MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

FEBRUARY 4, 2022
SUMMARY MINUTES

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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 February 4, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on COVID-19 vaccine safety and efficacy, myocarditis and pericarditis following Moderna COVID-19 vaccine, myocarditis after Moderna and Pfizer/BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine primary series for individuals ≥18 years of age, Canadian experience and evidence with COVID-19 vaccine primary series extended intervals, and extended intervals for mRNA COVID-19 vaccines in the US.

FRIDAY: FEBRUARY 4, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the February 4, 2022 ACIP meeting. She conducted a roll call, which established that a quorum was present. No conflicts of interest (COIs) were declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. The following conflict of interest (COI) was declared: Dr. Chen reported that his employing institution, the University of Maryland, received a grant from Emergent BioSolutions that supported work he conducted to develop a Shigella vaccine.

CDC Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, 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 the ACIP is at its heart a public body. Engagement with the public and transparency in the ACIP processes is vital to the committee's work. She indicated that there would be an oral public comment session prior to the vote at approximately 11:10 AM Eastern Time (ET). To create a fair and more efficient process for requesting to make an oral comment, people interested in making an oral comment are requested to submit a request online in advance of the meeting. Priority is given to these advanced requests, and if more people request to speak than can be accommodated, a blind lottery is conducted to determine who the speakers will be. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Members of the public also can submit public comments through https://www.regulations.gov using Docket Number CDC-2022-0022. Information on the written public comment process, as well as information on how to make a comment, can be found on the ACIP meeting 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 these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding

other vaccines of the concerned company, a member may participate in discussions with the provision that he or she abstains from all votes related to the vaccines of that company. ACIP members state any COIs at the beginning of each meeting.

FDA Announcements

Dr. Doran Fink (FDA) shared 2 announcements on behalf of FDA. First, FDA granted full approval on Monday, January 31, 2022 of Moderna's COVID-19 vaccine, now known as Spikevax®, for use in people ≥18 years of age as a 2-dose primary series.[1] Moderna COVID-19 vaccine has been available under Emergency Use Authorization (EUA) for individuals ≥18 years of age since December 18, 2020. FDA's approval was based on updated data and analyses from the same Phase 3 clinical trial involving approximately 30,000 participants that initially supported the EUA in December 2020. FDA's approval also considered real-world experience from post-authorization use of the vaccine in many millions of individuals. In the updated efficacy analyses, which included a median placebo-controlled blinded follow-up of 4 months, VE (VE) against any symptomatic COVID starting 14 days after Dose 2 was approximately 93% and VE against severe COVID was approximately 98%. The review of safety data from additional follow-up conducted in the clinical trial, as well as data from the post-authorization experience, did not raise any new safety concerns compared to the safety profile that the FDA labeled in the EUA Fact Sheet. Important but very uncommon adverse reactions continue to be anaphylaxis and myocarditis and pericarditis, particularly following Dose 2 and among males less than 40 years of age. The approved US prescribing information for Spikevax® includes warnings about these adverse reactions, which will continue to be followed through post-marketing surveillance. FDA recognizes that approval of the Biologics License Application (BLA) Spikevax® represents an important step in building and maintaining the armamentarium of countermeasures against COVID-19, as well as an important regulatory step for this particular vaccine. It certainly will not be the last step. There are other uses of this vaccine, such as booster doses that are currently available under the EUA. Work is ongoing to eventually transition some of these products over to licensure. FDA anticipates that in the future, there will be supplements to the license or amendments to the EUA to address other needs as they arise.

Second, FDA announced publicly earlier in the week that the Vaccines and Related Biological Products Advisory Committee (VRBPAC) would meet on February 15, 2022. In mid-December, Pfizer/BioNTech announced initial safety and immunogenicity results from infants and children 6 months to 4 years of age enrolled in their ongoing clinical trial of the Pfizer/BioNTech COVID-19 vaccine. Pfizer/BioNTech also announced their plans to amend the trial to evaluate a third dose of the vaccine in this age group. As reports of pediatric hospitalizations increase in association with the Omicron variant surge in late December 2021, FDA requested Pfizer to provide more detailed data for review as the information became available. At the same time, FDA has received many inquiries from healthcare providers, advocacy groups, and the general public expressing intense interest in the details of the data and prospects for EUA of the vaccine for use in this age group. During its ongoing review, FDA recognized that additional immunogenicity and efficacy data have become available to better inform vaccine benefits. In the meantime, the Omicron surge is now receding in some parts of the nation but is certainly not over. Furthermore, it is imperative not only to react to the present situation but also to be prepared when confronted with the next unexpected twist. The decision to hold this VRBPAC was motivated not only by the need for transparency on the newly available data, but also on the declining unpredictability of the pandemic. FDA intends to conduct an open, transparent,

[1] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine

and thorough discussion of the available data; to listen carefully to the assessment of its expert committee members, and to end the meeting better prepared to build upon FDA's response to COVID-19 whether this follows from a clear recommendation for an authorization or from recommendations for additional data that could support an expedient authorization in the near future.

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 Work Group (WG). Through January 30, 2022, there have been over 75 million cases of COVID-19 in the US since the start of the pandemic. the case range had reached approximately 497,000 per day.[2] Although case counts have been declining in the last several weeks, the US is still averaging hundreds of thousands of cases of COVID-19 every day. During the pandemic, more than 880,000 individuals in the US have died from COVID-19. Based on the most recent 7-day moving average, more than 200,000 individuals will die today from COVID-19. Achieving disease prevention requires not only an effective vaccine, but also an effective vaccination program. There also need to be adequate vaccine supplies, the people and processes to administer vaccines, and public acceptance of vaccines. More than three-quarters of US adults across every age group have received at least 1 dose of a COVID-19 vaccine. While these are perhaps lower vaccination than hoped, this is still and important accomplishment.[3] Several recent studies have tried to estimate COVID-19-associated hospitalizations and deaths prevented by COVID-19 vaccination in the US. Based on these new studies, it has been estimated that up to 10.3 million hospitalizations had been averted through November of 2021 through vaccination,[4] and an estimated 1.1 million deaths have been averted through November 2021 by vaccination.[5]

In terms of the FDA updates Dr. Fink announced, it is important to note that the Moderna COVID-19 vaccine remains under EUA for the following indications:

- ❑ Third primary series doses for individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise
- ❑ Single booster dose for individuals 18 year of age and older at least 5 months after completing a primary series

During January and February 2022, the COVID-19 Vaccines WG has reviewed data on the safety and efficacy of Modern COVID-19 vaccine from the Phase 3 clinical trials; a meta-analysis for global real-world effectiveness data from Moderna COVID-19 vaccine; safety updates for Modern COVID-19 vaccine specifically and for mRNA COVID-19 vaccines in general; addition, GRADE (Grading of Recommendation Assessment, Development and Evaluation) and the Evidence to Recommendations (EtR) Framework data for Moderna COVID-

[2] https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed February 1, 2022
[3] https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed February 01, 2022
[4] Moghadas SM, Sah P, Fitzpatrick MC, et al. COVID-19 deaths and hospitalizations averted by rapid vaccination rollout in the United States. medRxiv. Published online July 8, 2021:2021.07.07.21260156; doi:10.1101/2021.07.07.21260156; and Eric C. Schneider, Arnav Shah, Pratha Sah, Seyed M. Moghadas, Thomas Vilches, Alison Galvani. The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted.
[5] Moghadas SM, Sah P, Fitzpatrick MC, et al. COVID-19 deaths and hospitalizations averted by rapid vaccination rollout in the United States. medRxiv. Published online July 8, 2021:2021.07.07.21260156; doi:10.1101/2021.07.07.21260156; and Gupta S, Cantor J, Simon KI, Bento AI, Wing C, Whaley CM. Vaccinations Against COVID-19 May Have Averted Up To 140,000 Deaths In The United States. Health Aff (Millwood). 2021;40(9):1465-1472.

19 vaccine primary series; global data for myocarditis after mRNA COVID-19 vaccines; and emerging data about safety/effectiveness of longer inter-dose intervals for mRNA COVID-19 vaccines. The agenda for this meeting included the following presentations:

- ❑ mRNA 1273 COVID-19 vaccine BLA safety and efficacy data (followed by Public Comment)
- ❑ Updates on myocarditis and pericarditis following Moderna COVID-19 vaccination
- ❑ Updates on myocarditis outcomes from the MOVING study, which is looking at longer-term outcomes following vaccine-associated myocarditis
- ❑ Vaccine Safety Technical Subgroup (VaST) assessment of the current state of knowledge around COVID-19 vaccine safety specifically focused on Moderna COVID-19 vaccination
- ❑ GRADE: Moderna COVID-19 vaccine
- ❑ EtR Framework regarding the use of Moderna COVID-19 vaccine for a primary series in individuals ≥18 years of age
- ❑ Vote on the routine use of Moderna COVID-19 vaccine for individuals ≥18 years of age
- ❑ Updates to Clinical Course
- ❑ Canadian experience and evidence with COVID-19 vaccine primary series extended intervals
- ❑ Vaccine Safety Datalink (VSD): Myocarditis after Moderna and Pfizer/BioNTech COVID-19 vaccines
- ❑ Myocarditis and COVID-19 vaccine intervals: International data and policies
- ❑ Summary and Work Group Interpretation: Extended intervals for mRNA COVID-19 vaccines

Overview of BLA for Use of Moderna's COVID-19 Vaccine (Spikevax®) in Individuals ≥18 Years of Age

Rituparna Das, MD, PhD (Moderna) present an overview of the BLA for the Moderna COVID-19 vaccine or Spikevax®, which was approved at the beginning of the week. She discussed the contents of the BLA and Phase 3 safety and efficacy data. The follow-up time included 5.3 months post-vaccination for the blinded study and 7.6 months for the blinded and open-label phases of the study together. The BLA does not include the authorized indication for a third 100 µg dose for immunocompromised populations (EUA approved August 13, 2021), an indication for the 50 µg booster dose (EUA approved October 18, 2021), or data for the Omicron variant. Therefore, these were not covered in this presentation. Spikevax® is indicated for immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥18 years of age. It is administered as an intramuscular injection in a series of 2 doses 0.5 mL in volume 1 month apart.

Protocol 301, the Coronavirus Efficacy (COVE) trial, is the pivotal safety and efficacy study. This study enrolled 30,400 people who were randomized 1:1 to receive the vaccine mRNA-1273 or a saline placebo, with about 15,200 in each group. The study started in July 2020 and completed enrollment by October 2020. The initial efficacy readout came from the interim analysis, which was at the end of November 2020. That led to the approval of the EUA on December 18, 2020. Thereafter, participants were offered unblinding and placebo recipients were allowed to be vaccinated. All participants then continued to be followed in an open-label manner according to the original schedule of events. At baseline, all participants had a nasopharyngeal (NP) swab and a blood sample to assess their SARS-CoV-2 status. After vaccination, everybody was given an e-diary to monitor solicited adverse events (AEs) for 7 days. Unsolicited AEs were monitored via weekly phone calls for 28 days. The same protocol was repeated after Dose 2. Serious adverse events (SAEs), medically attended adverse events (MAAEs), and adverse events leading to discontinuation were to be monitored for the duration of the study, which was planned to be 2 years. Throughout the study, case monitoring was conducted through weekly eDiary prompts and monthly phone calls. If the participants met the criteria for a clinic visit, went to the

site, had a sample collected for central laboratory testing, and were followed daily through telemedicine contact for 14 days or until the resolution of symptoms, whichever was longer. Additional clinic visits were planned for 3, 6, 12, and 24 months after vaccination.

Regarding demographics, the mean age of the population in the study was about 52 years. The goal of the study was to reach the populations most affected by severe COVID-19. Accordingly, 25% of participants were ≥65 years of age. About 1,500 participants were ≥75 years of age and another 17% were 18-64 years of age with comorbid conditions including chronic lung disease or moderate to severe asthma, significant cardiac disease, obesity, diabetes, liver disease, or stable human immunodeficiency viruses (HIV) infection. The HIV group had about 90 participants in the vaccine and placebo groups. Baseline SARS-CoV-2 status was assessed. Approximately 2% of participants had baseline evidence of prior SARS-CoV-2 infections. The racial and ethnic distribution of the study was generally similar to the US population, and this was a key objective in the recruitment of the study. There were 10% Black or African American participants and 20% Hispanic or Latino participants.

