. Influenza and zoster vaccine were among the most common vaccine type specified. The most commonly reported AEs included extra dose or expired product, systemic symptoms, or AEs unique to Zoster. VAERS will continue to monitor AEs following co-administration.

Now turning to data from v-safesm. As a reminder, v-safesm is a voluntary smartphone-based safety surveillance system. v-safesm allows existing participants to report that they are receiving an additional dose of COVID-19 vaccine, and new participants enter information about all doses of COVID-19 vaccine received and complete health surveys on their most recent dose. v-safesm health surveys are sent during the week following each dose of vaccine and include questions about local injection sites and systemic reaction and health impacts, including inability to perform normal daily activities, inability to work or attend school, and/or inability to receive medical care. Additional health surveys are sent weekly through 6 weeks after vaccination and at 3, 6, and 12 months after vaccination. The key strengths of v-safesm are that it is easy and quick to use, includes active outreach to participants, and collects longitudinal data. The key limitations include that enrollment in v-safesm is voluntary and requires a smartphone, and cannot determine causality of AEs.

⁴³ <https://vaers.hhs.gov/>

⁴⁴ Includes data collected during August 12–October 10, 2021

Over 274,000 v-safesm participants had reported an additional dose of COVID-19 vaccine to v-safesm as of October 10, 2021. Among the participants, 52% were female, 39% were 65-74 years of age, 90% identified as non-Hispanic, and 84% identified as white. In terms of patterns of vaccination for v-safesm participants who reported an additional dose, over 98% of participants reported a third dose from the same manufacturer as the primary mRNA vaccine series. Most participants reported 3 doses of Pfizer-BioNTech vaccine. Looking at the top 10 solicited reactions reported at least once during Day 0-Day 7 after Dose 3 of Moderna or Pfizer-BioNTech vaccine, pain, fatigue, myalgia, and headache were among the most frequently reported solicited reactions for both vaccines.

Reactions and health impact events reported at least once during Days 0-7 after Pfizer BioNTech vaccine by dose showed that injection site reactions, systemic reactions, any health impact, inability to perform daily activities, and inability to work were all less frequent following Dose 3 than Dose 2. Notably, this analysis included 188,514 participants who completed at least one survey in the first week after each dose, with data collected during August 12–October 10, 2021. Dose 2 was compared to Dose 3 to assess statistically significant differences (p-value <0.05) using a multivariable generalized estimating equations model that accounted for the correlation between registrants and adjusted for demographic variables. Looking at reactions and health impact events reported at least once during Day 0-7 after Moderna vaccination by dose, injection site reactions were more frequently reported following Dose 3 of Moderna vaccines than Dose 2, while systemic reactions, health impacts, and inability to work were less frequent following Dose 3 than Dose 2. While these differences were statistically significant, the magnitude was small.

v-safesm also is monitoring reactions reported following co-administration of COVID-19 vaccine and other vaccines. Over 65,000 v-safesm participants reported receiving another vaccine at the time of their COVID-19 vaccination. Most (89.9%) were 18-75 years of age. Nearly 90% of co-administered vaccine is given with Dose 3 of COVID-19 vaccines. v-safesm will continue to monitor reactions following co-administration.

These data are subject to a number of limitations. First, both VAERS and v-safesm are voluntary systems and are likely not representative of the vaccinated US population. Second, additional dose recommendations included immunocompromised persons who completed a primary period of mRNA COVID-19 vaccine. However, v-safesm does not include specific information about immune status. Additional dose recipients likely included immunocompromised and non-immunocompromised persons, and immunocompromised persons might have different reactogenicity than an immunocompetent person. Third, approximately half of mRNA third doses are among persons aged 65 years and older, who may have different reactogenicity than persons in different age groups. Fourth, at this time, data are limited to determine patterns of AEs after receipt of second dose of Janssen or from a manufacturer different than the primary series. This also limited the ability to identify rare AEs. Finally, complete medical record review of deaths following vaccination reported to VAERS is dependent on the availability of medical records, death certificates, and autopsy reports, which may be delayed or not available.

To summarize, no unexpected patterns of AEs were observed. However, the data are limited at this point to identify rare AEs. Nearly all (≥92%) reports to VAERS were non-serious. Most commonly reported were vaccination errors and systemic symptoms. Most v-safesm participants reported a primary mRNA vaccine series followed by Dose 3 from the same manufacturer. For Pfizer-BioNTech, local and systemic reactions were reported less frequently following Dose 3 than Dose 2. For Moderna, local reactions were reported slightly more frequently and systemic reactions slightly less frequently following Dose 3 than Dose 2. VAERS and v-safesm will

continue to monitor safety of additional doses of COVID-19 vaccination. Additionally, the Vaccine Safety Datalink (VSD) will incorporate additional doses into its ongoing safety monitoring, and CISA will be available to consult on clinically complex AEs. ACIP will be updated as additional data become available.

COVID-19 Vaccine Safety Updates

Dr. Tom Shimbukuro (CDC/NCEZID) presented an overview of myocarditis following COVID-19 vaccination, an update on the safety of Janssen COVID-19 vaccine, and a brief analysis on the safety of Janssen COVID-19 primary vaccination followed by an additional mRNA COVID-19 vaccination. He reported that evidence from multiple safety monitoring systems in multiple countries supports the finding of an increased risk of myocarditis and myopericarditis following mRNA COVID-19 vaccination.⁴⁵ The risk is highest in adolescents and young adults, higher in males compared to females, and higher following Dose 2 compared to Dose 1. Symptom onset clusters within a few days of vaccination, mostly within a week, and cases have tended to be clinically mild. Dr. Shimbukuro then provided highlights from FDA, Department of Defense (DoD), and Department of Veterans Affairs (DVA) monitoring in addition to briefly mentioning some international surveillance efforts and providing an update on the CDC investigation of long-term effects of myocarditis.

First to highlight updates from a presentation that Dr. Hui-Lee Wong from FDA gave at VRBPAC⁴⁶ the previous week on surveillance of myocarditis and pericarditis and mRNA COVID-19 vaccination in the FDA's Biologics Effectiveness and Safety (BEST) Initiative. Within BEST, FDA has assessed myocarditis and pericarditis in the first 1-7 days following receipt of mRNA COVID-19 vaccines in terms of incidence rates and incidence rate ratios for Moderna versus Pfizer-BioNTech COVID-19 vaccination. To summarize the key points, the incidence rate estimates are highest in males 18-25 years of age. More events are observed post-Dose 2 than post-Dose 1. There was a wide range of incidence rates among the four BEST databases, with wide confidence intervals. Based on the preliminary results, the incidence rate ratio estimates comparing Moderna versus Pfizer vaccines, the FDA analysis does not support a significant difference for males 18-25 years between the 2 vaccines. However, the estimates had large uncertainty.

The Military Health System (MHS) continues to identify and follow patients with myocarditis following COVID-19 vaccination. The overall rate of myocarditis within 7 days of vaccination is 10 cases per million doses, but the risk is strongly dependent on patient age, sex, and vaccine dose and type. The rate of myocarditis in males under 20 years of age after the second dose is greater than 100 cases per million doses. Approximately two-thirds of patients report feeling fully recovered within 6 weeks of diagnosis. The standard American College of Cardiology (ACC) recommendations limits strenuous activity for 3 to 6 months. Follow-up within the MHS is ongoing.⁴⁷

⁴⁵ Gargano et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977–982; Mallapaty S. Heart-inflammation risk from Pfizer COVID vaccine is very low. *Nature*. 2021 Oct 8. doi: 10.1038/d41586-021-02740-y; Myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in Ontario. Available at: Myocarditis and Pericarditis Following Vaccination with COVID-19 mRNA Vaccines in Ontario: December 13, 2020 to August 7, 2021 (publichealthontario.ca); Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis. Available at Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis | European Medicines Agency (europa.eu); and Paterlini M. Covid-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people "as a precaution". *BMJ*. 2021 Oct 11;375:n2477

⁴⁶ <https://www.fda.gov/media/153090/download>

⁴⁷ Courtesy of Margaret Ryan MD, MPH, Defense Health Agency (DHA)

The DVA and the VA conduct active surveillance Rapid Cycle Analysis (RCA) for COVID-19 vaccines. They use a weekly analysis comparing observed to expected numbers of pre-specified outcomes from historical rates, adjusting for sequential tests. They also conduct near-real-time chart reviews for assessment of specific incident events, including an initial chart review to assess presumptive events and more detailed chart review. There have been 3.5 million total Moderna doses administered, 3.1 million total Pfizer-BioNTech doses administered, and limited use of the Janssen vaccine in the VA population of approximately 270,000 doses. The vaccinated population is 89% male and 60% aged 65 years and older. The Janssen vaccinated cohort is somewhat younger than the mRNA vaccinated cohort. There have been no statistical signals for myocarditis or pericarditis with any of the COVID-19 vaccines, although limited data are available for Janssen. Of the 7 chart-confirmed myocarditis or myopericarditis cases in the VA surveillance, 6 were in males and 1 was in a female. The median age was 37 years. The median onset was 3 days, with most occurring after Dose 2. The highest rate was observed in persons 18-39 years of age and all cases clinically resolved. The conclusion is that the absence of a myocarditis signal in the VA data are likely due to age differences in the VA population.⁴⁸

There is ongoing surveillance in other countries, particularly in Israel where the Pfizer vaccine has been used, but also in Canada, Europe, and elsewhere. The findings have been generally consistent with what has been observed in the US in terms of an increased risk of myocarditis with mRNA vaccination. In some cases, such as in Canada and some of the Nordic countries, the risk is higher for Moderna compared to Pfizer.⁴⁹

To briefly update the CDC enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports, the purpose of this enhanced surveillance activity is to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after COVID-19 vaccination who have met the case definition. It is a 2-component survey conducted at least 90 days after the onset of myocarditis symptoms. It includes a patient survey, followed by a healthcare provider survey. Data collection began in late August and is anticipated to continue at least through November. As of August, VAERS had received 826 reports of myocarditis or myopericarditis after COVID-19 vaccination that met the case definition. To date, around 680 patients have reached the 90-day post-myocarditis diagnosis window. Of these, 282 have received at least one phone call. Of the 282 patients who have received at least one call, 168 have completed the survey and 67 were unreachable or declined to participate. Of the 168 patients surveyed, 132 provided cardiologist or health care provider contact information. Contacting the cardiologist or the healthcare provider they are seeing as an outpatient is the last step in the sequential process. Of the 132 providers, 26 have completed the survey. The remaining 106 are in the process of being contacted, and CDC will continue to collect information.⁵⁰

⁴⁸ Courtesy Fran Cunningham, Pharm D, Department of Veterans Affairs

⁴⁹ a) Mevorach et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. *N Engl J Med*. 2021 Oct 6. doi: 10.1056/NEJMoa2109730; b) Witberg et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. *N Engl J Med*. 2021 Oct 6. doi: 10.1056/NEJMoa2110737; c) https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-myocarditis-pericarditis-vaccines-epi.pdf?sc_lang=en; d) Paterlini M. Covid-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people "as a precaution". *BMJ*. 2021 Oct 11;375:n2477; e) <https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis>

⁵⁰ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html>

Moving to an update on the safety of Janssen COVID-19 vaccine, Dr. Nair from the FDA presented post-authorization safety data for Janssen during the VRBPAC meeting for which the full presentation has been posted online.⁵¹ Based on the data presented, the most commonly reported AEs to VAERS after Janssen COVID-19 vaccination were systemic and local reactions. This study reviewed some existing safety concerns and described some emerging potential safety concerns following Janssen vaccination. CDC and FDA will continue to follow cases of GBS and TTS reported to VAERS. Information regarding these AEs is currently communicated in the EUA Fact Sheets. FDA and CDC continue to assess cases of myocarditis, pericarditis, immune thrombocytopenia, and thromboembolic events reported to VAERS following Janssen COVID-19 vaccination. FDA's near-real-time surveillance has not revealed any safety signals for these AEs at this time.