In terms of safety, solicited injection site reactions were more common among vaccine recipients compared to placebo recipients. Following Dose 1, injection site pain among participants 18-64 years and ≥65 years was the most common reaction and local reactions were very similar between these age groups. Solicited local reactions after Dose 2 were very similar and were primarily Grade 1 or 2. Overall, local reactions also were of short duration and generally resolved in 1 to 3 days. Delayed local reactions with an onset after 7 days were seen but were relatively rare, occurring in 2.4% of vaccine recipients and 1.45% of placebo recipients. The solicited system reaction, most of which were Grade 1 or 2, were observed more frequently in vaccine compared to placebo recipients. Fatigue and headache were the most common reaction. Solicited reactions were more common following Dose 2 compared to Dose 1. Participants ≥65 years had a numerically lower reactogenicity compared to their younger counterparts. The duration of solicited systemic AEs also were short, ranging from 1 to 3 days. Unsolicited events occurring within 28 days of vaccination were similar among vaccine and placebo groups. MAAEs, SAEs, and deaths also were similar. Broken down by System Organ Class (SOC), SAEs were generally balanced. The same was noted for MAAEs.

Looking specifically at myocarditis and pericarditis, there were no myocarditis events during the blinded or the open label periods of the study. In the blinded phase, there were 2 pericarditis events in the vaccine group and 2 in the placebo group. The first event that was considered related was in a female 59 years of age with non-serious chest pain, dyspnea, and fatigue 4 days after Dose 2 that resolved within 2 days. She then experienced chest pain and syncope 68 days after Dose 2. When pericarditis and effusion were diagnosed, this was considered by the investigator to be vaccine-related. The second case was a post-myocardial infarction pericarditis 73 days after Dose 2 that resolved the following day and was considered by the investigator to be unrelated. Again, no myocarditis was observed in the open label study. There was 1 pericarditis event in a 23-year-old male who had COVID-19 about 2 months prior to vaccination. Subsequent to vaccination, he developed bradycardia and was diagnosed with a pericardial effusion. This also was classified as a vaccine-related event. All of the events of pericarditis that occurred in either the blinded phase or the open label phase of the study results.

Now turning to efficacy. As a reminder, 30,000 participants were randomized to receive vaccine or placebo. The first read on efficacy was at the interim analysis conducted in November 2020, which showed 94.1% efficacy.[6] For the BLA, a final blinded analysis was performed with 5.3 months of follow-up that was calculated post-Dose 1 through March 2021. Subsequently, the study entered the open label phase during which placebo recipients were offered vaccine. Effectiveness has been followed since then in an open label manner. Additionally, boosting of study participants started in September 2021 and is ongoing. In the final analysis of efficacy,[7] the results were very similar to the initial interim analysis. There were 744 cases of COVID-19 infection in the placebo group compared to 55 cases in the vaccine group, for an efficacy of 93.2%. The median duration of follow-up was 5.3 months. Since the blinded period of the study was conducted between July 2020 and March 2021, the predominant SARS-CoV-2 variant identified in the majority of the COVID-19 cases were the original variant. Some additional variants that were identified (Epsilon, Gamma, and Zeta). The case numbers for the other variants were small, but there was no indication that efficacy against other variants was impacted. There was no Delta or Omicron circulation during that timeframe. Efficacy was consistent and durable over the observation period. High efficacy started after vaccination and was maintained consistently through >4 months after vaccination. VE to prevent severe COVID-19 also was consistent with 106 cases in the placebo group and 2 cases in the vaccine group, for an efficacy of 98.2%.

Looking at efficacy by primary and secondary endpoints, even asymptomatic infection was prevented by vaccination with an efficacy point estimate of 63%. Efficacy was consistent regardless of baseline serostatus. However, the group sizes and the number of cases became too small for an analysis of baseline SARS-CoV-2 seropositive only. Demographically, efficacy was consistent across age groups. Persons ≥65 of age and persons ≥75 years of age had very high and consistent efficacy, although the case number had become small at this point. Efficacy also was consistent across race and ethnic groups. Efficacy also was similar and consistent across the co-morbid conditions targeted to be recruited in the trial.

In summary, mRNA-1273 was well-tolerated in individuals ≥18 years of age. Pain was the most commonly reported local reaction. Fatigue, headache, myalgia, and arthralgia were the most commonly reported systemic reactions. Systemic reactions were more common after Dose 2 than after Dose 1. There was no difference in AEs for persons 18 to 64 years of age versus those ≥than 65 years of age. After a median of 5.3 months following Dose 1 of efficacy follow-up, there was 93.2% efficacy against COVID-19 starting 14 days post-Dose 2. Efficacy was 98.2% against severe COVID-19 starting 14 days post-Dose 2. There was an 82% reduction of infection regardless of symptoms and a 63% reduction in asymptomatic infection starting 14 days post-Dose 2. Efficacy was consistent regardless of risk factors, age, gender, race, or ethnicity.

Discussion Points

Dr. Poehling asked whether Moderna has had a chance to assess VE for persons with and without co-morbid conditions.

Dr. Das indicated that they have assessed all of the co-morbid conditions identified for the study (e.g.,chronic lung disease or moderate to severe asthma, significant cardiac disease, obesity,

[6] Baden et al NEJM, 2020
[7] El Sahly, NEJM, 2021

diabetes, liver disease, or stable HIV infection). Efficacy was consistently above 80% for all of these comorbid conditions.

Referring to Slide 8, Dr. Loehr wondered how the asymptomatic data were assessed. He did not see anything about this in terms of blood tests. Referring to Slide 26, he noted that the curve flattened for the placebo group and it was not clear why that would occur if they were still getting more cases.

Dr. Das indicated that there was no weekly or bi-weekly screening for asymptomatic infection. The numbers came from the nucleic protein assays. Participants also had NP swabs each time they had a blood draw, entered the study, and/or presented for a clinic visit. All of the positive participants were checked for symptom. All of the participants who were positive but did not have any symptoms contributed to the asymptomatic infection analysis. In terms of the flattening curve, they still were subject to the ebbs and flows of the overall trajectory of the pandemic. Their COVID-19 infection curve does the same.

Dr. Sanchez observed that on Slide 18, there were 16 deaths in the vaccine group and 16 in the placebo group. Only the COVID-related deaths were analyzed, but he inquired as to the cause of the other deaths in the vaccine group. In addition, he asked whether they were able to assess the development of diabetes during the study.

Dr. Das clarified that the deaths on Slide 18 are total deaths. The COVID-related deaths analysis included 3 deaths in the placebo group and no deaths in the vaccine group. None of the deaths were considered to be related to the vaccine and are reflective of the type of population enrolled (e.g., persons with multiple comorbid conditions). The database was locked on May 4th and all of the data are through the March timepoint.

Dr. Das did not recall whether there was a signal for new diabetes and will check with her colleagues to determine whether there was a specific analysis performed for new diabetes.

Dr. Poehling asked whether Dr. Das could share more information about the results for anaphylaxis in the trial.

Dr. Das indicated that anaphylaxis was balanced between the vaccine and placebo groups. In the placebo group, anaphylaxis was reported in 2 participants on Day 10 and Day 11 after the first injection. Anaphylaxis also was reported in 2 participants in the vaccine group. The anaphylaxis events in the vaccine group were reported almost 2 months after the second dose and neither was considered to be related. Although an imbalance of anaphylaxis was not seen in the trial, anaphylaxis is listed in the label as a possible side effect.

Dr. Sanchez requested information about the severity of the previous COVID-19 infection in the 23-year-old male patient in the placebo group who developed pericardial effusion after receiving the second dose of the vaccine. The question is often raised about how long after having COVID-19 someone should wait to be vaccinated.

Dr. Das indicated that this individual was not hospitalized or meet the criteria for severe COVID-19 because he was one of the cases in the in the blinded phase of the analysis. His COVID-19 case was mild. The information Moderna has is that 43 days after Dose 2, he was diagnosed with bradycardia and a pericardial effusion. There was some kind of bradycardia prior to that, which was not associated with any chest pain. The second dose was administered 2 months after the first dose.

Public Comment

The floor was opened for public comment during the February 4, 2022 ACIP meeting at 11:10 AM ET. All speakers submitted a request in advance of the meeting and the final list of public commenters was determined via a lottery. Everyone was reminded that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2022-0022. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Milena Berhane
National Consumers League

My name is Milena Berhane. Today I'm representing the National Consumers League (NCL). Since NCL's founding in 1899 by social reformer Florence Kelley, we have advocated for the critical role immunizations play in the preservation and improvement of public health. We extend our gratitude to this committee for the opportunity to present public comment. An estimated 890,000 Americans have died from COVID-19 during this pandemic that has persisted in the US for the past 2 years. The COVID-19 virus continues to threaten the health and safety of many, especially vulnerable populations such as the elderly and immunocompromised groups. The currently available COVID-19 vaccines have worked to save lives and avoid preventable illness, hospitalizations, and deaths in our communities. The National Consumers League commends the FDA and CDC on the approval of the Moderna COVID-19 vaccine, which will continue to be a key tool in the public health response to this pandemic. This vaccine has been and will continue to be a safe and effective measure for protecting Americans 18 years of age and older. America's families are hopeful that the Pfizer COVID-19 vaccine will be granted emergency use approval for children under 5 years of age. Hospitalization of children under 5 years of age has soared—further evidence of the need for expanding vaccine access to children in this age group. Vaccinating children under the age of 5 will protect them from illness but also protect their families, caretakers, and teachers from contracting COVID-19 as well. We are also concerned about the widespread drop in routine childhood immunization rates during the pandemic. According to CDC data released last May, over 11.7 million children have missed doses of their recommended vaccines. We are particularly worried that our nation's most vulnerable children, those who qualify for the Vaccines for Children (VFC) program are getting caught up at a much slower rate than children with commercial insurance. The National Consumers League recognizes the extreme importance of immunizations and protecting the health and safety of all Americans and will continue with efforts to increase vaccine confidence and uptake across lifespan. We look forward to the upcoming recommendations by this committee regarding these COVID-19 vaccines.

Laura Burns
TRAIPAG

Good morning. My name is Laura Burns and I represent TRAIPAG, the Transplant and Immunocompromised Patient Advocacy Group. There are about 2,000 of us linked by a Facebook group. About half of us are participants in the Johns Hopkins VE studies for transplant patients and the immunocompromised. TRAIPAG strongly supports approval of the BLA for the Moderna vaccine, but we wish that the approval could take the straitjacket off our doctors and give them the ability to individualize our care. I'd like to quote something Dr. Dorry

Segev, the head of the Johns Hopkins studies, said in an interview a couple of weeks ago, "So, for example, if one of my patients got 3 doses, and they ended up with a relatively low but still positive antibody, I would want to give them a fourth dose to boost them up so that it'll be much higher. But I can't do that today. The only fourth dose that people can get is if they had 3 doses 6 months ago. Now they can get a fourth dose as a booster, but not to complete the primary series." Our group is very active on Facebook and we are all discussing our individual dilemmas. For example, a number of people get infusions twice a year. Many find their 5-month booster falls at the same time as their infusion, but they know from their doctors that the infusion will negate the VE. What to do? We're seeing the same thing with Evusheld™. People know they should get boosted before Evusheld™ and wouldn't it be better to get the booster now, 4 months after their third dose, and then Evusheld™ rather
than waiting a month for the booster and then another 2 weeks for Evusheld™. Six weeks! Likewise, many of our doctors tell us they wish we could get a full dose of Modern for our booster. They think it makes more sense for the immunocompromised, especially if we had a weak response to the primary series. I'll close with another quote from Dr. Segev's interview. As doctors, I'm sure you'll be able to appreciate it, "Look, this really needs to be individualized. We can't keep going to the CDC/FDA guidelines can't be this really complex decision tree of, 'Well, did you have 3 doses and was your antibody level less than 250? And if it was, are you taking MMF, and if you are, then you should get a fourth dose, but it should be at 2 months whereas this other person should get it a the 4.' I mean, that's just way too complicated for a big government agency to be doing. But that is what doctors do. That's like what medical providers do. They individualize care for their patient. The difference is for any other medication I give my patient, I have the permission to do so. For vaccines, we don't have permission to do so." Committee members, thank you so much for your attention and for all that you're doing to keep us safe. Again, we fully support the BLA for Moderna.