CDC conducts RCA through the VSD. This is near-real-time sequential monitoring for pre-specified surveillance outcomes of interest that is conducted weekly. A relatively small number of Janssen vaccinations have been administered compared to mRNA COVID-19 vaccinations at about 440,000 compared to 14 million total mRNA COVID-19 vaccinations. No statistical signals have been detected for any VSD RCA pre-specified surveillance outcomes following Janssen COVID-19 vaccination in the 1-21 day risk interval. Descriptive analyses indicate an imbalance of GBS cases following Janssen vaccination compared to mRNA COVID-19 vaccination, with proportionally more GBS cases being observed after Janssen COVID-19 vaccination.

A CDC health alert went out in April after CDC and FDA detected cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia after receipt of the Janssen COVID-19 vaccination. There was a pause on vaccination while CDC and FDA assessed the signal, and vaccination was resumed shortly thereafter.⁵² Since that time, CDC and FDA have continued to closely monitor TTS cases after Janssen vaccination. As of October 13th there were 47 confirmed cases after 15.3 million doses administered. Looking at reporting rates by age group and by sex, the basic epidemiology or trends have not changed from earlier presentations that have been given during previous ACIP meetings. The reporting rates are higher in females compared to males, and highest in the females 30-39 years of age and 40-49 years of age. These cases include 5 deaths related to complications from TTS. The median age in these deaths is 37 years, and 4 of the 5 were female. All 5 had CVST, none received Heparin, and the median platelet count was 15,000. Anti-PF4 antibody ELISA testing was performed on 4 of the 5, and all were positive with optical density values >2.0.⁵³

To summarize Janssen COVID-19 vaccine safety monitoring, the current evidence suggests a causal association for TTS, though the condition is rare. Most cases have been in women, with most being 18-49 years of age. Monitoring in VAERS and VSD suggests a possible association between GBS and the Janssen COVID-19 vaccination. CDC, FDA, and federal partners will continue to assess emerging potential safety concerns, which include myocarditis/pericarditis, immune thrombocytopenia (ITP), and thromboembolic events.

As mentioned earlier, the VSD conducts RCA. In terms of the safety of Janssen COVID-19 primary vaccination followed by an additional mRNA COVID-19 vaccine dose based on data from the VSD as of October 16th, approximately 14.3 million doses have been administered and around 7.2 million members are fully vaccinated. A relatively small number of individuals (about 5,400) are suspected to have had a Janssen plus an mRNA dose. Splitting out from that ~5,400 the individuals who received a Janssen primary dose plus an mRNA dose with a minimum interval of 60 days between doses resulted in a total of 3,662 individuals. In terms of the

⁵¹ <https://www.fda.gov/media/153132/download>

⁵² <https://emergency.cdc.gov/han/2021/han00442.asp>

⁵³ Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>

demographics of the 3,662 individuals with that vaccination combination, there were slightly more males than females. That is consistent with Janssen vaccination in general in the VSD. Looking at VSD pre-specified surveillance outcomes among the 3,662 persons who received a Janssen primary vaccination and the subsequent mRNA vaccination at a minimum interval of 60 days after the Janssen primary dose, 2 pre-specified surveillance outcomes were detected in the 1- to 42-day risk interval. There was an acute myocardial infarction in a male between the ages of 50-64, with an interval between the Janssen primary and the subsequent mRNA COVID-19 vaccination of 125 days. In addition, there was a seizure in a female in the age range 25-29 years, with an interval between the Janssen primary and the mRNA vaccination of 142 days.

To summarize the VSD data of heterologous dose safety, limited data are available on the Janssen primary vaccination followed by an additional mRNA COVID-19 vaccination at a minimum interval of 60 days after the Janssen primary. There is a lack of evidence to date of a safety problem with respect to any of the pre-specified VSD surveillance outcomes for this vaccination practice. Dr. Shimbukuro emphasized to partners in the healthcare community, the public health community, and members of the public that they all could participate in vaccine safety monitoring. This can be done by anyone reporting AEs following COVID-19 vaccination to VAERS even if they are not sure the vaccination caused the AE; COVID-19 vaccine recipients enrolling in v-safesm, parents or guardians enrolling their children who receive COVID-19 vaccine in v-safesm, and HCP encouraging their patients to enroll in v-safesm.⁵⁴

Myocarditis: VAERS

Dr. John Su (CDC/NCEZID) reported that as of October 6th, a combined total of 402,469,096 doses of Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccine had been administered. During that time period, a total of 3,336 reports of myocarditis or pericarditis were made to VAERS, among which 2,459 were myopericarditis and 877 were pericarditis alone. As a reminder, myocarditis and myopericarditis are referred to collectively as myopericarditis. Through October 6th, the pattern remained similar to past updates where most reports were after Dose 2. Among the Dose 2 reports, most were after Pfizer-BioNTech vaccine. In terms of descriptive characteristics, the overall epidemiological trends remained the same. Generally after Dose 2, there was a younger median age, a slightly earlier median time to symptom onset, and a greater proclivity towards males relative to after Dose 1.

While in the past observed versus estimated expected counts by age groups were presented, it was thought that perhaps a more neutral way of presenting those data would be to present reporting rates by age and vaccine manufacturer. Of the mRNA vaccines, there were 366,062,239 doses of Dose 1 or Dose 2 of the mRNA vaccines administered. Inclusive of both sexes, reporting rates exceeded the estimated 1 to 10 per 100,000 person-years observed in background incidence after Dose 2 for Pfizer among persons 12-24 years of age and after Dose 2 of Moderna among individuals 18-29 years of age.

In terms of reporting rates for males after mRNA vaccines, there were 169,740,953 doses administered to males for Dose 1 and Dose 2 combined. For Pfizer Dose 2, reporting rates among persons 12-29 years of age exceeded the background rate. For Moderna Dose 2, reporting rates among persons 18-29 years of age exceeded the background rate. There were 193,215,313 doses of mRNA vaccines administered to females for Dose 1 and Dose 2 combined. The reporting rates for females did not appear to exceed background incidence.

⁵⁴ vsafe.cdc.gov/en/

Taking into consideration that COVID-19 vaccines have been in use for less than a year and that there was a lower incidence of myocarditis among females relative to males, after Moderna Dose 2 for persons 18-29 years of age, there was a potential increased incidence of myocarditis among males relative to females. However, it is important to note that this possibility is not firm.

With regard to care and outcomes, there were 1,640 reports among persons 29 years of age or younger. Of those, 877 met the CDC case definition of myopericarditis or myocarditis. Of those 877, most (829) were hospitalized. Of the 829 who were hospitalized, 789 were discharged. Three-quarters of those who were discharged were known to have recovered from their symptoms at time of the report. Overall, a pattern was seen that was consistent with past updates.

To summarize, as of October 6th there were a total of 3,336 reports of myopericarditis or pericarditis to VAERS. The epidemiology has remained consistent with previously reported updates. Myocarditis is being seen primarily in younger males after Dose 2 of mRNA vaccination. The limited follow-up information in VAERS case reports suggests that most patients recover from their symptoms. Reporting rates of myocarditis exceed background rates among males after Dose 2 of Pfizer for people 12-29 years of age and Dose 2 of Moderna for persons 18-29 years of age. All of these data are from VAERS and are subject to the limitations of VAERS (e.g., voluntary reporting, inconsistent quality/completeness of information, reporting biases, and inability to determine causality of AEs).

Myocarditis: VSD

Dr. Nicky Klein (KPNC) reminded everyone that the VSD was established in 1990 as a collaborative project between the CDC and 9 integrated healthcare delivery organizations, with data on more than 12 million members of VSD healthcare sites. The aims of the RCA are to: 1) monitor the safety of the COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members; and 2) describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity. Surveillance began in December 2020. While a total of 23 outcomes are being monitored, the focus of this presentation was on the outcome of myocarditis/pericarditis based on COVID-19 vaccine uptake and primary analyses data through 10/09/2021.

At the time of this analysis, over 14.2 million doses of COVID-19 vaccines had been administered in the VSD population. To date, nearly 72% of the VSD population has been fully vaccinated. The vast majority of vaccines distributed and administered to VSD members have been Pfizer and Moderna mRNA vaccines. Just under 450,000 doses of Janssen have been administered. Looking at the first dose by week of administration among persons 18-39 years of age, administration over time has not varied much and was very similar between the Pfizer and Moderna vaccine products. Most VSD members in that same age group received Dose 2 of the Pfizer vaccine at Day 21 as per the recommended intervals, with some scattered days around that in the week or two afterward. Similarly for Moderna, most people in that age group received their second dose on Day 28, again with small variability in a week or so afterward.

Now moving on to the analytic strategy for RCA monitoring. For the primary analysis, the number of outcomes observed in the risk interval of 1-21 days after COVID-19 vaccination were compared to the number expected. The expected outcomes were derived from the “vaccinated concurrent comparators” who were in a comparison interval on Days 22-42 after COVID-19 vaccination. On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval.

Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, and calendar date. Based on the most recent surveillance, myocarditis/pericarditis met the signaling criterion of having a 1-sided p-value of less than 0.0048. There were signals in the VSD for myopericarditis for all ages based on adjusted analyses by VSD site, age, sex, race/ethnicity, and calendar date.

Focusing now on a subgroup analysis of cases of confirmed myopericarditis after mRNA vaccine, chart reviews were completed through October 9, 2021 for 132 of 135 cases identified anytime post-vaccination among persons 12-39 years of age. There are 3 chart reviews pending. All cases following initial chart review were adjudicated by either an infectious disease clinician or a cardiologist. This adjudication confirmed that 103 of the 138 (78%) were myocarditis/pericarditis cases. Of those, 74 were among persons 12-39 years of age and 44 were among persons 18-39 years of age in the 0-21 days after Dose 1 and 39 were among persons 18-39 years of age in the 0-7 days after Dose 1.

In terms of the day of onset of confirmed myocarditis/pericarditis among persons 12-39 years of age after one dose of mRNA vaccine, the cases clustered within the first week after vaccination. Normal temporal scan statistics identified 3 overlapping clusters between Days 0-4, Days 0-3, and Days 0-5. These all had p-values of <0.0001 . Looking at confirmed myocarditis/pericarditis for Days 0-7 risk interval among persons 12-39 years of age products and dose and the vaccinated concurrent competitors with the same analysis showed previously, the rate ratio for both mRNA vaccines was nearly 22 and they were all statistically significant. Given that Pfizer included persons 12-39 years of age and Moderna included persons 18-39 years of age, these two rate ratios could not be compared. The takeaway is that for both vaccines in VAERS, the Day 3-7 risk intervals were associated with an elevated rate ratio of myopericarditis. For the confirmed cases in the Day 0-7 risk interval among persons 18-39 years of age, there was an elevated rate ratio after both mRNA vaccines that was statistically significant. Numerically, the rate ratio after Moderna may be higher than the rate after Pfizer. This may indirectly suggest that Moderna might have a higher rate than after Pfizer. For Pfizer only among persons 12-17 years of age in the 0-7 and 0-21 day risk interval by dose, the number of events in the risk interval was up to 30 after both doses in 0-21 days and there were zero events in the comparison interval. The rate ratios were very high, but could not be estimated precisely because there were cases in the comparison interval that were very high. The lower bound of the confidence interval was elevated for both the Dose 1 analysis and the Dose 2 analysis.