Leila Sahni, PhD, MPH
Texas Children's Hospital

Good morning. My name is Leila Sahni. On behalf of Texas Children's Hospital, I would like to thank the CDC employees and ACIP members who have diligently analyzed COVID-19 epidemiology and vaccine safety and efficacy data and adeptly provided risk/benefit assessments based on this information. Using your in-depth analyses, my colleagues and I have been able to assure families of the safety and effectiveness of COVID-19 vaccines. As an epidemiologist with more than a decade of experience conducting pediatric infectious disease research, I know that vaccines are the best way to protect people from COVID-19 and are our best hope for ending the pandemic. As you continue your discussions today and in the future, I urge you not to minimize the risk of COVID-19 to our youngest children under 5 years of age. To date, almost 10 million children have been diagnosed with COVID-19, with almost 2 million cases and almost 400 deaths occurring in children younger than 5. Early in the pandemic, compared to the elderly, children were thought to be relatively unaffected by COVID-19 and pediatric hospitalizations and deaths have been largely overshadowed, causing many requesting the need for COVID-19 vaccine for children. However, with the arrival of the Omicron variant, children's hospitals across the nation have reported dramatic increases in COVID-19 hospitalizations. As we continue to vaccinate persons 5 years of age and older, we drive COVID-19 into the unprotected group of our youngest children. As a result, hospitalization rates in children younger than 5 years are the highest they've been at any point in the pandemic, peaking in January at almost 5 times higher than they were last year. Children younger than 5 are typically unable to wear masks for extended periods of time and don't understand the concept of social distancing. At the same time, we know that interaction with other children and early childhood education are essential for child development. Parents of young children have

no good choices. They must either accept the risk of infection as a consequence of social interactions in preschool attendance in communities with high levels of COVID-19 and minimal mitigation measures, or they must forgo the important benefits these activities confer. They deserve better options. Although the immunogenicity of 2-dose primary series of COVID-19 vaccines for children under the age of 5 produced a less than best immune response than desired, there is every reason to believe that it provides some protection. The safety profile of this vaccine is reassuring, and the third dose currently being studied is expected to provide comparable protection in COVID-19 vaccines given to older children and adults. For these reasons, ACIP must act expeditiously to recommend COVID-19 vaccines for children younger than 5 years of age as soon as emergency use authorization is granted. As we approach the 2-year mark of the COVID-19 pandemic, we must do everything we can to minimize further detrimental effects to young children, many of whom cannot remember life before the pandemic. COVID-19 vaccines are safe and effective for children of all ages, and I urge you to give these factors your every consideration. Thank you for your time.

Mr. Kermit Kubitz
Individual

Good morning. My name is Kermit Kubitz, and I support the comments before me of the National Consumers League and the transplant group. The success and positive benefit-risk of COVID-19 vaccines is clear, and the most important slide that I saw in the presentations this morning was the success in vaccination of preventing more than 10 million hospitalizations and more than 1.1 million deaths. That is, without the COVID-19 vaccines, we could have had 2 million deaths from COVID-19 in the United States instead of the 890,000 so far, and further vaccination will allow a return to normalcy. So, I support the COVID-19 vaccine BLA for Moderna. Increased vaccination will allow a return to normalcy. Denmark, for example, has recently lifted COVID restrictions because of its high vaccination rate of more than 80% compared to the US of about 64% fully vaccinated. If we want a return to normalcy, if we want a return to schools without masks, if we want a return to dining in restaurants, if we want a return to meeting in groups—we must have vaccinations to the level that reduces the pandemic to an endemic, if that is the future. I also support rapid development and approval of lower-cost vaccines like Biological E's Corbevax™, which is capable of promoting more widespread worldwide vaccination. The development of variants around the world threatens all of us. No one is protected until everyone in the world is protected. We must support global vaccine equity and increased vaccination of the 70% of the world, which has not received the same vaccination levels in the United States. And I want to thank all the doctors and nurses around the country struggling with the pandemic and the result of the pandemic of the unvaccinated causing hospitals to be overwhelmed. Thank you CDC, and FDA, and ACIP members for all you do.

Aaron Prosser, MD, MSc
McMaster University

I want to thank the committee for the opportunity to provide comments. My name is Dr. Aaron Prosser, Medical Resident at McMaster University in Canada. COVID-19 vaccines have been a vital tool for reducing the burden of this disease on healthcare systems. My comments pertain to COVID-19 vaccine mandates. This is because policy set by the CDC influences whether COVID-19 vaccination will, for example, be a condition of employment or education. In addition to increasing vaccination levels, mandates isolate those who remain unvaccinated from accessing various settings. The hope is isolation will reduce transmission from the unvaccinated. This is based on the idea that unvaccinated people are at high absolute risk of transmission in non-household settings. These risks are thought to be high enough to justify

excluding the unvaccinated. However, these absolute risks have not been quantified. The arithmetic is simple and the data is publicly available. These absolute risks are the combined probabilities that an unvaccinated person gets infected and transmits COVID-19 in a given type of setting. My colleagues and I have quantified these absolute risks in a recent paper for which a preprint is timely. Dividing one by these absolute risks gives the metric similar to the number needed to treat, which we call the number needed to isolate. In the United States, once a wave of infections subsides, we found that on any given day the absolute risk of a transmission event in healthcare or educational settings is between 1 in 1,000 and 1 in 3,000. In other words, on any given day, we would have to exclude between 1,000 and 3,000 unvaccinated people from working in healthcare or accessing education to prevent one transmission event. Please know, this is to prevent usually mild, sometimes asymptomatic infections, especially given the high levels of immunity already present in the population, particularly the most vulnerable. And so, my comment is one of proportionality and compassion. COVID-19 has been devastating. COVID-19 vaccines are beneficial, especially for preventing severe illness, but our policy responses towards the unvaccinated people needs to be proportionate to the risks, compassionate to the harms of these policies, and open to accommodation. In medicine, there is a clinical intuition that if one has to apply an intervention to hundreds or thousands of people to extract one benefit, a careful weighing of harms and benefits is needed. We may disagree with the viewpoints of people who remain unvaccinated, but we must consider the harms of exclusion through mandates, which includes making people unemployed, unemployable, and unable to access education. My one request is that you clarify your position on COVID-19 vaccine mandates. Since your decision today on this question will echo throughout the United States and beyond, I think it is important that this be part of the public record. Thank you very much for your time.

Mr. Steven Kirsch
Executive Director
Vaccine Safety Research Foundation

My name is Steven Kirsch. I'm the Executive Director of the Vaccine Safety Research Foundation. I have no conflicts. My remarks, as well as all the supporting data, are posted on my website at stevekirsch.substack.com. There are 4 compelling reasons why you should not approve the Moderna vaccine. Reason number one, after 90 days, the Moderna vaccine has negative efficacy against Omicron. You cannot possibly approve a vaccine which after just 90 days shows negative efficacy against the predominant variant. This was very clearly shown for the Moderna vaccine in the Denmark study and subsequently confirmed by data from the German government. There are now over 13 studies including the famous Harvard study that clearly shows that the infection rate is highest in those countries with the greatest vaccination rate. If the vaccines worked as claimed, how do you explain these studies? Reason number two, the Moderna vaccine kills more people than it's likely to save. A conservative estimate of the number of deaths using the VAERS data and the CDC's own methodology shows the Moderna vaccine has killed at least 64,000 people. The Moderna trial data shows that over 13,000 lives may have been saved, but that is optimistic because the dominant variant has shifted. In short, the Moderna vaccine will kill at least 4.8 people from all-cause mortality for every life we might save from COVID. It simply makes no sense. Reason number three, the vaccine fails on an absolute safety basis. The Moderna vaccine kills at least 643 people per million, as I just pointed out. That makes these vaccines nearly 1,000 times deadlier than the smallpox vaccine, which previously was the most deadly vaccine in human history and is considered too unsafe to use by experts. Reasons number four, you should not approve the vaccine until you see all the safety signals. Although the Phase 3 trials claim no safety concerns were identified, there are hundreds of very serious adverse events that are being ignored. For

example, according the VAERS US data, the average rate of pulmonary embolism reports is just 3 per year. With Moderna, we have 1,245 events—415 times normal. How can that not be flagged as an adverse event? The only way that can happen is if the people who are in charge of monitoring the safety signals are either blind or corrupt. The public is not being informed of hundreds of safety signals like this. Some people believe that the reports in VAERS are unreliable. There's no evidence of this. In fact, the individual doctors report seeing adverse event rates that are 20,000 times higher than any other vaccine. These doctors are afraid to speak out due to threats and intimidation by state medical boards and others. There were Facebook vaccine injury support groups with 250,000 people that were deleted by Facebook. Both of these anecdotes are impossible to explain if the COVID vaccines are truly safe and effective as claimed. Again, all of the supporting data is posted to my substack at stevekirsch.substack.com. Thank you.

Dr. David Wiseman, PhD
Synechion

FDA has repeated the regulatory misdirection used for collinearity by BLA-approving a non-available Spikevax® and maintaining an EUA for a legally distinct Moderna product with "certain differences that do not impact safety or effectiveness." This nonsense, somewhat repeated in a presentation later today, was rationalized at the August 30th ACIP by the suggestion that full approval of one quasi vaccine would motivate 31% of vaccine-hesitants to take any of the 3 vaccines. This product is obsolete. Its pre-Omicron efficacy is irrelevant to this discussion, and no Omicron data have been presented today. The Spikevax® indication is prevention of COVID, but it fails to meet FDA's guidance VE target of 50% with a lower confidence boundary of 30%. Not shown in the GRADE presentation later today is a Danish study with an initial 37% Omicron VE waning to negative 39% by 3 months. Neither is the Canadian Buchan study with VE starting around zero, dropping to minus 40%. The February 3rd UK report shows Omicron VE waning to around 50% by 5 weeks and below 30% by 15 weeks before the 5-month authorized boost interval. None of these support the indication of COVID prevention within FDA guidance. Whatever VE can be mangled out of Spikevax® with boosting with a risk of immune erosion would only have been relevant had 3 doses, not 2, been included in the BLA. With almost no benefit, we are left with risk. There has now been enough time to collect data, but the labels said there are insufficient data to inform risks in pregnancy, something similar to lactation as well. Yet CDC still recommends vaccination in pregnancy and lactation. The label and CDC statement compete regarding immunocompromised, who may have a diminished immune response to Spikevax®. The effects of Spikevax® on immunogenicity and male fertility have still not been evaluated. I have already written comments documenting 10 safety signals of death, coagulopathy, and thrombotic events. For myocarditis, FDA and Pfizer have ignored under-reporting by 4.8 times. A recent *MMWR* paper revealed VAERS has 6.5 times under-reporting for hospitalization in children. Though Spikevax® is not regulated as a gene therapy product, as Moderna said in a 2020 FCC filing, “We still lack the full sequence of this nucleoside modified mRNA.” Moderna's founders previously wrote that their first application will likely not be a vaccine because the tolerance of side effects is very low in healthy individuals. The use of booster doses was considered the last “whack-a-mole” according to Dr. Long at the last ACIP meeting, using an obsolete product that ventures into negative VE territory before the authorized boosting interval must surely put us way beyond the last whack-a-mole. Thank you.

Ms. Elizabeth Ditz
Vaccinate California

Good morning, Dr. Lee and committee members, and thanks for your tireless work in this pandemic. My name is Liz Ditz and I'm speaking for myself as a citizen and as a grandmother. I strongly support the BLA for the Moderna vaccine and moving with all due speed to approve vaccines for under 5. The effects of the pandemic are universal. They're also hyperlocal and vaccine access and other NPIs are noticeable. I live in San Mateo County, California. Because of the strong public health leadership in my county and state, we have been doing relatively well. Eight-six percent of county residents 5 years and older have been vaccinated. Omicron testing trends are going in the right direction, dropping from 16% positive at the beginning of January to a 7% rate on January 31st. But we are failing to reach some of our most vulnerable populations. The Pacific Island population, the Black/African American community, and the Hispanic population are all less than 63% fully vaccinated. The February 1 report from the Kaiser Family Foundation is for me hard to put a shine on as 8 in 10 parents have unvaccinated kids and say that Omicron doesn't make a difference, and 1/4 of the parents stated they will definitely not get their 12 to 17-year-olds vaccinated for COVID-19. Why the resistance? On February 3rd, Brandy Zadrozny and other anti-vaccine national groups have enjoyed a pandemic windfall. She reported that Del Bigtree's Informed Consent Action Network reported $5.5 million in revenue in 2020, a 60% increase over 2019. Robert Kennedy's organization, Children's Health Defense, more than doubled its revenue in 2020. By contrast, 2 pro-public health groups, Voices for Vaccines' budget was $600,000 and Vaccinate Your Family noted that they had $1.6 million in revenue. Pro-public health groups are woefully losing the funding and so these bad ideas spread. I'd like to point your attention to the Urgency of Normal group that has developed a platform for parents to convince school boards to give up NPIs and throw it open. I have no solutions other than to push back against these ideas. The right to health is a fundamental right—even for the smallest children. None of us in safe until all of us are safe. Thank you for this opportunity to share my concerns with you.

Evelyn Pineiro
Parent

Good morning. As an informed member of the public, a teacher, a mother of small children, I am in complete support of the BLA for the Moderna vaccine. I also belong to a group of parents and physicians called Protecting the Future, and we specifically implore you to expedite the authorization of this vaccine for children under 5 once it's deemed safe and effective. This is the only segment of the population who does not have access to a vaccine. Pediatric hospitalizations surged during the Omicron wave, and a full half of them in New York were from the 0-5 age group. At a time when districts are repealing their masking mandates and going back to normal, which mine just did last night, we still have no normal. I have no protection for my preschooler in school now, and parents of children under 5 note the same thing to me. While myocarditis has been a side effect under discussion, physicians note that this doesn't seem to be an issue in prepubescent children. If the committee feels they must limit usage to certain age groups due to this risk, we ask you to humbly bypass the age de-escalation barriers that would prevent the vaccine from being used in the younger age groups. We do have the upcoming possibility of a Pfizer vaccine, but especially in the 2 to 4-year-old population, this will be the subject of much debate. We desperately need access to the Moderna vaccine for the under 5 age group. In addition, I also implore you to allow off-label use for our children, especially those at high risk. Once Moderna is deemed safe and effective in the under-5 age group, please do everything in your power to expedite its EUA, including bypassing age de-escalation barriers.

Updates on Myocarditis and Pericarditis Following Moderna COVID-19 Vaccination

Tom Shimabukuro, MD, MPH, MBA (Vaccine Safety Team, CDC COVID-19 Vaccine Task Force) provided an update on myocarditis and pericarditis following Moderna COVID-19 vaccination in terms of the reporting rates of myocarditis following Moderna COVID-19 primary series vaccination and the Vaccine Adverse Event Reporting System (VAERS) among persons ages 18 years and older; care and outcomes of persons ≥18 years of age with myocarditis after Moderna primary series vaccination reported to VAERS; and a Vaccine Safety Datalink (VSD) subgroup analysis of confirmed myocarditis and pericarditis cases after primary series Moderna vaccination among persons aged 18-39 years.

VAERS is the nation's early warning system for vaccine safety. It is a spontaneous reporting or passive surveillance system that is comanaged by CDC and FDA and has been in effect since 1990. As a passive surveillance system, VAERS accepts reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. The key strength for VAERS is that it can rapidly detect potential safety problems and rare AEs. Key limitations of VAERS is that it is a passive surveillance system with spontaneous reporting that is subject to include inconsistent quality and completeness of information; there are reporting biases; and generally, cause-and-effect cannot be determined from VAERS data alone. Reports to VAERS do not necessarily mean that the vaccine caused the AE.

Beginning with reporting rates per 1 million doses administered of myocarditis among males after Moderna COVID-19 vaccination in Days 0-7 after vaccination, Day 0 was the day of vaccination. Through January 13, 2022, there had been 76.6 million total doses of Moderna COVID-19 vaccine administered to males. This includes both Dose 1 and Dose 2. Through that time, there have been 283 myocarditis case reports in Days 0-7 after vaccination that met the CDC case definition. These reports were followed-up for medical records or interviews the providers to confirm that the case report met the CDC case definition. After Dose 1 in the age groups 18- 24, 25-29, and 30-29, the reporting rate exceeded the background incidents a 5.8 per million, 2.9 per million, and 3.3 per million, respectively. After Dose 2, the reporting rates exceeded background incidence in the 18-24, 25-29, 30-39, and 40-49 age groups. Reporting rates were consistently higher after Dose 2 versus Dose 1. However, reporting rates do not exceed incidence in the 50-64 and 65+ groups and there is not much difference between Dose 1 and Dose 2 as might be expected. Roughly 85.7 million total doses of Moderna administered to females during this same time period. During this analytic period, there were 76 myocarditis case reports in Days 0-7 that met the CDC case definition. The reporting rates exceeded background incidence after Dose 2 in the age groups 18-24 and 25-29. The reporting rates exceeded background incidence in more age groups for males for Dose 1 and Dose 2 and the overall reporting rates were higher.

In terms of the care and outcomes of myocarditis cases reported to VAERS after the Moderna primary series among persons aged 18 years and older in the 0-7 days after vaccination, of the 359 case reports meeting the case definition, 337 were hospitalized, 335 were discharged, 230 (69%) were known to have recovered from symptoms at the time of the report, 2 had disposition under review, and 22 were not hospitalized—they were seen in an emergency department (ED), urgent care, outpatient clinic, or it was not specified.

The Vaccine Safety Datalink (VSD) is a collaborative project between CDC and 9 integrated healthcare organizations across the country. This is an electronic health record-based system that was established in 1990. Rapid Cycle Analysis (RCA) is conducted in the VSD to monitor the safety of COVID-19 vaccines weekly, using prespecified outcomes of interest among the VSD member population and to describe uptake of COVID-19 vaccines over time among eligible VSD members overall and by strata of age, sex, race, and ethnicity. Monitoring began in December 2020 when the vaccines became available. The VSD COVID-19 vaccine RCA prespecified surveillance outcomes and settings in which they are monitored are shown in this table:

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction – **First Ever**	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis – **First in 7 days**	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy – **First Ever**	Emergency dept, Inpatient, Outpatient
Cerebral venous sinus thrombosis	Emergency dept, Inpatient
Disseminated intravascular coagulation	Emergency dept, Inpatient
Encephalitis / myelitis / encephalomyelitis	Emergency dept, Inpatient
Guillain-Barré syndrome	Emergency dept, Inpatient
Immune thrombocytopenia	Emergency dept, Inpatient, Outpatient
Kawasaki disease	Emergency dept, Inpatient
Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A)	Emergency dept, Inpatient
Myocarditis / pericarditis – **First in 60 Days**	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism – **First Ever**	Emergency dept, Inpatient
Seizures	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome – **First Ever**	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism – **First Ever**	Emergency dept, Inpatient, Outpatient

In terms of the analytic strategy for the primary analysis, the number of outcomes observed in the risk interval after vaccination were compared to the number expected. The expected counts were derived from vaccinated concurrent comparators who were in a comparison interval 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. The comparisons were adjusted for age group, sex, race/ethnicity, VSD site, and calendar date. The myocarditis and pericarditis electronic case identification follows a pathway. Cases are initially identified using the following International Classification of Disease (ICD)-10 codes:

- ❑ B33.22 Viral myocarditis
- ❑ B33.23 Viral pericarditis
- ❑ I30.* Acute pericarditis
- ❑ I40.* Acute myocarditis
- ❑ I51.4 Myocarditis, unspecified
- ❑ I31.9 Disease of the pericardium, unspecified

This is followed by chart review and adjudication of these cases by clinical subject matter experts (SMEs) using the CDC case definition.

Through the analytic period, there were about 923,000 Moderna Dose 1 and about 901,000 Moderna Dose 2. This table shows confirmed myocarditis and pericarditis cases identified in the Day 0-7 risk interval among persons 18-39 years of age compared with outcome events in vaccinated comparators on the same calendar days from Moderna COVID-19 vaccination through January 15, 2022:

Moderna COVID-19 vaccine	Events in risk interval, 0–7d* (per million doses)	Events in comparison interval, 22–42d*	Adjusted rate ratio† (95% CI)	2-sided P-value	Excess cases in risk interval (per million doses)
Both doses	38 (21.1)	7	9.18 (4.12 – 22.89)	<0.001	18.8
Dose 1	9 (9.7)	7	3.46 (1.12 – 11.07)	0.031	6.9
Dose 2	29 (33.0)	4	18.75 (6.73 – 64.94)	<0.001	31.2
Dose 2 males	26 (65.7)	4	16.96 (6.02 – 59.17)	<0.001	61.8
Dose 2 females	3 (6.2)	0	NE‡ (0.93 – ∞)	0.056	6.2

For Dose 1, the adjusted rate ratio is 3.46 and is statistically significant. That equates to an excess in cases of 6.9 per million doses administered. For Dose 2, the adjusted rate ratio is 18.75 and is highly statistically significant with a confidence interval from about 6.7 up to 65. This equates to 31.2 excess cases in the risk interval per million doses administered. The 2 bottom rows are subsets of Dose 2 looking at males and females separately. The adjusted rate ratio in males is 16.96 with a confidence interval of 6 up to about 59, with excess cases of 61.8 per million doses administered. For Dose 2, females had a small number of events. The adjusted rate ratio was not estimable because there were no events in the comparison interval. It was possible to calculate a lower bound of the 95% confidence interval, which was 6.2 excess case in the risk interval per million doses administered.

Discussion Summary

Related to a public comment made earlier, Dr. Poehling asked Dr. Shimabukuro to help explain the difference in the reported cases of myocarditis and those that met the CDC definition and why that is so important.

Dr. Shimabukuro indicated that the VAERS data are based on spontaneous reports that anyone can submit (patient, parent, healthcare provider, caregiver). These reports come into CDC in different states of completeness. When reports are received that are suspicious for myocarditis, CDC tries to contact the healthcare provider or the healthcare facility to obtain medical records in order to review them for missing information in the report, confirm information in the report, or correct information that may be erroneous in the report. They sometimes speak to the healthcare provider over the phone and are able to gather enough information to be confident in applying the CDC case definitions for myocarditis and pericarditis, which are published in the *MMWR*. This adjudication is done by clinicians who are trained in doing this. The reports are classified by those that meet the CDC case definition, those that do not have enough information to evaluate, and those that for which the information that is provided leads CDC to believe that this is not a true case of myocarditis. The reporting rate analyses in the evaluation of these reports is based on reports that have been reviewed and adjudicated to meet the CDC case definition.

Dr. Loehr asked whether the Day 8 to 21 window was assessed for comparison. For instance, he wondered what would happen with a report of someone having chest pain and elevated troponin on Day 10 after the vaccine.

Dr. Shimabukuro indicated that they also do that analysis and follow-up on these in the enhanced surveillance. Follow-up in done on all cases that meet the CDC case definition for myocarditis. It is known from VAERS, VSD, and data that have been generated from international partners that these cases cluster in Days 2, 3, and 4 after vaccination. In order to focus the analysis for this particular presentation, the decision was made to concentrate on cases that present or have symptom onset within the week of vaccination. They have performed analyses that assess other intervals, mainly up to 21 days.

Dr. Brooks asked whether the rate in the Day 22 to 42 window was equivalent to what is expected based on the background. Of the 359 cases in the VAERS data, he asked whether there were any additional data on the 2 under review and if there were any deaths.

Dr. Shimabukuro indicated that he did not have the VSD data for the 22-42 days post-vaccination. In terms of the interval question, the VSD has assessed the Days 0-7 and 0-21 windows and have noticed that most reports are concentrated in Days 0-7. Therefore, they are confident that the vaccine-associated cases tend to cluster fairly closely after vaccination. Regarding follow-up on the reports after receipt of the primary series of Moderna vaccination, there are reports of deaths in which there was histopathologic or clinical evidence of myocarditis following vaccination, and CDC has thoroughly reviewed those cases and has not been able to conclude definitively that the vaccine was in the causal pathway for the deaths. Looking at all deaths, not just those among Moderna vaccine recipients, there have been death reports to VAERS among persons under 30 years of age with myocarditis after a primary series mRNA vaccination. There were 13 death reports with concern for myocarditis identified through January. Of these, 3 did not have adequate information available to assess. For instance, there may have been clinical evidence of myocarditis but additional tests and/or an autopsy were not performed. This left 10 with available information. Of those 10, 2 are ongoing and evaluation has been completed for the other 8 cases. Of those, 3 were not myocarditis and 5 were myocarditis. All 5 deemed to be myocarditis had other potential etiologies identified, which left no deaths related to the vaccine.