To summarize myocarditis/pericarditis for Moderna versus Pfizer, the analyses of the vaccinated concurrent competitors indicated that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in persons 12-39 years of age. As a reminder, Pfizer results included persons 12-39 years of age and while Moderna's included persons 18-39 years of age. The analysis of the vaccinated concurrent comparators indirectly suggests that Moderna vaccine is associated with more risk of myocarditis/pericarditis than Pfizer vaccine. However, to directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, a head-to-head comparison was conducted on persons 18-39 years of age with the same confirmed cases of myocarditis/pericarditis through October 9th. Looking at the days between Dose 1 and Dose 2 for confirmed cases in the 0-21 risk interval, the same pattern was seen in the entire VSD population in the same age group that most individuals received their second doses per recommended 21 days after Pfizer or 28 days after Moderna or shortly thereafter. During the first 7 days after vaccination, the incidence rate after Moderna was higher than after Pfizer.

This analysis differed from what was shown in terms of the vaccinated concurrent comparators because in this case, Moderna and Pfizer vaccinees were directly compared only during the risk interval within groups. These groups were comprised of individuals inside the risk intervals of either 0-7 days or 0-21 days after vaccination. Individuals were in the same categories of age group, sex, race/ethnicity, and VSD sites and on the calendar day when an mRNA vaccinee had myocarditis/pericarditis. The rate ratios were estimated with 95% confidence intervals, or the rate post-Moderna divided by the rate post-Pfizer. The null hypothesis was tested that the rate of myocardial/pericarditis after vaccination does not differ between Moderna and Pfizer. For example, a 28-year-old male had myocarditis on June 28th. He had been vaccinated on June 23rd and therefore was within the 0-7 day risk interval. The comparators for this case include everyone who on June 28th was within the 0-7 day post-vaccination risk interval after either vaccine. That is, they were vaccinated between 6/21 and 6/28.

In terms of the results of myocarditis/pericarditis in persons 18-39 years of age directly comparing Moderna versus Pfizer, the adjusted rate ratio was 2.56 after both doses of vaccines in the 0-7 day risk interval. That was statistically significant in the lower bound of the confidence intervals and had a significant p-value. The results were similar for the 0-21 day risk interval. The results after Dose 2 also were very similar in the 0-7 and 0-21 day risk intervals. Looking at myocarditis/myopericarditis and excluding pericarditis from this analysis among persons 18-39 years of age directly comparing Moderna versus Pfizer, there was a statistically significant elevated rate ratio of 2.24 during the 0-7 day risk interval after both doses. That was similar also for Dose 2. While the 0-21 day interval was similar, it just missed statistical significance. In this head-to-head comparison of Moderna versus Pfizer there was an elevated rate ratio regardless of whether the analysis included myocarditis, both sexes, or males. This analysis also shows that the rate ratio was elevated for both sexes and that the Moderna vaccine was not associated with more myocarditis than Pfizer in males particularly. There were 13.3 excess cases per million doses when comparing Moderna to Pfizer after Dose 2 for both sexes.

To summarize, for the initial analysis of the vaccinated concurrent comparators RCA analysis, the VSD formally signaled for myocarditis/pericarditis 21 days after both mRNA doses in the overall VSD populations, including all ages ≥ 12 years. In the subgroup of individuals 12-39 years of age, the rate ratio for myocarditis/pericarditis was elevated after both Pfizer and Moderna during Days 0-21 after vaccinations, especially during Days 0-7. As a reminder, the Pfizer results included persons 12-39 years of age and the Moderna results included persons 18-39 years of age. In the subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons 12-39 years of age. In terms of summary of the head-to-head comparison of Moderna versus Pfizer among persons 18-39 years of age, the rates of myocarditis/pericarditis after Moderna were significantly higher than after Pfizer during both the 0-21 and 0-7 day risk intervals. The results were consistent when the analyses excluded pericarditis. Comparing Moderna versus Pfizer during the 0-7 days after Dose 2, there were an estimated 13.3 excess cases of myocarditis/pericarditis per million doses. Among persons 18-39 years of age, there were no clear clinical differences amongst myocarditis/pericarditis cases between Moderna and Pfizer recipients. Most had a hospital length of stay of 1 day and none were admitted to the Intensive Care Unit (ICU). The takeaway for all of these analyses together is that both mRNA vaccines were associated with increased risk of myocarditis/pericarditis for persons 18-39 years of age as was Pfizer for persons 12-17 years of age. The head-to-head comparison provides evidence that the risk of myocarditis/pericarditis is higher after Moderna than after Pfizer.

VaST Assessment

Dr. Keipp Talbot (VaST Chair) provided a summary from the VaST WG. As a reminder, the objectives of the VaST WG are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccination safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring; 3) advise on analyses, interpretation, and presentation of vaccine safety data; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the entire ACIP on COVID-19 vaccine safety. VaST continues to review COVID-19 vaccination safety data from passive and active surveillance systems. US safety monitoring systems include VAERS, VSD, FDA's BEST System, VA, Indian Health Service (IHS), and DoD. In addition, there are data from Israel, Canada, and the Global Advisory Committee on Vaccine Safety (GACVS). Special evaluations are underway, such as follow-up studies on myocarditis cases. From December 21, 2020 to the present, VaST has had 38 independent meetings to review vaccine safety data and 10 joint meetings with the COVID-19 Vaccines WG focused on safety. VaST previously reviewed US safety for the September 22, 2021 ACIP vote on boosters. This session focused on an overview of selected Moderna and Janssen COVID-19 vaccination safety data; VaST assessments of Moderna and Janssen COVID-19 vaccination and heterologous boosting, VaST's future plans.

In terms of myocarditis/pericarditis, myocarditis following mRNA COVID-19 vaccination was first identified in May 2021.⁵⁵ CDC issued clinical guidance for myopericarditis following vaccination, and the data were presented at the VRBPAC meeting in June 2021. Data and the VaST assessment were presented to ACIP later in the month of June⁵⁶ and an *MMWR* was published. EUA Fact Sheets were revised with Pfizer's warning added on June 25, 2021. Even when Pfizer-BioNTech received its final FDA approval, information on myocarditis/pericarditis was included in the package insert.⁵⁷ Data available to date show association of myocarditis with both mRNA vaccines in adolescents and young adults, with association among males greater than females. Some systems show greater risk after Moderna than Pfizer. This includes data from the US VSD and DoD and from Canada and Scandinavian countries. Other US safety monitoring systems do not show a difference between the 2 mRNA vaccines. Hence, further data are being compiled to understand the differences between the safety systems, optimal management strategies, and long-term outcomes.

In terms of Moderna COVID-19 vaccination safety data specifically and Dose 3, there clinical trial data based on a 50 µg dose in 173 participants. There was no evidence of increased reactogenicity following a booster dose relative to Dose 2, with the exception of increased axillary swelling/tenderness of the vaccination arm.⁵⁸ There are post-authorization safety data for Moderna Dose 3 using the 100 µg dose as the 50 µg dose⁵⁹ has not previously been available. These data come from v-safesm and VAERS. Only people who are immunocompromised are currently recommended to receive a third dose of Moderna, but it is unclear whether these were just patients who are immunocompromised. Approximately 14,000 persons reported Dose 3 to v-safesm. Local reactions were reported slightly more frequently and systemic reactions slightly less frequently following Dose 3 than Dose 2. VAERS had approximately 1,400 reports after a third dose. Over 92% of reports were non-serious.

⁵⁵ <https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html>

⁵⁶ <https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.htm>

⁵⁷ <https://www.fda.gov/media/151707/download>

⁵⁸ <https://www.fda.gov/media/153087/download>

⁵⁹ Hause A, ACIP October 21, 2021

Now to discuss the safety of the Janssen vaccine, specifically with regard to TTS⁶⁰ and GBS.⁶¹ TTS surveillance continues in VAERS, which identified reports of CVST and TTS. The use of the vaccine was paused temporarily on April 13th. EUA Fact Sheets were updated with warnings about TTS and the pause was lifted on April 23rd. Through October 13th, there have been 47 cases of TTS. Most cases were in women 18-49 years of age and evaluation is ongoing. While increasing rates have not been observed, there has been a steady rate. VAERS identified reports of GBS higher than expected, especially in males greater than females. EUA Fact Sheets were updated with information about observed risk on July 12th. Through July 24th, 130 cases of GBS have been identified and observed reports have been higher than expected across multiple age groups.

In terms of Janssen COVID-19 vaccination safety data for Dose 2, there are clinical trial data.⁶² Approximately 9,000 participants received 2 doses at least 2 months apart. Approximately 2,700 have had at least 2 months of safety follow-up. No new safety signals have been identified following a second dose. Interpretation of the data is limited by a small sample size and short interval, particularly for the 6-month interval post-Dose 1. There are some post-authorization safety data from people who decided to get a second dose without a recommendation.⁶³ In v-safesm, there have been 83 reports and in VAERS there have been 39 reports. All the reports were non-serious in VAERS.

To summarize the VaST assessment, there appears to be a slightly increased risk of myocarditis among persons 18-39 years of age after receipt of the Moderna primary series compared with Pfizer primary series, especially in males. Preliminary data from a follow-up study based on data from patients and parents suggest that the cases are generally mild, but this study is ongoing. In terms of Janssen COVID-19 vaccination, the risks for TTS and GBS appear to be unchanged from earlier assessments. While they are serious, they are rare. It is important to continue to communicate the balance of benefits and risks to the public and patients.

In summary of the VaST assessment of booster doses, for Moderna COVID-19 vaccination there are limited data on risk of myocarditis after Dose 3. It is important to remember that the data available are based on the original 100 µg dose. Data on the safety of the reduced 50 µg dose are available only from a small clinical trial. It is unclear whether the risk of myocarditis will be the same or reduced with the reduced dose of the Moderna booster. For Janssen COVID-19 vaccination, there are limited trial data and data from safety monitoring systems for Dose 2. Risks for TTS and GBS after booster dose are unlikely to be greater than with primary vaccination. Again, it is important to communicate the balance of benefits and risks to the public and patients.

In terms of the VaST assessment of the heterologous booster, preliminary data from NIH mix-and-match study⁶⁴ and limited data from post authorization safety data suggest that boosting of Janssen COVID-19 vaccine recipients with an mRNA vaccine, or of mRNA COVID-19 vaccine recipients with Janssen COVID-19 vaccine, poses no additional safety risk compared with homologous boosting. There is no evidence to date of safety concerns with respect to any of the pre-specified VSD surveillance outcomes for Janssen COVID-19 vaccine recipients to receive an additional dose of mRNA COVID-19 vaccine.

⁶⁰ Shimabukuro T, ACIP October 21, 2021

⁶¹ <https://www.fda.gov/media/153132/download>

⁶² <https://www.fda.gov/media/153130/download> and <https://www.fda.gov/media/153129/download>

⁶³ Hause A, ACIP October 21, 2021

⁶⁴ Atmar R, ACIP October 21, 2021

With regard to next steps, VaST will continue to review safety regarding additional and booster doses as data become available; continue to collaborate with global vaccine safety colleagues on key issues that impact the benefit-risk balance; and provide updates to the ACIP COVID-19 Vaccines WG and ACIP during future meetings.