Dr. Sanchez observed that in the randomized study, it would be important to know whether cases that occurred later at around 43 days after Dose 2 were related to vaccine administration. He also recalled that there was an increase in males in 40-49 years of age, but that was not part of the analysis.

Referring to Slide 5, Dr. Shimabukuro indicated that the VAERS analysis identified an increased reporting rate above what would be expected based on the baseline rates in males aged 40-49 years after Dose 2. That age group is being monitored for myocarditis the VSD, as are all ages. When CDC performed their analysis, it was restricted to the 18-39 age group for Moderna. That was largely a numbers issue as the more it is extended, the less numbers there are relative to doses administered. Therefore, the analysis was based largely on the number of cases.

Update on Myocarditis Outcomes: MOVING

Ian Kracalik PhD MPH (Vaccine Safety Team, CDC COVID-19 Vaccine Task Force) provided an update on myocarditis outcomes following mRNA COVID-19 vaccination. There is evidence from safety monitoring systems in multiple countries that supports the finding of an increased but small risk of myocarditis following mRNA COVID-19 vaccination.[8] This risk of vaccine-associated myocarditis appears to be highest in adolescent and young adults, males compared to females, and following Dose 2 compared to Dose 1. Onset is typically within a few days of vaccination, with most presenting within the week following vaccination. The severity of cases varies. Most who presented to medical care have responded well to medications and rest. Assessment of myocarditis health effects after COVID-19 vaccination are in progress.

CDC initiated enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports. The purpose of this enhanced surveillance was to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after receiving and mRNA COVID-19 vaccination. This enhanced surveillance involved a 2-component survey conducted at least 90 days after the onset of myocarditis symptoms. The first component was a patient survey focused on persons 12-29 years of age to ascertain functional status, clinical symptoms, quality of life measures, and the need for medication or other medical treatment. The second component was a healthcare provider survey, the objective of which was to gather data on cardiac health and functional status. The timeline for data collection was approximately August 2021 through January 2022.

First, preliminary data from surveys of patients 12-29 years of age at least 90 days post-myocarditis diagnosis. As of November 2021, VAERS had received approximately 989 reports of myocarditis or myopericarditis after COVID-19 vaccination that met the CDC case definition. Of these, approximately 850 patients aged 12-29 years had reached 90 days post-myocarditis diagnosis. Of the approximately 850 patients 90 days post diagnosis, 81% had a phone number listed. Of the 648 who were called, 56% completed the survey, 42% were unreachable, and 3% declined to participate. For the 360 patients interviewed, the time from myocarditis onset to interview was 143 days, with an interquartile range of 131 to 162 days.

In terms of some of the demographic characteristics, most patients diagnosed with myocarditis were young males. The median patient age was 18 years, with an interquartile range of 15 to 22 years. Of the 360 patients 90 days post-myocarditis diagnosis, 86% or 308 were males. Most patients were White, non-Hispanic. Hispanic of any race made up 20% of patients. Asian non-Hispanic comprised 5%. Black, non-Hispanic and multi-racial, non-Hispanic made up 4% each. Other, non-Hispanic were 3% and American Indian or Alaskan Native (AI/AN), non-Hispanic comprised less than 1%.

Prior to myocarditis diagnosis, 87% of patients reported having received 2 doses of a COVID-19 vaccine. Of those who received 2 doses, 98% reported receiving both doses before they were diagnosed with myocarditis and 9% had evidence of COVID-19 with a positive COVID-19 test before their myocarditis diagnosis. Looking at some of the self-reported previous medical history among these patients with myocarditis after mRNA COVID-19 vaccination, 17% reported having any condition, 3% reported having an arrhythmia. 2% each had congenital heart disease or a history of myocarditis, less than 1% had Kawasaki disease or a history of previous heart failure, 9% had a history of asthma, 2% had an autoimmune disorder, 1% each had a genetic or chromosomal condition or were immunosuppressed, and then less than 1% each had a history

[8] https://www.who.int/news/item/09-07-2021-gacvs-guidance-myocarditis-pericarditis-covid-19-mrna-vaccines

of leukemia or Type I diabetes. Most patients with myocarditis after receiving COVID-19 vaccination reported being hospitalized at the time of their diagnosis. Of the patients with myocarditis post-vaccination, 92% were hospitalized and 4% were readmitted following myocarditis. Of those who were readmitted, 62% were readmitted because of the concern with the heart and 20% had been prescribed medication for their heart at their last appointment with their provider. Looking at absenteeism related to missed school or work within the 2 weeks prior to the date of the interview reported among patients, 8% reported missing school. Of these, 37% believed it was due to their myocarditis. Of the 5% who reported missing work, 37% believed it was due to their myocarditis.

Self-reported symptoms within 2 weeks prior to the date of the interview among myocarditis patients included chest pain, shortness of breath, palpitations, and/or fatigue. About a third were experiencing chest pain and about a quarter each were experiencing shortness of breath, palpitations, and fatigue. In terms of any symptom reported across all patients, 49% reported experiencing at least one of these symptoms in the prior 2 weeks of the interview.

The EuroQoL 5-dimension, 5-level (EuroQol-5D-5L) severity measurement of health status among patients who developed myocarditis after vaccination was used to assess the patients' quality of life in terms of their ability for self-care, their mobility, their ability to perform usual activities, whether they were experiencing any pain or discomfort, and whether they were experiencing any anxiousness or depression. The 5 levels of severity measurements can range from experiencing no problems to experiencing extreme problems. Most patients reported experiencing no problems with self-care, mobility, usual activities, or pain or discomfort. However, almost half experienced anxiousness or depression.

Next, preliminary data from completed cardiologist or other healthcare provider (HCP) surveys. Outreach to cardiologists or other HCP involved interviews with 360 of the 648 patients. About 346 of these patients listed contact information for a cardiologist or other HCP. Of the 346 providers for whom contact information was provided, 229 completed the survey. An additional 151 providers completed the surveys they had submitted for multiple patients in VAERS or provided contact information via the VAERS report. CDC was unable to reach 268 providers. In total, 380 providers completed the survey with a median of 191 days and interquartile range of 170 to 216 days from a patient's myocarditis onset to the date of the provider's survey. A proportion of myocarditis patients cleared for physical activity by their cardiologist or healthcare provider had increased. At the time of myocarditis diagnosis, 83% of patients had restrictions on their physical activity. At the time of the provider's survey at least 90 days post-diagnosis, only 39% had restrictions on physical activity.

Based on the cardiologist or other healthcare provider assessment, most patients appeared to have fully or probably fully recovered from their myocarditis. In total, 81% of cardiologists or healthcare providers indicated that the patient was fully or probably recovered and more than 90% showed some improvement. Looking at the proportion of myocarditis patients deemed to be fully or probably fully recovered by their HCP, about 80% of patients were fully or probably fully recovered at about Week 38. Regarding results from the most recent cardiac function test or biomarker test among 6 specific tests (e.g., troponin, cardiac MRI, echocardiogram, electrocardiogram, exercise stress test, and ambulatory rhythm monitoring), the most the recent cardiac function tests were normal with the exception of cardiac MRIs, which were abnormal.

Looking more closely at abnormal findings from the most recently cardiac function tests, for a cardiac MRI, the most common abnormal finding on cardiac MRI was late gadolinium enhancement. On the electrocardiogram, the most common abnormal finding was T wave abnormalities. For the exercise stress test, there other cardiac concerns were identified. During ambulatory rhythm monitoring, the most common abnormality found was an arrhythmia. Overlapping the abnormal findings among the most recent cardiac function tests, 51% of abnormal MRI findings also had an elevated troponin, 25% of abnormal MRIs also had an abnormal EKG, 3% of abnormal MRIs also had an abnormal ambulatory rhythm monitoring finding, and 1% of abnormal MRIs also had an abnormal exercise stress test finding. There was a low percentage of abnormal findings for the most part in the overlap of abnormal echocardiogram findings and abnormal findings among the other tests.

Comparing cardiac function tests at the time of diagnosis and the time of follow-up, many patients did not have an initial cardiac MRI performed. Those with an initial cardiac MRI that was abnormal (79%) also did not have a follow-up cardiac MRI. Most patients had an initial echocardiogram that was normal and a follow-up echocardiogram that was normal. There were 17 patients who had a follow-up echocardiogram that was abnormal. Most patients who had an initial troponin that was elevated did not receive a follow-up test or the test was not available. One follow-up, 20 patients had an elevated troponin level. Looking at the cardiac assessment and symptoms among patients deemed to be recovered and not recovered in their myocarditis, few patients among those deemed to be fully or probably fully recovered had a complete normal baseline function or absence of symptoms across this subset of tests and clinical assessments. Some also had normal baseline function, but were missing cardiac MRI results. Even among patients deemed not recovered, some had normal or baseline function or absence of symptoms across all of the subsets of tests and clinical assessments, which suggests that there is some heterogeneity in the way patients are deemed recovered and there is likely a lot of HCP judgment in the assessment of these patients.

In summary, at least 90 days after myocarditis diagnosis, most patients reported no impact on their quality of life and most did not report missing school or work. A few were readmitted to the hospital. Most HCP indicated the patient probably or fully recovered. However, there did not appear to be a single test that was indicative of recovery. To CDC's knowledge, there were no vaccine-associated myocarditis deaths in this group of patients they interviewed. Currently, there are ongoing efforts to continue patient follow-up and contact of myocarditis patients who were not yet recovered at the time of the survey. Additional surveys are being modified for children 5-11 years of age for whom follow-up will begin in February 2022.

Discussion Summary

Dr. Poehling noted that these analyses focused individuals 12-29 years of age in the VAERS database and that some of the numbers looked different from what Dr. Shimabukuro presented earlier. She inquired whether she was correct to assume that the data just presented included Pfizer or Moderna vaccines and this was why the numbers differed.

Dr. Kracalik confirmed that the data he presented were for both the Pfizer and Moderna vaccines.

Ms. Bahta asked whether the surveys assessed social or behavioral impact and if so, whether those types of impact from the myocarditis have been resolving. Looking at Slide 19, it appeared to her that 50% recovery happened shortly after 16 weeks. That is a long time for a person with limited activity or who may not be able to work or attend school. She emphasized

the importance of assessing no only the physiology, but also the whole impact on a person who ended up with myocarditis after getting vaccinated.

Dr. Kracalik indicated that they attempted to get at this using the EuroQol-5D-5L, which does assess measures such as anxiousness, depression and the ability to perform usual activities. While most appeared to be able to perform usual activities, about half were experiencing some level of anxiousness or depression that could have been extreme.

Dr. Lee expressed gratitude to the teams involved in this study. The ACIP recognizes that the study went above and beyond to respond to the pandemic and ensure that the committee and the public had the information needed about the long-term follow-up of these cases. The medical information from long-term cardiology follow-up continues to reflect disease that is mild and consistent with what has been seen previously. What she found remarkable and telling was that some of the patient- and family-centered measures, such as the EuroQol-5D-5L measures, showed that there is substantial impact on individuals. They also must acknowledge that these data likely reflect the experience that many people are having living through this pandemic, regardless of whether they have been infected or vaccinated. She is hopeful that other ongoing studies supported by the CDC, NIH, and FDA will continue to shed light on the impact of this pandemic on children and young adults.

Dr. Kotton emphasized that these data, while clearly robust, interesting, and helpful to see, do not allow them to understand what this means in isolation. Most of time in the medical world, they do not look at data without a control population or other populations to compare to. She encouraged CDC to assess people who had myocarditis from true infections, which has been devastating and has a much bigger impact. For the epidemiology, it would be helpful to have controlled populations. Without good comparison populations, there is some danger in focusing on vaccines and myocarditis when the “elephant in the room” is true disease and true infection from COVID-19 and the potentially devastating, even life-threatening myocarditis, occurring in that context.

In terms of the data on those fully recovered versus not fully recovered, Dr. Brooks observed that the top 4 (shortness of breath, chest pain, daily medication, and physical activity) were the ones the patient would feel, while the bottom 4 (troponin, ECHO, EKG, cMRI) were abnormal findings not found in the fully recovered. Troponin was elevated, but these patients recovered on quality of life relative to the physical findings, which is reassuring. For the public, it is important to do this dissection of myocarditis in order to have a more full picture of what is occurring.

VaST Assessment

H. Keipp Talbot, MD, MPH (VaST Chair) provided the VaST’s assessment of the data that was just presented and some other that have been reviewed. The objectives of VaST are to: 1) review, evaluate, and interpret post-authorization and approval of COVID-19 vaccination safety data; 2) serve as a central hub for technical subject matter expertise from federal agencies conducting post-authorization and approval safety monitoring; 3) advise on analysis, 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.[9]

[9] https://www.cdc.gov/vaccines/acip/workgroups.html

VaST continues to review COVID-19 vaccination safety data from passive and active surveillance systems. US safety monitoring systems include VAERS, VSD, the FDA Biologics Effectiveness and Safety (BEST) System,[10] the Department of Veterans Affairs (VA), Indian Health Service (IHS), and the Department of Defense (DoD). VaST also continues to work with international partners, including the Public Health Agency of Canada (PHAC) and the Global Advisory Committee on Vaccine Safety (GACVS). VaST also reviews special evaluations, such as the myocarditis case follow-up studies just presented.

From December 21, 2020 through February 4, 2022, VaST has had 45 independent meetings to review vaccine safety data. There also have been 12 joint meetings with ACIP COVID-19 Vaccines WG and 15 ACIP meeting presentations or reports with VaST assessments. VaST reviews of the Moderna COVID-19 vaccine post-authorization data have included CDC safety monitoring systems (VAERS, V-Safe, and VSD), other US monitoring systems, and systems of international partners.

Previously, VaST monitored anaphylaxis following mRNA COVID-19 vaccinations. Anaphylaxis following mRNA COVID-19 vaccines was identified in December of 2020. Safety data and VaST assessments were presented to ACIP in January and March 2021.[11] CDC and FDA recommended risk mitigation strategies, including screening for risk prior to vaccination, monitoring for symptoms post-vaccination, early recognition and management of anaphylaxis on-site, and provider and patient education by CDC and partners. Anaphylaxis following vaccination was reviewed again in August 2021 for the Pfizer BLA.[12] There has been no substantial change in the benefit-risk balance with risk mitigation strategies.

Myocarditis following mRNA COVID-19 vaccination was identified in May 2021.[13] CDC issued clinical guidance for myocarditis/pericarditis following mRNA vaccines in May 2021. Data were presented to the FDA VRBPAC on June 10, 2021. Data and a VaST assessment were presented during ACIP meetings on June 23, 2021[14] and an *MMWR* was published. EUA Fact Sheets were revised with a warning added June 25, 2021. FDA approval of the Pfizer/BioNTech COVID-19 vaccine on August 23, 2021, with information included on myocarditis/pericarditis in the package insert.[15] The FDA approved Moderna COVID-19 vaccine on January 31, 2021, with information on myocarditis/pericarditis in the package insert.[16]

Data from VAERS, which is a collaboration between CDC and FDA, reporting rates per 1 million doses administered of myocarditis in the window of 0-7 days after Moderna vaccination, showed that reporting rates exceeded background incidence in males after Dose 1 for males 18-39 years of age and especially after Dose 2 in males 18-49 years of age. In females, reporting rates exceeded background incidence after Dose 2 in those 18-29 years of age.[17]

[10] https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system
[11] https://www.cdc.gov/vaccines/acip/meetings/slides-2021-1-27-21.html; https://www.cdc.gov/vaccines/acip/meetings/slides-2021-02-28-03-01.html
[12] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/05-COVID-Lee-508.pdf
[13] https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html
[14] https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.htm
[15] https://www.fda.gov/media/151707/download
[16] https://www.fda.gov/media/155675/download
[17] Source: Shimabukuro, Feb 4, 2022 ACIP presentation

In VAERS for all mRNA vaccines, 359 reports met the CDC case definition among adults ≥18 years in the 0-7 days post-vaccination. Among those identified, 94% were hospitalized and almost 70% had recovered from symptoms at time of the VAERS report. In follow-up surveys of myocarditis cases in VAERS, 360 patients were interviewed with ≥ 90 days of follow-up. Of these, 92% were hospitalized. Among the 380 providers contacted, 81% indicated that the patient was fully or probably fully recovered. VSD information for Moderna vaccination alone identified 38 chart-confirmed cases among individuals 18-39 years of age, of whom 79% were hospitalized. Of the hospitalized patients, 75% were hospitalized for 2 days or less and 100% had been discharged to home.[18]

The VaST assessment is as follows. Data available to date show association of myocarditis with Moderna mRNA COVID-19 vaccination in adolescents and young adults. Risk is low overall, but highest in adolescent and young adult males—especially following Dose 2. Data continue to show that most cases of post-COVID-19 vaccination myocarditis appear to be clinically mild. More data are being accumulated and analyzed to further define myocarditis clinical course and risk. Presently, data do not suggest new safety concerns regarding Moderna vaccination among persons aged 18 years or older beyond those that have been previously identified and discussed.

VaST's work is not finished. In terms of next steps, VaST will continue to: 1) review data on myocarditis from national safety monitoring systems and manufacturer post-marketing requirements; 2) review real-time monitoring of vaccine safety as vaccination efforts expand to younger age groups, booster doses, and new vaccines; 3) collaborate across US federal agencies evaluating vaccine safety; 4) collaborate with global vaccine safety colleagues on key issues that impact benefit/risk; and 5) provide updates to the ACIP COVID-19 Vaccines WG and ACIP during future meetings.

Discussion Summary

Dr. Daley noted that as Dr. Talbot went through her presentation, he was struck by how she balanced what has been learned so far with the idea that there is still work to do. This work is going to extend across new indications and across learning more about the outcomes for the individuals with vaccination-associated myocarditis.

GRADE: Moderna COVID-19 Vaccine

Megan Wallace, DrPH, MPH (CDC/NCIRD) presented the GRADE assessment for Moderna COVID-19 vaccination for which the policy question was, "Should vaccination with Moderna COVID-19 vaccine be recommended for persons aged 18 years of age and older?" For the PICO question, the population under consideration is persons ages 18 years and older, the intervention is 2 doses of the Moderna COVID-19 vaccine, and the comparison is no vaccine. The WG identified these 6 outcomes their level of importance for the policy as: Symptomatic Laboratory-Confirmed COVID-19 (Critical), Hospitalization Due to COVID-19 (Critical), Death Due to COVID-19 (Important), Asymptomatic SARS-CoV-2 Infection (Important), SAEs (Critical), and Reactogenicity (Important). For all outcomes, data from randomized controlled trials (RCTs) were evaluated. For all benefits, observational studies of VE were evaluated. For SAEs, safety surveillance data were reviewed for specific outcomes.

[18] Sources: Shimabukuro, Feb 4, 2022 ACIP presentation; Kracalik, Feb 4, 2022 ACIP presentation; Klein, Feb 4, 2022 ACIP presentation

To identify relevant RCTs, the WG relied on clinicaltrials.gov as the source. Phase 1, 2, or 3 trials of Moderna COVID-19 vaccine were included that fit the PICO question. Additional resources were sought as well, including obtaining unpublished data from the vaccine manufacturer. To identify relevant VE studies, the WG used an ongoing, publicly available systematic review conducted by the International Vaccine Access Center (IVAC) and the World Health Organization (WHO) using studies identified through December 10, 2021. From this database, studies were selected that provided VE estimates for at least 1 of the benefits in the PICO question. Of note, only studies that specifically evaluated VE against symptomatic or asymptomatic infection were included. Studies that reported on VE against any infection were not included. Only studies that had estimates of VE specifically for the Moderna COVID-19 vaccine were include and not those that included estimates for mRNA vaccines as a group. The WG reviewed studies of the general population and of special populations as long as they included persons aged at least 18 years. For observational data on vaccine safety, in consultation with VaST, the WG included data from safety surveillance systems that have been presented to ACIP.

In terms of the evidence retrieval for all records included in the evidence synthesis, 127 records were identified from the IVAC systematic review and 7 were identified through other sources, including 5 records from clinical trials and 2 CDC safety surveillance systems. A total of 38 full text articles or other resources were assessed for eligibility and 33 were included in the evidence synthesis. A total of 26 records of observational studies were identified that met inclusion criteria and addressed one or more of the PICO outcomes. The WG conducted a risk of bias assessment using the Newcastle-Ottawa scale, which assigns up to 9 points based on specific criteria related to selection of cohorts, comparability of cohorts, and assessment of outcome or ascertainment of exposure. Studies with Newcastle-Ottawa scores less than 7 were considered to have serious study limitations.

For each outcome, the WG assessed the body of evidence for suitability for pooling. Given that the WG was working with the fluid evidence base that includes data that had not been peer-reviewed, they excluded estimates with serious limitations from the pooled estimates used for GRADE. If multiple studies were conducted in the same population, the most representative study was selected. Meta-analyses were conducted using the remaining studies. Initial estimates were evaluated for heterogeneity using I^2. Sensitivity analyses were conducted to assess the influence of study characteristics (e.g., special population vs. full population, preprint vs. peer-reviewed, standard/extended dosing interval, study design, circulating variants). The pooled estimates were developed to summarize the estimates across several studies succinctly for GRADE and described the best available real-world data for this policy question at this time. However, the WG acknowledges that the included studies represent different populations and times and that the science in this area is developing quickly. This GRADE analysis did not aim to parse out effects of time since vaccination or circulating variants in the VE studies.

The GRADE evidence type assesses the certainty of estimates from the available data. Initial evidence type is determined by the study design. A body of evidence from an RCT starts with an initial evidence type of 1, indicating high certainty. A body of evidence from observational study starts with an evidence type of 3, indicating low certainty. The evidence type can then be downgraded due to risk of bias, inconsistency in directness, or imprecision and other considerations could downgrade or upgrade the evidence type. The final evidence type may range from type 1 (high certainty), which indicates we are very confident the true effect lies close to that of the estimate, to type 4 (very low certainty), meaning the WG has little confidence in the effect estimate. The evidence type is not measuring the quality of individual studies, but

rather how much certainty there is in the quantitative estimates of effect across each outcome. For each outcome, Dr. Wallace reviewed data from RCTs and from observational studies and the GRADE assessment for both.

For the critical outcome of symptomatic COVID-19, 1 randomized study provided data. This was the Moderna Phase 3 RCT that was conducted in the US and enrolled over 30,000 participants.[19] The data were published and additional data were obtained directly from the sponsor. The WG used data through the unblinding date with a data cut-off date of May 4, 2021. Unblinded safety follow-up continues in trial participants. To consistently apply GRADE in a rapidly evolving pandemic, the WG considered the data for benefits in the context of the pandemic during the study time. Using the available efficacy population for all persons aged 18 years and older, there were 55 cases among 14,287 persons in the vaccine arm and 744 cases among 14,164 persons in the placebo arm, which resulted in a VE estimate of 92.7% and a 95% confidence interval of 90.4% to 94.4%. This is the primary outcome of the study and the outcome used for GRADE. VE also was over 90% in a number of key subgroups, including those aged 65 and older, 75 and older, those at risk due to the presence of a comorbidity, those aged 65 years and older and at risk, and those with evidence of prior infection. In terms of timing, VE remained above 90% through unblinding.

Moving on to the observational studies for symptomatic laboratory-confirmed COVID-19, Dr. Wallace briefly summarized the 14 VE studies reviewed that evaluated this outcome. The most common study design was test-negative design followed by retrospective and prospective cohort studies. Study locations were predominantly in North America. The pre-print study captured a more recent time period than the peer-reviewed studies. Among these 14 studies, 11 were included in the final pooled analysis for this outcome. The pooled VE estimate from the observational studies for the outcome of symptomatic laboratory-confirmed COVID-19 was 89.2%. For the GRADE assessment for the outcome of symptomatic laboratory-confirmed COVID-19, the WG evaluated data from 1 RCT for which the evidence type started at 1. The relative risk of 0.07 and 95% confidence interval strongly favored vaccination and there were no serious concerns in the certainty estimate. The final evidence certainty was Type 1 (high certainty) for this critical outcome. The WG evaluated 11 observational studies for this outcome. The relative risk of 0.11 strongly favored vaccination, with a 95% confidence interval of 0.06 to 0.18. There were no serious concerns in the certainty assessment and certainty increased due to strong association. For the observational studies, the final certainty was Type 2 (moderate).