Discussion Summary

- Dr. Sanchez recalled comments earlier about co-administration of the zoster vaccine with the COVID vaccine, which he has been asked a lot about. He anticipated that the topic of co-administration also would arise in future meetings with regard to smallpox vaccine.
 - Dr. Shimabukuro indicated that the observation earlier was specific to when COVID vaccines are administered with zoster vaccine. It is known from monitoring zoster vaccine that HZ is an AE reported after zoster vaccine, for which there are probably many reasons. One thing is that it is possibly something that a provider would not expect, so it gets noticed and reported to VAERS. However, it is not totally unexpected based on monitoring zoster vaccine alone. There is no evidence that administering the two vaccines increases the risk for AEs. There is some type of disproportionality, but it is probably the result of the of the co-administered zoster vaccine and is not related to a COVID-19 vaccination.
- Dr. Long noted that while they like to talk about excess cases, to consider a case of traditional myocarditis as the baseline for myopericarditis following mRNA vaccines did not hold water and is not clinically relevant. These are not the same patients, so it is comparing apples and oranges. While she knows there is no question that there is an association, she did not think they should get hung up on trying to tell the public the number of excess cases, because they are not the same disease.
- Dr. Lee inquired about whether there are estimates by gender and age for GBS following receipt of the Janssen vaccine.
 - Dr. Shimabukuro indicated that the age distribution of the Janssen cases in the various reports has been younger than for the mRNA vaccination reports in VSD. There also has been a different age distribution observed in VSD monitoring where the Janssen vaccinated cases were somewhat lower than the mRNA vaccinated cases. It was unclear if that was the result of the way the program was rolled out or something else.
 - Dr. Nair added that an article was recently published in *JAMA* discussing the cases of GBS that occurred following the Janssen vaccine, for which they will circulate the link. This was a case series of 130 GBS cases for which the median age was 56 years, with roughly 60% men and 40% women. Essentially, 86% of those cases were in the age range of 18-64 years and 14% were older than 65 years of age.
 - Dr. Klein indicated that the mean age of the cases after receipt of Janssen vaccine was 48 years and there were no cases amongst individuals greater than 65 years of age.

- To avoid confusion, Ms. McNally requested that someone explain why the VSD and DoD in the US and Canada and Scandinavian countries were showing a greater risk while the FDA BEST systems and the VA were not.
 - Dr. Shimabukuro indicated that VAERS is a spontaneous reporting system. It is not a population-based; large, linked database; or EHR claims database system. VAERS is subject to the limitations of passive reporting. That said, looking at the VAERS data in terms of the reporting rates by age, sex, and product type, the interpretation is that no obvious signs are observed for a differential risk though there are some trends. They are not able to conduct the type of head-to-head formal statistical comparison as was done in VSD, so there are limitations to how VAERS data can be interpreted.
 - Dr. Cunningham said that in regard to DVA, it was likely due to the age of the patient population. While cases of myocarditis and myopericarditis were observed within their results, they did not signal. The majority of their patients who have received the vaccine are over 65 years of age, and myocarditis and myopericarditis occurs in the younger patient population. Their trends do follow that of the other systems in that they have more male patients and the myocarditis and myopericarditis occur in a short period of time after the vaccination and after Dose 2.
 - Dr. Forshee from FDA/CBER noted that with regard to active surveillance systems in particular and the slightly different results they are seeing, there are a couple of things to keep in mind when interpreting these results. The first is that these are still rare outcomes, which impacts certainly in the analysis. The confidence intervals are large, even in the meta-analysis they conducted of the four data partners that they use. There are also some differences in the patient pools and the different sites, such as geography. The BEST analysis was limited to people 18-25 years of age, which is a narrower age range than some of the others that have been reported. They also looked at males 18-25 years of age in their analysis.
- ACIP members highlighted the following topics of interest for further exploration:
 - The Moderna versus the Pfizer associated risks with myocarditis is interesting and suggests that the etiology or pathogenesis of this occurrence might be related to some direct effect of the spike protein and the cardiac muscle. It would be interesting to better understand whether there may be a relationship with the larger Moderna dose of 100 µg in terms of the pathogenesis.
 - While both Pfizer and Moderna vaccines have been connected to myopericarditis, especially in people 12-39 years of age, nothing can really be said about Moderna for individuals 12-17 years of age who have received Moderna. Therefore, it is not terribly clear whether the youngest in the group who received Pfizer vaccine are more or less likely to have pericarditis.
 - Perhaps it would be worth considering incorporating chest pain as a solicited AE not only for clinical trials, but also for the manufacturers, particularly in thinking about expansion of vaccine to the pediatric population. Dr. Shimabukuro said that consideration could be given internally to adding chest pain, but it is somewhat non-specific compared to myocarditis.

- While the need for a second dose for Janssen recipients was clear, concern remained about administration of a second dose due to the risk for TTS and GBS. More information about this would be beneficial. The opportunity for a heterologous boost is priceless at this point in the pandemic and in the understanding of the risks for TTS in young women with Janssen and myocarditis in young men with mRNA, particularly given that the full outcome is not yet understood.
- Information about the relative use of the Janssen vaccine in individuals over 65 years of age would be beneficial to know.
- Incidence of the risk of myocarditis associated with COVID-19 disease itself is important to consider. Dr. Oliver indicated that she would distribute the paper published out of Israel that compared the risks following COVID-19 infection to vaccination, which demonstrated a substantial rate of myocarditis associated with COVID infection.

COVID-19 Vaccine Effectiveness: Primary Series

Dr. Jefferson Jones (CDC/NCIRD) presented a summary of VE for the Moderna and Janssen vaccines using data available from CDC platforms or published via CDC's *MMWR* and briefly summarized a global VE systematic review. Due to time constraints, VE study methods, platform descriptions, Pfizer data, and other details were included in supplementary slides for this presentation. Dr. Jones presented data by risk group, outcome, product and by pre-delta versus post-delta time period or time since vaccination for evidence of waning. Results presented previously to ACIP suggested that VE against infection had declined for mRNA vaccines, while studies for VE against hospitalization showed small to no reductions.

Focusing on recent data, 4 state public health departments provided rates of cases by month of vaccination, age, and vaccine type. Based on cases reported for July 2021, decreasing case rates were seen in the Moderna cohorts with more recent vaccination (e.g., May and June). This suggests waning protection and was consistent in all age groups. Janssen denominators were lower and confidence intervals were wider, but increased case rates were seen among people vaccinated in March versus people vaccinated during other months. Younger age groups had higher case rates in all months for both vaccines. Rates were higher among Janssen recipients than among Moderna recipients. Hospitalization rates were not available from this data source. A different dataset, Cosmos, was used for hospitalization rates. This dataset utilizes data from over 700 participating hospitals and 10,000 clinics in all 50 states that use the Epic health record system. In terms of COVID-19 hospitalizations through August 2021, the Moderna COVID-19 hospitalization rates did not substantially differ depending on the month of vaccination. For Janssen, hospitalization rates were higher in those vaccinated in the most recent 2 months, June and July. For both vaccines, rates were higher among those ≥ 65 years of age than among younger age groups. Rates were higher among Janssen recipients than among Moderna recipients.

Regarding VE among people ≥ 65 years of age, New York State (NYS) updated their data from a prospective study of adults in NYS that were published in the *MMWR* and presented during a previous ACIP meeting.⁶⁵ VE calculated using a hazards proportion method were updated and presented by vaccine product and month of vaccination. These results included approximately 155,000 cases and 40,000 hospitalizations. For Moderna, all ages had similar trends with

⁶⁵ Rosenberg et al. MedRxiv. <https://www.medrxiv.org/content/10.1101/2021.10.08.21264595v1.full.pdf>

decreases over time as Delta became the prominent variant in circulation. In August, small differences in VE were seen by cohort, with lower VE observed among those vaccinated in January and February compared with those vaccinated in April, suggesting waning VE against infection. VE decreased over time for Janssen, particularly for younger age groups. VE was higher in those vaccinated more recently, but the 95% confidence intervals were wide and frequently overlapped. In general, for both vaccines, no large differences were seen in VE by age. In terms of VE against hospitalization for NYS, no substantial decreases were seen for Moderna among persons 18 to 49 years of age or aged 50 to 64 years of age. Moderna had a small decrease among persons ≥ 65 years of age, but remained at above 94%. VE for Janssen was lower than VE for Moderna. For Janssen, clear decreases in VE over time or in VE by month of vaccination were seen. For both vaccines, VE did not differ by month of vaccination, suggesting no waning in VE against hospitalization by month of vaccination. For both vaccines, VE for ≥ 65 years of age was lower than VE for younger ages.

The Increasing Community Access to Testing (ICATT) platform was presented previously and has been updated. ICATT is a nationwide, community-based platform that utilizes COVID-19 testing performed via pharmacies and partners. VE is calculated using a test-negative case control design. Looking at VE against symptomatic infection for the Moderna vaccine, VE against symptomatic infection was lower during the Delta period than during pre-Delta, and waned during both periods. For persons ≥ 65 years of age, VE was lower than for other age groups. However, no clear trend has been seen over time. For the Janssen vaccine, there was a lack of sufficient pre-Delta samples. VE against symptomatic infection during the Delta period appeared to be stable over time, and there were no clear differences by age. However, the confidence intervals are wide among the older age groups.

The Surveillance Platform for Enteric and Respiratory Infectious Organisms (SUPERNOVA) is a platform with data from 5 VA hospitals using a test-negative case-control design that was presented previously. It was updated with data through September 17th and stratified by age group. The updated data showed that VE remained lower in people 65 years of age and older at 78% than in younger ages at 95%. Analyzing VE by time from vaccination among all ages showed a decline in VE against hospitalization. VE was lower in people vaccinated 120 days or more prior at 82% than in those people vaccinated more recently at 90%, but the 95% confidence intervals overlapped

To summarize VE among people ≥ 65 years of age who received Moderna, VE against hospitalization was lower in people ≥ 65 years of age compared with VE in younger adults. Some studies showed moderate declines in VE against infection and small declines in VE against hospitalization. For Janssen, VE was lower compared with mRNA vaccines for VE against infection and hospitalization. The evidence of VE over time was inconsistent across studies. Fewer data were available so VE estimates were less reliable for Janssen compared with mRNA vaccine estimates.

Now looking at VE for adults aged < 65 years with underlying medical conditions, the data presented excluded those with immunocompromising conditions since that group already was authorized to receive a booster dose. The Influenza and Other Viruses in the Acutely Ill (IVY) Network is a collection of 21 medical centers in 18 states. VE was estimated using a test-negative case-control design for VE against hospitalization among immunocompetent adults ≥ 18 years for the period of March 11 through September 15, 2021 for Moderna and Janssen vaccines. For Moderna recipients, VE was higher for all ages among people with no chronic conditions and remained high for people vaccinated 120 days or greater prior. For people with chronic conditions, VE was lower than for people without chronic conditions. VE was mildly

lower for people vaccinated greater than 120 days prior among the chronic condition group, but the 95% confidence intervals overlapped. For Janssen vaccine recipients, insufficient data were available to calculate VE by age and by time vaccinated. VE in people with chronic conditions was lower than VE in people without chronic conditions. Again, the confidence intervals overlapped. VE for Janssen was lower than VE for mRNA vaccines.