The second outcome for consideration was hospitalization for COVID-19. The protocol included a definition of severe COVID-19 with at least 1 of the following: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. This did not necessarily require hospitalization. The WG obtained data on hospitalization due to COVID-19 from the sponsor as an ad hoc analysis. The 2 VE estimates from the RCT were severe COVID-19 and severe COVID-19 with hospitalization. VE against severe COVID-19, a secondary endpoint defined in the Phase 3 protocol, was 98.1%. For VE against severe COVID-19 requiring hospitalization, which was the PICO outcome and the outcome used for GRADE, the VE estimate was 95.9%. To summarize the 19 observational studies that evaluated VE against hospitalization due to COVID-19, the most common study design was test-negative design and study locations were predominantly in North America. Among the 19 observational studies, which provided 20 VE estimates, 14 studies providing 15 estimates were included in the final

[19] A) Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors; b) El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors

pooled analysis. For the outcome of hospitalization due to COVID-19, the pooled VE estimate was 94.8%.

For the GRADE assessment for the outcome of hospitalization due to COVID-19, the WG evaluated 1 RCT for which the evidence type started at 1. The relative risk of 0.04 (95% CI: 0.01–0.31) strongly favored vaccination but there were serious concerns of imprecision due to the small number of events observed from a single RCT. The final certainty estimate for hospitalization for COVID-19 based on RCT data was Type 2 (moderate certainty). The WG evaluated 14 observational studies which provided 15 VE estimates for this outcome for a pooled relative risk of 0.05 (95% CI: 0.04–0.07). There were no serious concerns in the certainty assessment and the certainty was increased due to a strong association. The final certainty estimate based on the observational data was Type 2 (moderate).

The next outcome was death due to COVID-19. This was a secondary efficacy endpoint in the trial protocol defined as "any participant who died during the study with a cause directly attributed to a complication of COVID-19." There were a total of 3 deaths due to COVID-19 among trial participants, all among placebo recipients. The available data indicate a VE of 100%. A total of 5 observational studies provided VE estimates for the outcome of death due to COVID-19. These were all cohort studies and the study locations were predominantly in North America. The pooled VE estimate from these studies was 93.8%. For the GRADE assessment for the outcome of death due to COVID-19, the WG evaluated 1 RCT. The relative risk of 0.14 (95% CI: 0.01 to 2.79) favored vaccination, but the very wide 95% confidence interval did not rule out harms, leading to very serious concern for imprecision due to the small number of events observed in a single RCT. The final evidence certainty was Type 3 (low certainty). The body of evidence from observational studies started with an evidence type of 3. There were no serious concerns in the certainty assessment. In light of the strong association, the certainty was raised one level to Type 2 (moderate certainty).

The next outcome of interest was asymptomatic SARS-CoV-2 infection, which was a secondary endpoint in the Phase 3 RCT. Asymptomatic SARS-CoV-2 infection was defined as having a "Negative SARS-CoV-2 status with both negative RT-PCR and negative binding antibody levels against SARS-CoV-2 at baseline prior to Dose 1; AND positive RP-PCR at the participant-decision visit; OR seroconversion due to infection assessed by binding antibody levels against SARS-CoV-2 at day 57 (28 days after Dose 2); AND absence of COVID-19 symptoms, including both symptoms for the primary endpoint of COVID-19 and the CDC definition of COVID-19." Using the per protocol population for all persons aged 18 years and older, the VE for asymptomatic infection was 57.4 (50.1, 63.6).

To summarize the 3 observational studies that examined VE against asymptomatic SARS-CoV-2 infection and met the inclusion criteria, all were peer-reviewed and 2 used a test-negative study design. The most recent data were from September 2021. Notably, there was substantial heterogeneity in the effect estimates. The pooled VE from these studies was 69.8% (95% CI: 60.9% to 76.7%). In the GRADE assessment of the outcome of asymptomatic infection, one RCT provided data. The relative risk of 0.43 (95% CI: 0.36–0.50) favored vaccination and there were no serious concerns in the certainty assessment. The final evidence certainty was Type (high certainty). The WG evaluated 3 observational studies that had a pooled relative risk of 0.30 (95% CI: 0.23–0.39). There was serious concern for inconsistency because the magnitude of relative risk from the 3 studies and the body of evidence varied widely. The final evidence certainty was Type 4 (very low).

In terms of the data for the GRADE evaluation of harms, 4 randomized studies provided data. These included the Phase 3 trial (Baden 2021, El Sahly 2021), the Phase 2 trial (Chu 2021), and 2 published articles on the Phase 1 trials that did not have an unvaccinated comparator (Jackson 2020; Anderson 2020). The Phase 3 study included data on persons aged 18 years and older in the US. The data evaluated had a final analysis cutoff date of May 4, 2021 and consisted of roughly 30,000 participants. The Phase 2 dose confirmation RCT enrolled healthy adults aged 18 years and older in the US. The WG evaluated data on the 200 participants who received the 100 µg dose and the 200 participants who received placebo. The primary outcomes for the Phase 2 trial for safety including reactogenicity and SAEs. From the Phase 2 trial, there were no SAEs in either treatment group. In the Phase 3 trial, SAEs were balanced across treatment groups, with 1.8% of vaccine recipients and 1.9% of placebo recipients reporting an SAE. There were 12 participants who reported 15 SAEs, which were deemed by blinded investigators to be related to vaccination.

The WG also assessed specific SAEs that have been identified in safety surveillance during the period of the EUA, which previously have been described to ACIP. An RCA from the VSD evaluated chart-reviewed cases of myocarditis occurring among persons aged 18-39 years following Dose 2. Based on events occurring in the 7-day risk interval after vaccination versus a comparison interval in vaccinated individuals, the adjusted rate ratio was 18.75 (6.73 – 64.94). Data from VAERS showed an elevated ratio of observed to expected chart-confirmed myocarditis cases in the 7-day interval following vaccination among females aged 18-29 years and among males aged 18-49 years, with higher observed to expected ratios in males and females. Although VAERS data are subject to the limitations of a passive surveillance system, the elevated risk of myocarditis following Moderna vaccination is consistent with that observed in VSD. Regarding anaphylaxis, an RCA of data from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged 18 years and older. Based on events occurring in a 0-1 day risk interval after vaccination, the estimated incidence of confirmed anaphylaxis was 5.1 (95% CI 3.3–7.6) per million doses.[20]

The GRADE assessment for SAEs was based on 2 RCTs. The pooled relative risk indicated a balance of SAEs between vaccinated and placebo groups with a relative risk of RR 0.92 (95% CI: 0.78–1.08). The certainty assessment was reduced 1 point due to serious concern of imprecision because the confidence interval indicates that both reduced and increased risk of SAEs are possible. The final evidence certainty was Type 2 (moderate certainty). The observational data concerning the specific SAEs of myocarditis and anaphylaxis included the description of the quantitative data described earlier. The WG started with Type 3 data from observational surveillance systems and did not decrease or increase the certainty. The final certainty was Type 3 (low certainty).

For the outcome of severe reactogenicity, the Phase 2 and 3 RCTs solicited events through electronic diaries for the 7 days following each dose. Both randomized studies used the same events and grading scales shown here:

- ❑ Grade 3: pain at injection site or axillary swelling/tenderness that prevents daily activity; redness >10 cm; and swelling >10 cm
- ❑ Grade 4: emergency room visit or hospitalization for severe pain at the injection site or axillary swelling/tenderness, necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only)

[20] Klein et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-1399

The local reaction solicited were injection site pain, redness, swelling, and axillary swelling and tenderness. The systemic events listed were fever, nausea and vomiting, headache, fatigue, chills, muscle pain, and joint pain. The events and grading scales are shown here:

- Grade 3: fever >38.9°C to 40.0°C, vomiting that requires IV hydration; fatigue, headache, muscle pain, or joint pain that prevents daily activity
- Grade 4: fever >40.0°C, fatigue, headache, muscle pain, joint pain, or vomiting that require emergency room visit or hospitalization

In the Phase 2 study, Grade 3 or 4 systemic events were reported in 16% of persons in the vaccine arm and 3% of persons in the placebo arm. In the Phase 3 study, Grade 3 or 4 reactions were reported by 22.6% of persons in the vaccine arm and 4.5% of persons in the placebo arm. Pooling the data from these 2 trials, the estimated relative risk for any Grade 3 or 4 event was 5.03 (95% CI: 4.65–5.45). There were no serious concerns in the certainty assessment. The final evidence certainty was Type 1 (high certainty).

To summarize the GRADE assessment for the Moderna COVID-19 vaccine, the data available for benefits indicate that the vaccine is effective for preventing symptomatic COVID-19 with high evidence certainty. For hospitalization and death, the available evidence favors the intervention and certainty was moderate. For asymptomatic SARS-CoV-2 infection, the available data favors the intervention with high evidence certainty. In terms of harms in the RCTs, SAEs were balanced between the vaccine and placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare but more common following vaccination. SAEs had moderate evidence certainty. In terms of reactogenicity, severe reactions were more common in vaccinated persons. In 21.3% of vaccine recipients versus 4.5% of placebo, recipients reported Grade 3 or 4 reactions. The evidence type for reactogenicity was high.

There are important limitations that should be acknowledged. In this rapidly evolving pandemic, the available body of evidence often does not represent the most recent epidemiology, including the impact of a new dominant variant on VE. The evidence available for inclusion in this GRADE analysis does not capture the impact of the Omicron variant on VE. The VE estimates presented represent the best estimates within the context of the pandemic during the time of the study, but may not be representative of VE in different phases of the pandemic or with different circulating variants. The evidence available for inclusion in this GRADE evaluation is predominantly from the time periods in which Alpha and Delta were the dominant circulating variants.

In conclusion, the GRADE evaluation focuses on recommendations following licensure of the Moderna COVID-19 vaccine that has been in use for a year under an EUA. Evidence for benefits are supported by a body of evidence comprised of 1 large Phase 3 RCT and numerous observational studies conducted worldwide. The RCT evidence demonstrated efficacy for all beneficial outcomes, including the 2 critical outcomes of symptomatic disease and hospitalization. Efficacy data were further supported by a body of evidence from observational studies. Regarding harms, Grade 3 reactions were more common in vaccine than placebo recipients. RCT evidence showed that SAEs occurred at a similar frequency in vaccine and placebo groups overall. However, 2 specific rare but serious AEs have been associated with vaccination as identified through safety surveillance systems.

Discussion Summary

Dr. Poehling offered very special thanks to the COVID-19 Vaccines WG for the tremendous amount of work they did in pooling these data and recognized how reassuring it was that the RCTs and the observational studies showed the same patterns.

Dr. Daley emphasized that these data are all very important and that Dr. Wallace presented them in a clear and consistent way. He noted that he was sitting at his desk, but would give her a standing ovation if he could.

EtR Framework: Moderna COVID-19 Vaccine Primary Series in Adults ≥18 Years of Age

Sara Oliver, MD, MSPH (CDC/NCIRD) provided updates to the EtR Framework on the Moderna COVID-19 vaccine, Spikevax®. She reminded everyone that the policy question they would vote on later in the day was, "Should vaccination with the Moderna COVID-19 vaccine (Spikevax®, 2-dose primary series) be recommended for persons 18 years of age and over?" The WG presented this previously with the Pfizer BLA, but as a reminder with the FDA authorization of an EUA, ACIP has made interim recommendations. As the vaccine receives full FDA approval under the BLA, ACIP reviews the totality of the data available and votes to make a standard recommendation. In addition, for regulatory action GRADE (e.g., the EtR framework, and the ACIP vote) Moderna COVID-19 vaccine was considered compared to no vaccine. Additional questions for discussion later in the session would focus on implementation, myocarditis, and intervals. Those discussions would be open to discussion of data for both the Moderna and Pfizer COVID-19 vaccines.