The VISION Network involves over 185 hospitals. Through this network, VE against COVID-19 ED and urgent care (UC) visits was estimated among immunocompetent adults without chronic conditions for the period of June-September 2021 using a test-negative case control design. In all age groups (18-44, 45-64, ≥65), Moderna VE was higher than Janssen VE. In all age groups, Moderna VE showed a modest waning trend and there was no consistent pattern of waning for Janssen. For adults with chronic conditions, Moderna VE was higher than Janssen VE in all age groups. For Moderna, modest waning was observed in persons 45-64 year of age and persons ≥65 years of age. For Janssen, no consistent waning was seen. For both vaccines, waning in VE was more pronounced in the oldest age group. In all age groups, Moderna VE was higher than Janssen VE against hospitalization for adults with chronic conditions. In all age groups, Moderna VE showed a modest waning trend but was most pronounced among persons ≥65 years of age. Again, Janssen showed no consistent waning in VE.

In summary, for adults aged less than 65 years with underlying medical conditions there was a mild decline in VE against hospitalization, ED, and urgent care visits among Moderna recipients. Nevertheless, VE remained high. For Janssen, VE was lower compared with VE for mRNA vaccines for both infection and hospitalization and there was no consistent evidence of waning.

Data looking at VE for workers employed in occupations with high risk of exposure to SARS-CoV-2 was not updated and was previously presented to ACIP. The Healthcare, Emergency Response, and Other Essential Workers Surveillance Study-Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (HEROES-RECOVER) platform includes a cohort of over 4000 healthcare workers, first responders, and other frontline workers in 8 US locations who were vaccinated almost exclusively with the mRNA vaccines. Results from this platform showed that VE against infection decreased with increasing time from vaccination from 85% to 73%, but confidence intervals overlapped. VE during Delta was 66% and during pre-Delta was 91%. The study did not have sufficient power to look at time since vaccination during both the pre-Delta and Delta periods and no difference in VE was seen between the mRNA products.⁶⁶

In terms of global data, there is an ongoing systematic review conducted by the World Health Organization (WHO) and the International Vaccine Access Center (IVAC) at Johns Hopkins University (JHU). The IVAC/WHO review shows that CDC results are consistent with other published studies. Studies that were captured included those from the US, UK, Canada, and Qatar. Most studies included pre-Delta data and published data from CDC studies, some of which have been presented. The forest plot of VE against death and severe disease, including hospitalization, showed VE of 89% to 100% for Moderna. For Moderna, VE against any infection ranged from 75% to 100%. VE specifically against asymptomatic infection ranged from 70% to 90%.⁶⁷

⁶⁶ <https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e4.htm>

⁶⁷ <https://view-hub.org/resources>

Next to review a pre-print study conducted in the US that examined VE over time since vaccination. This study was funded by Moderna and used a test-negative design with Kaiser Permanente Southern California (KPSC) patients. There were 8153 cases diagnosed between March and July 2021, each of which was matched with 5 controls. VE against infection with Delta declined from 94% for those 14 to 16 days after the second dose and declined to 80% for those vaccinated 151 to 180 days after the second dose. VE in individuals ≥ 65 years of age or older was lower (75%) compared with VE in younger persons (88%). VE against hospitalization over time was not presented in the manuscript due to small numbers, but was greater than 96% for Delta and non-Delta.⁶⁸

Returning to the IVAC/WHO systematic review for Janssen vaccine, VE against severe disease ranged from approximately 60% to 85%, which was lower than the estimates for mRNA vaccines. VE against any infection or symptomatic disease ranged from 12% to 95%, but many studies had wide confidence intervals because of the small numbers of people who had received the Janssen vaccine.

Next to highlight a study that examined Janssen VE against medically-attended infection and hospitalization over time in the US.⁶⁹ This Janssen-funded cohort study used HealthVerity insurance claims data and matched approximately 390,000 vaccinated individuals between March and July 2021 with approximately 10 unvaccinated controls each by location, age, sex, and comorbidity index. VE was estimated using a proportional hazards design. Medically-attended COVID-19 was defined as COVID-19 ICD-10 code or PCR-positive results, and COVID-19 hospitalization was defined as a discharge diagnosis of COVID-19 or any COVID-19 positive test within 21 days of hospitalization. It was assumed that there was 40% unreported vaccination in the control group. After assuming under-reporting of 40% of vaccination, the correction increased the VE point estimates by approximately 8% to 10%. The study found VE against medically-attended COVID-19 and VE against hospitalization to be stable over time. Without correcting for unreported vaccination, VE was found to be lower in people ≥ 50 years of age (54%) than in people 18-49 years of age (75%). VE against hospitalization was lower for persons ≥ 50 years of age (71%) than for people 18-49 years of age (79%).

Several limitations leading to biases or potential biases should be considered for VE studies in general. Individuals prioritized for vaccination early in vaccination campaigns were often those at high-risk for SARS-CoV-2 infection and/or severe COVID-19, such as frontline workers, older adults, and long-term care facility residents. This could lead to overestimations of waning of VE when comparing VE in those vaccinated early with those recently vaccinated. However, high-risk groups may practice prevention measures more frequently and lead to over-estimation of VE estimates. After vaccination, people may change their behavior, engaging in riskier activities, or seek testing less because of confidence of protection. However, some studies report vaccinated people practice preventive measures more frequently. The use of a test-negative study design partially addresses test-seeking behavior. As more time elapses since vaccination, it is possible that there may be more misclassification of vaccination status. For instance, vaccination status is not documented for some people and may result in falsely assigning them to the unvaccinated group. In addition, SARS-CoV-2 infection and subsequent population infection-derived immunity will increase over time in the unvaccinated group, resulting in protection from further infection and leading to an apparent waning of VE.

⁶⁸ Bruxvoort, medRxiv, <https://www.medrxiv.org/content/10.1101/2021.09.29.21264199v1>

⁶⁹ Polinski et al., medRxiv, <https://www.medrxiv.org/content/10.1101/2021.09.10.21263385v1.full.pdf>

In summary, Moderna VE against infection declines over time. Both circulation of the Delta variant and increasing time from vaccination appear to contribute to these declines. For people ≥ 65 years of age, VE against hospitalization is lower compared with VE in younger adults. Some studies show moderate declines in VE against infection and small declines in VE against hospitalization. For adults < 65 years of age with underlying medical conditions, there is a mild decline of VE against both hospitalization and against ED or EC visits, but VE remains high. For people in occupations with a high-risk exposure to SARS-CoV-2, there currently are no Moderna-specific data available at this time. For mRNA vaccines, one study showed that VE against hospitalization was declining. For the Janssen vaccine, VE against both infection and hospitalization was lower compared with VE for mRNA vaccines. Evidence of waning of VE over time was inconsistent across studies. However, fewer data are available and VE estimates for the Janssen vaccine are less reliable.

Discussion Summary

- While protection or effectiveness against infection, hospitalization, and severe disease was clearly outlined, it is important not to be confused by protection against infection as that has not been the goal of this vaccine.
- Regarding mention that the persons who were vaccinated first were much sicker than those who were vaccinated later, concern was expressed that these data seemed to be comparing apples and oranges and as such might not be applicable. Even with the HCW, many hospital systems were counting the number of comorbid conditions and persons with 6 or more comorbid conditions were first in line.
- It is important to separate HCW and frontline workers who had underlying conditions from those who were young and otherwise healthy. Then the risk of pericarditis/myocarditis or TTS must be weighed looking at more severe disease in these individuals and over time.
 - Dr. Jones responded that they can work with the platform to determine what data potentially could be developed on that front. For now, they could compare with the other platforms (e.g., NYS, IVY, and VISION) that also assessed younger age groups or specifically the IVY and VISION groups that looked at younger age groups with chronic conditions. There is likely applicability to those that were in the general population versus the HCW group showing VE decreasing more for infection and having smaller declines in hospitalization.
- It is difficult to interpret the data on the Delta variant due to the very wide confidence intervals. While no doubt there has been some waning and a change in the Delta variant that impacted VE for Moderna, it may not be as striking as it seemed based on the data shown.
 - Dr. Dooling concurred about potential confounding in the health status of people who received vaccine earlier in the vaccine roll-out and how that might be affecting the VE being observed over time since vaccination. The Moderna long-term study of their RCT recipients and the follow-up study in which they crossed over and vaccinated placebo recipients do provide some informative data in that these were all trial study participants who were randomized at the beginning. In that study, which was presented earlier by Moderna, a slight decrease in VE was observed for people who were vaccinated earlier in the program.

- Dr. Jones added that there have been two types of evidence, the pre-Delta versus Delta and then the time from vaccination.
- If a person has an increased risk because of their occupation, it could be a failure to follow non-pharmaceutical interventions (NPIs) such as masking, ventilation, physical distancing, et cetera. In terms of booster doses, the American public should not receive a diluted message about the importance of layering all NPIs. This is extremely important, especially for those with occupational risk or others who have a higher risk of encountering the virus. Prevention of severe disease is very important. Trying to prevent all forms of infection might be too much to ask of either a primary series or booster.
- In terms of potential confounders influencing estimates of VE over time, perhaps there is a better way to characterize or quantify the impact of increasing risk behaviors or increasing natural infection among control groups that would lead to a better understanding of the extent to which these may be influencing current VE estimates. For instance, perhaps a 10% change in risk behaviors could be modeled to ascertain how much of an impact that would have on VE estimates.
 - Dr. Ferdinands acknowledged the challenge in trying to assess differences that might be associated with changes in risk behavior, given that they are very hard to characterize. That is a limitation of the VISIONS data.
 - Dr. Jones added that they would discuss the modeling suggestion with their other platforms and would get back to ACIP.

EtR Framework

Dr. Kathleen Dooling (CDC/NCIRD) reviewed the EtR Framework for Moderna and Janssen COVID-19 vaccine booster doses. As a reminder, vaccine policy development is conducted in close coordination with FDA. It begins with a data review of the evidence and is followed by FDA regulatory allowance, which was received the previous day. That is followed by ACIP deliberation and recommendations for input into CDC vaccine policy. At the time of this presentation, CDC recommended the following groups for Pfizer BioNTech COVID-19 vaccine boosters:

- The following recipients of Pfizer-BioNTech COVID-19 vaccine primary series should receive a single booster dose ≥ 6 months after completion of the primary series:
 - ≥ 65 years – ≥ 18 years and reside in long-term care settings
 - Aged 50-64 years with certain underlying medical conditions
- The following recipients of Pfizer-BioNTech COVID-19 vaccine primary series may receive a single booster dose ≥ 6 months after completion of the primary series based on their individual risks and benefits:
 - Aged 18-49 years with certain underlying medical conditions
 - Aged 18-64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting

The policy questions addressed during this session were: 1) Among risk groups for whom CDC recommends a Pfizer BioNTech booster dose, should those who received a Moderna COVID-19 vaccine primary series be recommended to receive a single Moderna COVID-19 booster dose (50ug) ≥ 6 months after completion of the primary series?; and 2) Among people aged ≥ 18 years

who were initially vaccinated with Janssen COVID-19 vaccine, should a booster dose of Janssen COVID-19 vaccine be recommended 2 months or more after receipt of the initial dose? To date, more than 189 million people in the US have been fully vaccinated. Approximately 105 million (~66%) fully vaccinated persons have received the Pfizer primary series, approximately 70 million (~37%) have received the Moderna primary series, and approximately 15 million (~8%) have received a dose of Janssen COVID-19 vaccine.⁷⁰

In terms of the public health problem, there have been almost 45 million cases of COVID-19 in the US since the beginning of the pandemic. The current wave, during which Delta variant predominated, peaked in early September and has been on the decline since then. Similarly, the daily trends in the number of hospitalized COVID-19 cases has been declining in the US over the past several weeks.⁷¹ In July and August 2021, hospitalization rates dramatically increased among unvaccinated individuals and increased only slightly among the fully vaccinated.⁷² Among the various age groups, hospitalization was 9-15 times higher among unvaccinated compared to vaccinated persons.⁷³

Hospitalization is not the only debilitating consequence of COVID-19. Long COVID-19 conditions are a wide range of new, returning, or ongoing health problems people can experience 4 or more weeks after first being infected with SARS-CoV-2 virus. The prevalence of post-COVID-19 conditions among both vaccinated and unvaccinated persons has been reported at between 5% and 80% depending upon on the study.⁷⁴ The prevalence of long COVID-19 among fully vaccinated persons who develop COVID-19, ranges from 5% reported in the study out of the UK in adults⁷⁵ to 19% in a study of Israeli healthcare workers.⁷⁶ Among COVID-19 cases in that same UK study, the odds of developing long-COVID were reduced by almost half among fully-vaccinated compared to unvaccinated cases.

To summarize the VE of the primary series of both Moderna and Janssen as Dr. Jones emphasized in his detailed presentation, waning of mRNA vaccines has been more pronounced against infection than against hospitalization. Compared to the pre-Delta period, VE generally has been lower in the Delta period. As demonstrated in published studies mostly involving mRNA vaccines, waning protection against infection was most pronounced in July during the Delta wave.⁷⁷ Nanduri et al reported VE among nursing home residents that was lower than what was found in younger adults, and it waned over time. Conversely, VE against hospitalization has remained fairly constant over calendar time.⁷⁸ VE against hospitalization also was constant when analyzed as time since vaccination. Janssen VE was lower than that observed for mRNA vaccines.

In summary of VE, more than 189 million people in the US are fully vaccinated. That is approximately 57% of the total population. Hospitalization rates are 9-15 times higher in unvaccinated as compared to fully vaccinated adults. The Moderna primary vaccine series has been used to vaccinate about 37% of those fully vaccinated. It appears to have declined against

⁷⁰ https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed October 20, 2021

⁷¹ https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed October 19, 2021

⁷² <https://covid.cdc.gov/covid-data-tracker/#hospitalizations> Accessed 10.20.2021

⁷³ <https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

⁷⁴ Cabrera Martimbianco AL, Pacheco RL, Bagattini AM, Riera R. Frequency, signs and symptoms, and criteria adopted for long COVID-19: a systematic review. *Int J Clin Pract* 2021;e14357. Epub May 11, 2021. PMID:33977626

⁷⁵ Antonelli, M et al. "Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study." *The Lancet Infectious Diseases* (2021)

⁷⁶ Bergwerk, M et al. "Covid-19 breakthrough infections in vaccinated health care workers." *New England Journal of Medicine* (2021)

⁷⁷ Nanduri et al (nursing home residents), Rosenberg, et al, Puranik, et al, (Pfizer), Puranik, et al (Moderna), Fowlkes et al (HCW, first responders), Keehner, et al (HCW, first responders)

⁷⁸ Tenforde, et al, Rosenberg, et al, Puranik, et al (Pfizer), Puranik, et al (Moderna), Bajema et al

infection over time and during the Delta period. On the other hand, there have been minimal to no declines in VE against hospitalization in younger adults and mild declines observed in some study platforms among older adults. Approximately 8% of fully vaccinated people received the Janssen COVID-19 vaccine. This vaccine has shown lower VE compared to mRNA vaccines. However, study platforms have shown persistent VE over time against infection and hospitalization—even among older adults.

In terms of the evidence for benefits and harms of Moderna and Janssen COVID-19 boosters, the population examined for Moderna were adults ≥ 18 years of age at least 6 months or more following the primary regimen and Janssen booster dose and for Janssen were persons ≥ 18 years who completed a COVID-19 vaccine primary series ≥ 2 months following the primary regimen. The intervention was a Moderna COVID-19 vaccine booster dose (mRNA-1273, 50 μg , IM) or a Janssen COVID-19 vaccine booster dose (Ad26.CoV2.S, 5×10^{10} VP, IM), and the comparison was those who received the primary series but no booster dose. The outcomes were consistent with those assessed for the Pfizer booster doses: symptomatic laboratory-confirmed COVID-19 (critical), hospitalization due to COVID-19 (critical), death due to COVID-19, transmission of SARS-CoV-2 infection, SAEs (critical), and reactogenicity.

The evidence retrieval for Janssen booster doses yielded 2 clinical trial records and no observational VE studies. Similarly, the evidence retrieval for a Moderna booster dose as intervention yielded 2 clinical trial records and no observational VE studies. Moderna's data for immunogenicity of a 50 μg booster following the primary series of 100 μg came from a study of 149 subjects. A larger group with immunogenicity data available following the primary series was used as a comparison group. At 28 days following the booster dose, neutralizing antibody titers were 1.8 times those in the comparison group, thus meeting the pre-specified endpoint for non-inferiority. However, no clinical outcomes were assessed and participants were not randomized to the intervention or comparison group. Therefore, the evidence type to assess the prevention of symptomatic COVID was Type 4, or very low certainty. There were no data available to assess prevention of hospitalization, death, or transmission of SARS-CoV-2. With respect to possible harms, no SAEs were attributed to the 171 subjects assessed for safety of a Moderna COVID-19 booster at 50 μg . The proportion with any SAE was balanced between the intervention and the comparison arm. In terms of reactogenicity, 10.8% of the Moderna 50 μg booster group experienced a Grade 3 or more severe reaction compared to 19.7% of the 100 μg primary series comparison group. Both of these harms outcomes were downgraded as a result of the study design, risk of bias, and small study size. Both were judged to be Type 4 evidence.

Janssen's evidence for use of a booster dose was primarily generated from a clinical trial in which subjects were randomized to receive 2 doses of Janssen vaccine 56 days apart versus placebo. Wherever possible, the effects of the booster dose administered to approximately 7484 participants was compared to a primary dose administered to over 19,000 participants in their initial clinical trial. The Janssen COVID-19 booster dose seems to be more effective at preventing symptomatic laboratory-confirmed COVID-19 than the primary dose alone. However, because participants were not randomized to the intervention and comparison groups and the results were compared across 2 separate studies that differed in time and geography, the evidence type was very low, Type 4. The Janssen booster dose may be more effective than the primary dose at preventing hospitalizations and deaths due to COVID, but because of concerns with study design, risk of bias from considerable dropout, and imprecision resulting from small numbers of outcomes, the evidence type for both was Type 4. There were no data to assess the prevention of transmission. For SAEs, over 8000 participants who received the Janssen booster dose were compared to placebo recipients. The proportion with any SAEs was balanced

between the booster and the placebo arms. However, three SAEs were attributed to the Janssen COVID booster dose by study staff. Those were facial paralysis, pulmonary embolism, and cerebrovascular event. With respect to reactogenicity, the proportion with Grade 3 reaction or a more severe reaction following a booster was similar to or less than after the primary dose. Because of loss to follow-up, short duration of follow-up, indirect comparison, and imprecision, the evidence was Type 4, or very low certainty for both arms that were assessed.

Another way to assess the benefit of a booster dose is calculating the number of people needed to vaccinate with a booster dose to prevent one hospitalization. An analysis for Pfizer, Moderna, and Janssen COVID-19 vaccine booster doses was based on current estimates of VE following the primary series and the estimated increase in protection resulting from a booster. The ≥ 65 years of age group required the fewest people to receive a booster dose to prevent a hospitalization, whereas younger adults required more people to be vaccinated with a booster to prevent a hospitalization.

Large-scale and rigorous post-authorization safety surveillance has identified safety issues that may be too rare to see in standard clinical trials. As discussed in detail during the safety presentations earlier in the day, myocarditis and pericarditis have been observed following the Moderna COVID-19 primary series. This has been noted and included in the EUA Fact Sheet. The risk was noted to be particularly high within 7 days following the second dose and was highest among males under 40 years of age. Although most cases resolve, the long-term sequelae are not fully understood.⁷⁹ The highest reporting rate has been in males 18-24 years of age in the 7 days following Dose 2 and has been reported at 39 cases per one million doses administered.⁸⁰

TTS has been identified following Janssen primary vaccination. TTS involves blood clots with a low level of platelets and has been reported at the highest rates in females 18-49 years of age.⁸¹ The highest reporting rate in females 30-39 years of age in the 21 days post-dose has been 10 cases per one million doses administered.⁸² GBS has been identified following receipt of Janssen vaccine. The highest reporting rate has been seen in males 50-64 years of age and has been reported at 16 cases per one million doses administered.⁸³

Heterologous boosting, also known as mix-and-match, could provide important immune benefits and enhanced feasibility of implementation of a booster dose program as presented earlier in the day by Dr. Atmar. To recap, the NIH-sponsored study showed that use of Moderna, Janssen, and Pfizer BioNTech COVID-19 vaccines as boosters led to strong serologic responses in groups primed by all 3 of those vaccines. For a given primary COVID-19 vaccine, heterologous boosts elicited similar or higher serologic responses as compared to their respective homologous boosting responses. mRNA vaccines resulted in higher antibody titers in the first 28 days after the boost. Although the study arms were small, involving somewhere between 49 to 53 subjects, no safety concerns were identified.

⁷⁹ Moderna COVID-19 Vaccine Fact Sheet for Health Care Providers (fda.gov)

⁸⁰ VAERS

⁸¹ Janssen COVID-19 Vaccine Fact Sheet for Recipients and Caregivers (fda.gov)

⁸² VAERS

⁸³ Janssen COVID-19 Vaccine Fact Sheet for Recipients and Caregivers (fda.gov); Rosenblum et al. MMWR, Volume 70, Issue 32 — August 13, 2021 (cdc.gov)

In terms of values and acceptability with regard to booster doses, published studies completed in August before the recommendation for booster doses showed that 76% to 87% of vaccinated adults reported that they would get a booster dose if available.⁸⁴ This increased to 93% in one survey of adults if the booster was recommended by their PCP. Prior to booster doses being recommended on September 23rd, approximately 3 million additional doses had been administered, presumably mostly to immunocompromised individuals. Following the booster dose recommendation, the total number of booster or additional doses increased to approximately 10.9 million. The vast majority of booster doses have been administered to people 65 years of age and older.⁸⁵

Regarding the feasibility and implementation of boosters, most recipients of the 3 available vaccines completed their primary vaccine regime more than 6 months ago. That is 12.9 million potentially eligible persons for Janssen, over 47 million for Pfizer-BioNTech, and over 39 million for Moderna. Among the total portion who would be eligible to receive a booster dose, almost 18 million people are over 65 years of age and about 21 million are younger people.⁸⁶ Implementation of the booster dose within long-term care facilities (LTCF) has already begun. CDC's Federal Retail Pharmacy Program (FRPP) provides vaccination support to LTCF, including on-site vaccination clinics where needed, to help residents access vaccines in the local community. Over 8 million doses were administered during the LTCF facility program roll-out that occurred from December 2020 to March 2021. That included 6.2 million (76%) Pfizer BioNTech doses and 1.9 million (24%) Moderna doses in that initial roll-out. Thus far, the program support for booster doses has been restricted to Pfizer BioNTech recipients based on current FDA and CDC guidance. This has left anybody who initially received Moderna or Janssen unable to participate in the LTCF program.

Now turning to the domain of resource use. All COVID-19 vaccines, including booster doses, will be provided free of charge to the US population. Although free to the end-user, health systems or health departments incur costs for vaccination program planning and implementation. Fees for administration of COVID-19 vaccines recommended by ACIP and CDC are reimbursed by insurance and other federal programs. Ultimately, cost-effective analyses for COVID-19 vaccines will take on increased importance in the future when the public health emergency is over.

For the domain of equity, race/ethnicity is known for the approximately 9.8 million people with a booster or additional dose administration. That represents about 90% of all of the additional doses or booster doses that have been administered since August 13th. Both Black non-Hispanic and Hispanic Latino groups comprise a lower share of booster dose recipients compared to their fraction of the US population. It should be noted that these data are not age-standardized.⁸⁷ It is important to note that while COVID-19 disease and COVID-19 vaccination vary by socioeconomic and sociodemographic groups, VE does not vary by race/ethnicity or economic variables. At present, only recipients of the Pfizer BioNTech COVID-19 vaccine primary series have been recommended to receive a booster, thus creating an inequity for recipients of Moderna or Janssen. Moreover, Janssen COVID-19 vaccine may have been used

⁸⁴ Axios Ipsos Poll. August 2, 2021; Axios Ipsos Poll. August 30, 2021; Marist Poll. September 3, 2021; <https://maristpoll.marist.edu/polls/npr-pbs-newshour-marist-national-poll-covid-september-3-2021/>; Morning Consult Poll. August 25, 2021. <https://morningconsult.com/2021/08/25/covid-booster-shot-poll/>; Reuters/Ipsos Poll. September 1, 2021. <https://www.reuters.com/business/healthcare-pharmaceuticals/most-vaccinated-americans-want-covid-19-booster-shots-reutersipsos-poll-2021-09-01/>

⁸⁵ Immunization Data Lake. Data as of October 19, 2021.

⁸⁶ CDC Immunization Data Lake. Data as of September 9, 2021

⁸⁷ Immunization Data Lake Aggregate Dataset (includes TX). Data reported as of 19OCT2021 0600.

more commonly for outreach to homeless or medically-underserved communities because it is a single-dose regimen.

In summary, the WG maintained that the top priority should be to continue vaccination of unvaccinated individuals. The goals of the booster program should be the prevention of severe disease, including hospitalization and death. Other considerations also are important, such as maintaining workforce and healthcare capacity, prevention of transmission, and individual benefit/risk balance. The balance of benefits and risks varies by age. For example, adults 65 years of age and older have the clearest benefits over risks. For Moderna vaccine, benefits are incrementally smaller with decreasing age, given the high effectiveness maintained for the primary series. Also, myocarditis risk is higher among young adults. For Janssen, the benefits may be smaller across all age groups compared with mRNA vaccines and TTS risk is higher among young females.

For people who received Moderna COVID-19 vaccine as a primary series, the WG supported using a single booster dose ≥ 6 months following the primary series in certain populations, which is consistent with CDC-recommended populations for Pfizer BioNTech COVID-19 booster. For people who received Janssen COVID-19 vaccine as a primary vaccination, the WG supported using a single booster ≥ 2 months following the initial dose in all people ≥ 18 years of age. A single dose of Janssen COVID-19 vaccine results in lower VE and antibody levels compared to an mRNA vaccine primary series. Data demonstrate that a single dose of Janssen or mRNA COVID-19 vaccine boosts immune responses in these individuals.

Discussion Summary

- It is important to remember that some international individuals may have received a WHO pre-qualified vaccine before coming to the US and that consideration must be given to whether there will be latitude within these clinical considerations for them to receive a mix-and-match booster dose.
 - Dr. Dooling indicated that this is under active consideration and certainly will be part of the clinical considerations.

Clinical Considerations

Dr. Sujan Reddy (CDC/NCEZID) reviewed updates to the interim clinical considerations for Moderna and Janssen COVID-19 vaccine booster doses in terms of indications for vaccine boosters doses, heterologous (mix-and-match) booster dosing, booster administration, the definition of “fully vaccinated,” co-administration with other vaccines, and contraindications and precautions. She reviewed the indications for a booster dose following an mRNA COVID-19 primary series, which Dr. Dooling presented earlier, noting that they were slightly different from what the FDA announced the previous day.

As a reminder, for the category of people who “may receive” an mRNA booster, an individual risk/benefit assessment was recommended that considers factors such as the following:

- Individual risk factors for SARS-CoV-2 infection:
 - Risk of exposure (occupational or institutional settings)
 - Risk of infection (time since completion of primary series)
- Potential impact of SARS-CoV-2 infection:

- Risk for severe infection (underlying conditions)
- Risk associated with a person's circumstances (living with/caring for at-risk individuals or consequences of inability to meet obligations due to infection)
- Potential benefits of booster:
 - Reduced risk of infection, including severe infection
- Potential risks of booster:
 - Rare risks of serious adverse events (myocarditis, pericarditis, anaphylaxis)
 - Common risks of transient local and systemic symptoms

For people who received a Janssen primary dose, the indications for boosters is much simpler:

- People aged ≥ 18 years who received a single dose Janssen primary series **should** receive a single Janssen COVID-19 booster dose at least 2 months after completing their primary series.

The considerations for heterologous (mix-and-match) booster dosing are as follows:

- The same product that was used for the primary regimen should be used for the booster:
 - If that is not available or another product is preferred, heterologous boosting with a single dose of any of the authorized COVID-19 vaccine boosters is acceptable
- Heterologous dosing may be considered for the booster dose only:
 - If all doses of the primary series and additional dose (if indicated for moderately to severely immunocompromised people who received 2 doses of mRNA vaccine) should utilize the same vaccine product.
- Individual benefit-risk assessment may inform which booster product to use:
 - Availability of booster product
 - Risk profile of vaccine boosters, including rare events
- Interval should follow the interval recommended by the primary series:
 - People who received a single dose Janssen primary series can receive a mRNA COVID-19 booster dose at least 2 months after completing primary series.
- If Moderna vaccine booster is used, the booster dose and volume should be utilized (50 μ g in 0.25ml):
 - Pfizer-BioNTech and Janssen booster doses are the same dose as primary vaccine.
 - If an individual who is moderately to severely immunocompromised received a primary dose of Janssen vaccine and receives a booster dose using Moderna, the 50 μ g dose should be used.

In terms of administration of COVID-19 vaccines, the Pfizer BioNTech recommendations are unchanged for primary, additional, and booster doses. The booster dose is the same for persons ≥ 18 years of age. In future weeks, that likely will change. For Moderna, the booster dose is 50 μ g for persons ≥ 18 years of age. However, the additional dose among those who are immunocompromised is 100 μ g. For Janssen, everyone ≥ 18 years of age would be getting a booster dose at least 2 months from their initial dose. The booster interval is based on homologous dosing (booster product is the same as primary series). The heterologous (mix-and-match) booster interval is dependent on the recommendation for the primary series.

The definition of “fully vaccinated” has not changed with these booster recommendations. People who completed their primary series, which is a 2-dose mRNA vaccine series or a single dose of Janssen, are considered fully vaccinated at least 2 weeks after completion of their primary series. This definition applies to all people, including those recommended to receive an additional dose due to their immunocompromised status and those who are recommended for a booster dose. People who received a booster dose should still follow the guidelines for fully vaccinated people to minimize the spread of SARS-CoV-2.⁸⁸

Similar to primary and additional doses, the COVID-19 vaccine boosters may be given with other vaccines without regard to timing. This includes all 3 of the authorized or approved vaccines. This also includes simultaneous administration of COVID-19 vaccines and other vaccines on the same day. If multiple vaccines are administered in a single visit, it is recommended that each injection be administered in a different injection site.⁸⁹ People have a contraindication to subsequent vaccine doses if they had a severe allergic reaction such as anaphylaxis after a previous dose or to a component of the vaccine. People also have a contraindication if they have had an immediate allergic reaction of any severity to a previous dose or a known diagnosed allergy to a component of the vaccine. A known polysorbate allergy is a contraindication to Janssen vaccine and a precaution to the other vaccine products. People who have a contraindication to mRNA vaccines, such as those who have a polyethylene glycol (PEG) allergy, have a precaution to the Janssen vaccine.⁹⁰ Additional tools are available for recognizing anaphylaxis.⁹¹

There are potential rare risks for mRNA vaccines, such as myocarditis and pericarditis. The risk of myocarditis and pericarditis is highest in males 12-30 years of age, but this is based on current data from the primary series. People who develop myocarditis or pericarditis after receipt of mRNA vaccine are recommended to defer a COVID-19 booster dose until at least the clinical syndrome has resolved completely. Consulting the clinical team may assist with decisions around proceeding with a subsequent doses and timing.⁹²

For the Janssen booster dose, there is a rare risk for TTS. Based on what was observed with the primary series, the highest risk is among women 18-49 years of age. For people who develop TTS after Janssen primary vaccine, the booster dose of Janssen is not recommended by experts. These individuals may receive a dose of an mRNA booster shot at least 2 months after their Janssen dose and after the clinical condition has stabilized. Conversations between the patient and their clinical team may inform decisions about the use of an mRNA COVID-19 vaccine booster and timing of the booster.⁹³

GBS is another known rare risk of Janssen vaccines. For people who develop GBS after Janssen primary vaccine, there are not a lot of data on the safety of administering either a Janssen or mRNA booster dose for this exact situation. Experts recommend that individuals who are in this situation should be made aware of their different options, including receiving an mRNA vaccine booster at least 2 months from their Janssen dose. The Janssen vaccine may still be utilized as a booster in these individuals, particularly if their GBS occurred over 42 days after vaccination or was assessed to be related to a non-vaccine factor such as other infections.

⁸⁸ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated-guidance.html>

⁸⁹ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#Coadministration>

⁹⁰ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#Contraindications>

⁹¹ <https://www.cdc.gov/vaccines/covid-19/downloads/IntermConsid-Anaphylaxis-covid19-vaccine-sites.pdf>

⁹² <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#underlying-conditions>

⁹³ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#janssen-vaccine-certain-populations>

Again, conversations between the patient and their clinical team may assist with decisions about administration of the COVID-19 vaccine booster and timing of the booster.

Discussion Summary

- It will be very important to distinguish what constitutes an additional dose versus a booster dose. This is especially important in terms of those who received Janssen as the primary vaccine, Moderna since the booster dose would be 50 µg versus 100 µg as part of a primary series, and when speaking to the public since this can be confusing.
- There is concern with regard to the Moderna product in that a primary series and booster dose will be drawn from the same packaging. While pharmacy and EHR inventory management systems are set up to be able to draw down and account for all doses, those who administer vaccine would greatly appreciate the differentiation between a half-dose and a booster dose on the packaging by way of NDC codes and CVX codes.
- Although the data so far do not show any indication of a safety problem with co-administration of COVID-19 vaccination with other vaccines, monitoring this will become even more important once children begin to be vaccinated.
 - Though concern was expressed regarding co-administration of mRNA COVID-19 vaccine with ACAM2000 due to its association with pericarditis, Dr. Cohn emphasized that ACAM2000 is currently being used only in the military population. However, CDC will take this into consideration and will think about the right way to address this potential concern.
- It was suggested that perhaps the language could be softened regarding use of the same product, given that some vaccinators would interpret this as the law rather than in terms of flexibility. There was support for more permissive use of a mix-and-match approach in the recommendation as well as the clinical guidance. For equity purposes, this would allow more flexibility for clinicians in the field to more easily adapt and serve the populations who they take care of as they see fit.
- While ACIP continues to state that their decisions should be supported by the best available evidence, the available evidence suggesting that people under 50 years of age should receive a booster at this point is unclear—setting aside Janssen. ACIP would be abdicating its responsibility not only to allow people to be immunized if they should be immunized, but also to protect them from immunizations that they do not need that have AEs. For instance, the data suggest that HCW do not have increased exposure from their work. Instead, they are more likely to be exposed in non-work community settings. It was not clear to all ACIP members that otherwise healthy individuals under 50 years of age need a booster vaccine at this time with either Moderna or Pfizer. To mitigate the harm, perhaps there needs to be some age restriction on the otherwise worried-well.
- Another workforce issue to take into consideration is the challenge with staffing capacity that is resulting in the need to triage patient care, including routine care. Allowing for the flexibility to receive a booster in order to reduce the risk of infection and missed days of work would make a major difference, especially in terms of the nursing workforce.

- Flexibility could be beneficial in some congregate settings, such as among people who are incarcerated.
- Notably, ACIP's vote language is often "front page news" and clinical considerations do not receive as much attention. Perhaps more explicit language could be included about the importance of vaccinators paying close attention to the clinical considerations, especially with regard to vaccine-associated risk and risk mitigation.
- It is critically important to make clear that the total number of mRNA doses is 3 for those who are not immunocompromised (initial 2-dose series and 1 booster dose at least 6 months later) and that the total number of doses for immunocompromised persons is 4 (3-dose primary series and 1 booster dose at least 6 months later).
- There is an ongoing need for patient education at an appropriate health literacy level and in multiple languages, which should continue to be a major priority.

Votes: COVID-19 Vaccine Booster Doses

Dr. Lee (ACIP Chair) expressed appreciation for everyone's honesty and willingness to speak up and represent the diverse viewpoints from the ACIP, emphasizing that this is exactly what the committee is supposed to do. She also recognized that part of their charge for the day was to look forward and not spend too much time looking backward, pointing out that they were not re-evaluating a prior decision. From the perspective of implementation and equity, the goal was to consider the current status of the pandemic and determine how to move forward together. She stressed that she wanted everyone to be able to express their viewpoints, but with the recognition that they were in a different context than they were a month ago.

Dr. Kathleen Dooling (CDC/NCIRD) presented the following proposed language for votes on Pfizer BioNTech and Janssen COVID-19 vaccine booster doses, with revisions based on the discussions throughout the day:

Motion/Vote #1: Proposed Language for a Pfizer BioNTech Booster Dose

A single COVID-19 vaccine booster dose is recommended at ≥ 6 or more months after completion of an mRNA primary series in the same risk groups for who CDC recommended a booster dose of Pfizer BioNTech under the FDA's Emergency Use Authorization.

Motion/Vote #2: Proposed Language for a Janssen Booster Dose

A single COVID-19 vaccine booster dose is recommended for persons aged ≥ 18 years at ≥ 2 or more months after receipt of the initial Janssen dose under the FDA's Emergency Use Authorization.

Motion/Vote #1:
Draft Interim Recommendation for a Pfizer BioNTech COVID-19 Vaccine Booster

Dr. Bell made a motion for ACIP to adopt an interim recommendation stating that “A single COVID-19 vaccine booster dose is recommended at ≥ 6 or more months after completion of an mRNA primary series, in the same risk groups for who CDC recommended a booster dose of Pfizer BioNTech, under the FDA’s Emergency Use Authorization.”

Dr. Sanchez seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A
0 Absent: N/A

Motion/Vote #2:
Draft Interim Recommendation for a Janssen COVID-19 Vaccine Booster

Ms. Bahta made a motion for ACIP to adopt an interim recommendation stating that “A single COVID-19 vaccine booster dose is recommended for persons aged ≥ 18 years at ≥ 2 or more months after receipt of the initial Janssen dose under the FDA’s Emergency Use Authorization.”

Dr. Ault seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A
0 Absent: N/A

Member Statements

Subsequent to the vote, Dr. Lee invited ACIP members to make a statement about the rationale for their votes and/or to share any additional general comments:

- Dr. Talbot: I think a lot of what I was concerned about has been said, but I just want to reiterate for Vote #1, Moderna still has very good VE. There will be some confusion with the higher versus the lower dose. So, those that are not at high risk should really be thoughtful about getting that dose. But I think the clinical considerations will be incredibly important. I did vote “yes” to simplify the recommendations for the American public and the American healthcare system, but I do think we need to be very aware of potential complications.

- Dr. Chen: I'm really pleased with our discussion today. I think that I heard from my colleagues a breadth of thoughts and I think that they were really terrific for me to hear. Certainly from my point of view, I really appreciated that we were finally able to look at, consider, and recommend a mix-and-match approach as part of our way to boost people's immunity, especially for the people who need it. I think we've already discussed that there is data that there are some people that really don't need the booster dose at this time, and I guess I'd like to just remind the American public now that there are the other non-pharmaceutical interventions and that we need to all have a multilayered approach when we're out in public, to continue to mask, keep employee distance, and try to have indoor ventilation and improved environment for the workspace. Those sorts of things are an important part and we're not just going to vaccinate ourselves out of this situation, but it really is a multi-layered approach. I think that we had a great discussion and the outcome was what I was hoping for, so thank you.
- Dr. Poehling: Thank you for the opportunity to speak. One of the things that was stated earlier was that we focused a lot on the booster dose. The WG emphasized, and we want to reiterate, the importance of increasing primary coverage for the entire population. That needs to remain an important focus. I completely agree with Dr. Chen about the importance of using other mitigating factors. Through those recommendations for those who the balance is favorable, we want to encourage people to make [inaudible]. Thank you.
- Dr. Daley: Thanks so much. I want to make a quick comment with regard to vaccine safety. Dr. Shimabukuro has, at prior ACIP meetings, reminded us all that the vaccine safety surveillance is the most intensive that has ever been undertaken, we're using that data to better quantify these rare risks, and it's a crucial factor in the decisions that we're making. But I think we want to just be cognitive to the fact that that intensive degree of vaccine safety surveillance is going to continue in the context of boosters and that data is going to be brought before this committee. So, every bit as much of safety surveillance with the primary series is going to be in place for the booster doses. Thank you.
- Ms. McNally: Similar to the comment that was made earlier in the meeting where we talked about "vaccines don't save lives, but vaccinations do," I have this same feeling about our recommendations and implementations. So our recommendations are one step of the way, but it's going to be so important as everyone mentioned for us to make sure that in our implementation, patients are truly educated about the benefit/risk balance based on their own personal situation. And it is the hardest thing for us to do, but I would encourage all of us to go beyond the recommendations at this point and do our best to educate our communities, our provider teams, and partner with public health. I'm going to say our hope is that we will also in the future be able to have those discussions with school communities and much broader communities than this. We look to our CDC partners here in the room and beyond for their expertise and for their continued dedication to ensure that these public health education efforts are prioritized, as they are so important for us to be able to do the right thing.

CERTIFICATION

Upon reviewing the foregoing version of the October 20-21, 2021 ACIP meeting minutes, Dr. Grace Lee, 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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ACRONYMS USED IN THIS DOCUMENT

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
AE	Adverse Event
AESI	Adverse Events of Special Interest
AHIP	America's Health Insurance Plans
AI/INF	Autoimmune and/or Inflammatory Conditions
AI/AN	American Indian and Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AMI	Acute Myocardial Infarction
Anti-PF4	Anti-Platelet Factor 4
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
APTR	Association for Prevention Teaching and Research
ARDS	Acute Respiratory Distress Syndrome
ARP	American Rescue Plan
ASPR	Office of the Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
BARDA	Biomedical Advanced Research and Development Authority
BCRP	Boston Combined Residency Program in Pediatrics
BEST	Biologics Effectiveness and Safety Initiative
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CICP	Countermeasures Injury Compensation Program
CMC	Chronic Medical Condition
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CVST	Cerebral Venous Sinus Thrombosis
DFO	Designated Federal Official
DHA	Defense Health Agency
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs

DVT	Deep Vein Thrombosis
ED	Emergency Department
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent Assay
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFP	Fit for Purpose
FP	Family Physician
FRPP	Federal Retail Pharmacy Program
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GMR	Geometric Mean Ratios
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCP	Healthcare Personnel / Providers
HSCT	Hematopoietic Stem Cell Transplant
HCW	Healthcare Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HM	Hematologic Malignancies
HPAI	highly pathogenic avian influenza
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
HZ	Herpes Zoster
IAC	Immunization Action Coalition
IBD	Inflammatory Bowel Disease
IC	Immunocompromising Conditions
ICATT	Increasing Community Access to Testing
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases 10 Clinical Modification
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IHS	Indian Health Service
IHS VTF	IHS Vaccines Task Force
I-STAR System	IHS Safety Tracking & Response System
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
IMD	Immune-Mediated Disease
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
ITP	Immune Thrombocytopenia
IVAC	International Vaccine Access Center
JAMA	<i>Journal of the American Medical Association</i>

JTM	<i>Journal of Travel Medicine</i>
JHU	Johns Hopkins University
KAP	Knowledge, Attitudes, and Practices
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
LAIV	Live Attenuated Influenza Vaccine
LTCF	Long-Term Care Facilities
MAAE	Medically-Attended Adverse Event
MHS	Military Health System
MMWR	<i>Morbidity and Mortality Weekly Report</i>
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAHN	National Association of Hispanic Nurses
NAIIS	National Adult and Influenza Immunization Summit
NANASP	National Association of Nutrition and Aging Services Programs
NAPNAP	National Association of Pediatric Nurse Practitioners
NBP	Non-Bacteremic Pneumococcal Pneumonia
NCBA	National Caucus & Center on Black Aging, Inc.
NCHS	National Center of Health Statistics
NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases
NDC	National Drug Code
NEJM	<i>New England Journal of Medicine</i>
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHCA	National Hispanic Council on Aging
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS-Child	National Immunization Survey-Child
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NPIs	Non-Pharmaceutical Interventions
NVAC	National Vaccine Advisory Committee
NYS	New York State
ODSCT	Office of Direct Service and Contracting Tribes
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PCP	Primary Care Provider/Practitioner
PCV13	13-Valent Pneumococcal Conjugate Vaccine
PHAC	Public Health Agency Canada
PHN	Postherpetic Neuralgia
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PID	Primary Immune Deficiency
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PPSV23	23-Valent Pneumococcal Polysaccharide Vaccine

QALY	Quality-Adjusted Life-Year
QIV-HD	High-Dose Quadrivalent Influenza vaccine
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RSV	Respiratory Syncytial Virus
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SDOH	Social Determinants of Health
SHEA	Society for Healthcare Epidemiology of America
SLE	Systemic Lupus Erythematosus
SME	Subject Matter Expert
SOT	Solid Organ Transplant
ST3	Serotype 3
STM	Solid Tumor Malignancies
SUPERNOVA	Surveillance Platform for Enteric and Respiratory Infectious Organisms
TTS	Thrombosis with Thrombocytopenia Syndrome
UC	Urgent Care
UK	United Kingdom
URF	Underreporting Factor
US	United States
USG	US Government
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC Program	Vaccines for Children Program
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccine and Related Biological Products Advisory Committee
VRC	Vaccine Research Center
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WG	Work Group
WHO	World Health Organization
ZVL	Zoster Vaccine Live