This PICO question used for the EtR framework included a population of people aged 18 years and older, and intervention of Moderna COVID-19 vaccine mRNA-1273 (100µg, 2 doses IM, 28 days apart), a comparison of no vaccine, and the following outcomes: symptomatic laboratory confirmed COVID-19, hospitalization due to COVID-19, death due to COVID-19, asymptomatic SARS-CoV-2 infection, SAEs, and reactogenicity. As a reminder, the EtR framework assess questions with the 7 domains of the public health problem, benefits and harms, values, acceptability, feasibility, resource use, and equity.

Beginning with the public health problem, there have been over 75 million COVID-19 cases reported to CDC from January 23, 2020 – February 1, 2022. The US recently experienced a substantial surge that peaked mid-January with a 7-day moving average of over 800,000 cases per day. Since mid-January, cases have been declining and the current 7-day moving average is now just over 400,000 cases.[21] As of February 1, over 888,000 deaths due to COVID-19 had been reported in the US.[22] In terms of rates of COVID-19 cases by vaccination status, unvaccinated people in all age groups had higher case rates than fully vaccinated people in the same age groups. Notably in November 2021, unvaccinated adults aged 18 years and over had a 4 times greater risk of testing positive for COVID compared to fully vaccinated adults.[23] Importantly, vaccines continue to provide substantial protection against severe disease and death. Unvaccinated adults 18 years of age and over had a 15 times greater risk of dying from COVID compared to fully vaccinated adults. Furthermore, people who were fully vaccinated and had received an additional or booster dose had an even further lower risk of testing positive and dying from COVID compared to people who were unvaccinated. The largest gap was between those who are unvaccinated and those who are fully vaccinated.

[21] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed February 3, 2022
[22] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed February 3, 2022
[23] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed January 24, 2022

In terms of weekly trends in COVID-associated hospitalization rates in the US, there is a reporting delay in recent weeks. However, hospitalizations have increased in recent weeks across all ages.[24] While COVID hospitalization rates have been increasing, it is important to evaluate the hospitalization rates by vaccination status. In terms of the rates of COVID-associated hospitalization by vaccination status in adults 18-49 years of age between January and December 2021, compared to fully vaccinated adults 18-49 years of age the monthly rates of COVID-associated hospitalizations were 12 times higher in unvaccinated adults 18 to 49 years in December. Additionally, compared to fully vaccinated adults 50-64 years of age, the monthly rates of COVID-associated hospitalizations were 18 times higher in unvaccinated adults in the same age range. In those adults 65 years of age and over, COVID-associated hospitalizations were 18 times higher in unvaccinated adults 65 years of age and over compared to fully vaccinated adults in that same age range.[25] Hospitalizations can take a toll on the health care system. As of February 3, over half of states where at 80% ICU capacity or greater.[26] Omicron is now the dominant circulating SARS-CoV-2 variant in the US.[27]

Now to look at the daily count of total doses administered and reported to CDC by date administered in the US. As of February 1, the 7-day moving average for doses administered was over 464,000 per day.[28] It is known that approximately 25% of people aged 18 years and over are not fully vaccinated. Looking at COVID vaccine administration by vaccine type, over 540 million COVID vaccines have been administered in the US and over 204 million of those were the Moderna COVID-19 vaccine. Over 212 million people are fully vaccinated in the US and over 74 million of these received the Moderna 2-dose series.[29] In terms of the percent of COVID-19 vaccination coverage by age and date administered, the highest coverage with at least one dose is 95% among the oldest groups aged 65-74 years and 75+ years. The lowest coverage is 75% with at least one dose among those 18-24 years of age.[30] Focusing on those fully vaccinated with Moderna by week and age group, similar patterns have been observed in which more doses were administered earlier in the rollout and older adults received their vaccines earlier.[31] Those who are fully vaccinated varies by geographic location as well.[32]

To summarize the public health problem, the Omicron variant is the dominant circulating variant of SARS-CoV-2 in the US. In January, COVID-19 cases, hospitalizations, and deaths increased, although cases have been declining in recent weeks. In November 2021, unvaccinated adults 18 years of age and over had 4 times the risk of testing positive and 15 times the risk of dying from COVID compared to fully vaccinated adults. Increasing cases are taxing health care resources, with many states facing ICU bed shortages again. While over 200 million people are fully vaccinated in the US, vaccination coverage varies by age and geography. The WG agreed that COVID-19 disease among adults continues to be of public health importance.

[24] CDC COVID-NET. https://gis.cdc.gov/grasp/covidnet/covid19_3.html Accessed February 3, 2022
[25] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed January 31, 2022
[26] HHS Protect Public Data Hub. https://protect-public.hhs.gov/pages/hospital-utilization Accessed February 3, 2022
[27] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed February 3, 2022
[28] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-trends Accessed February 3, 2022
[29] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed February 3, 2022
[30] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed February 3, 2022
[31] CDC Data Analytics and Visualization Task Force; Data included through the end of January 2022
[32] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-fully-percent-pop18 Accessed February 3, 2022

Moving now to the benefits and harms domain. Based on the GRADE evaluation, the clinical trial demonstrated efficacy against symptomatic laboratory-confirmed COVID, which was further supported by observational data. Overall efficacy was 92.7%, with high certainty. The clinical trial also demonstrated efficacy against hospitalization and was further supported by observational data. The overall efficacy was 95.9%, with moderate certainty of evidence. Thought deaths were uncommon in the clinical trial, observational data demonstrated effectiveness against death due to COVID-19. The pooled VE was 93.8%, with moderate certainty of evidence. The clinical trial demonstrated efficacy against asymptomatic SARS-CoV-2 infection. Overall efficacy was 57.4%, with high certainty. In terms of harms, SAEs were reported in a similar proportion among recipients of vaccine and placebo. There have been 2 specific rare SAEs identified as being associated with vaccination through safety surveillance. There was moderate certainty of evidence for these SAEs. Serious reactions were more common in vaccine recipients and any Grade 3 or more reaction was reported by 21% of vaccinated versus 4.5% of placebo groups. The reactogenicity had a high evidence certainty.

To summarize the benefits and harms domain, the GRADE evaluation focused on recommendations following licensure of the Moderna COVID-19 vaccine that has been used for a year under the EUA. Evidence for benefits is supported by a body of evidence comprised of 1 large Phase 3 RCT and numerous observational studies conducted worldwide. The RCT evidence demonstrated efficacy for beneficial outcomes, including the 2 critical outcomes of symptomatic disease and hospitalization. Efficacy data were further supported by the body of evidence from observational studies. Regarding harm, Grade 3 events were more common in vaccine than placebo recipients, but overall RCT evidence showed that SAEs occurred at a similar frequency in vaccine and placebo groups overall. However, these 2 specific but rare AEs have been associated with vaccination as identified through US safety surveillance systems.

In summary of the potential benefit and harm balance, VAERS has demonstrated reporting rates of myocarditis greater than the background rates for males 18-49 years of age and females 18-29 years of age after Dose 2. At least 90 days after myocarditis diagnosis, most patients reported no impact on their quality of life and most did not report missing school or work. Most HCP (81%) indicated that the patient was probably or fully recovered. For assessment of this benefit risk balance, the benefits were calculated per 1 million people who are fully vaccinated. The age group of 18-39 years was selected for this assessment because this age group has the highest rates of myocarditis and lowest hospitalization rates among adults and would therefore have the closest benefit-risk margin. Age- and sex-specific hospitalization rates were used from COVID-NET and VE estimates came from the COVIDNet and COVID Data Tracker platforms. The benefits were calculated over a 150-day or 5-month period. Harms were calculated as per 1 million persons who are fully vaccinated. The vaccine-specific myocarditis rates were used from the VSD. The vaccine-specific estimates of effectiveness against COVID hospitalization from both the Ivy Network and VISION were pooled to create a final VE estimate of 92%, which is the VE estimate used in the model. Looking at rates of myocarditis following the Moderna COVID-19 vaccine per million second doses administered among persons aged 18-39 from the VSD, myocarditis was most common in males who had a rate of 67.5 myocarditis cases per million second doses in the 7-day risk period. In terms of COVID-associated hospitalizations prevented by the Moderna vaccine compared with myocarditis cases expected per million fully vaccinated persons 18-39 years of age, many more COVID-19 hospitalizations would be prevented than myocarditis cases expected over the course of 5 months. Among males 18-39 years who have the highest rates of myocarditis overall, many more COVID-19 hospitalizations would be expected to be prevented than myocarditis cases expected.

For the benefit-risk balance there are a few limitations that should be noted. The benefit-risk analysis considered direct benefits and risks over the 150-day period comparing vaccine to no vaccine. The VE assumptions used in the model do not yet include Omicron specific VE estimates. The model assumes a static hospitalization rate over 5 months. The benefit-risk profile would change as hospitalization rates change. The model does not account for booster doses or prior infection. To summarize the benefits and harms, the clinical trial and observational studies demonstrated that the Moderna vaccine is effective in the prevention of COVID-19 in persons 18 years of age and over. The risk of myocarditis or pericarditis is noted after the mRNA vaccines and the highest risk was seen after the second doses in younger males. However, the benefits for the Moderna COVID-19 vaccine far outweigh any possible vaccine-associated risk. Therefore, the WG felt that the desirable anticipated effects were large, undesirable anticipated effects were small, and the balance favors the intervention.

In terms of the values domain, surveys were conducted among adults asking about their intent to receive the COVID-19 vaccine. Overall, intent has consistently increased since 2020 when the vaccines were authorized. In a survey of vaccination status and intent among adults 18 years of age and over in the US, almost 85% of adults reported that they are vaccinated or definitely will get vaccinated, 4% reported they probably would get vaccinated or are unsure, and 10% reported they would probably or definitely not get vaccinated.[33] A survey of the American general population was conducted among individuals 18 years of age and over between January 7-10, 2022. Unvaccinated survey respondents were asked, “Does the discovery of the Omicron variant make you more or less likely to get the COVID vaccine?” The majority (72%) of respondents expressed that it makes no difference, while a smaller proportion said that they would be less or more likely to receive the vaccine at 13% each.[34] When unvaccinated adults were asked, “What, if anything, would convince you to receive a COVID-19 vaccine?” half of unvaccinated adults said that nothing would convince them to get a COVID-19 vaccine. 12% said that more research or transparency would convince them, fewer said that they would get it if it was required for work or was mandatory (6%), if they received a large monetary incentive (5%), if their doctor recommended it (3%), or if the vaccine prevented 100% of infections (3%).[35]

Following FDA's full approval of the Pfizer vaccine in the US, initial data indicated that there was a slight uptick of 17% in the average number of Americans getting their first COVID-19 vaccine dose in the days immediately following approval. In the week prior to full approval, an average of about 404,000 Americans were initiating vaccination each day. Following approval, approximately 473,000 Americans were getting their first dose each day. Although not a rapid surge in vaccinations in the days immediately following approval, full approval may have been enough to convince some to finally get immunized.[36]

Another ongoing survey was designed by CDC and the University of Iowa to assess vaccine intent of unvaccinated Americans in response to this FDA BLA for the Moderna vaccine. Data were collected from January 27-31, 2022. The current sample size is around 500 respondents. When asked about reasons surrounding vaccine hesitancy, concerns about vaccine side effects

[33] CDC COVID Data Tracker. Trends in COVID-19 Vaccine Confidence in the US. https://covid.cdc.gov/covid-data-tracker/#vaccine-confidence. Accessed January 21, 2022
[34] Axios/Ipsos Poll. January 2022. https://www.ipsos.com/en-us/news-polls/axios-ipsos-coronavirus-index Accessed January 19, 2022
[35] KFF COVID-19 Vaccine Monitor: Early Omicron Update (Dec 15 – 20, 2021). https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-early-omicron-update/. Accessed January 19, 2022
[36] Rise in COVID-19 vaccinations following full FDA approval
ABC news. August 31, 2021. More Americans getting vaccinated following full FDA approval of Pfizer COVID vaccine. https://abcnews.go.com/Health/americans-vaccinated-full-fda-approval-pfizer-covid-vaccine/story?id=79750505

and general mistrust of COVID-19 vaccines were the top reasons for remaining unvaccinated. During the data collection period, 29% of the unvaccinated respondents said that they thought the Moderna COVID-19 vaccine already had full approval from the FDA. In relation to vaccine intentions in response to the Moderna BLA, 5% of unvaccinated respondents said that they would get a vaccine as soon as they could if the Moderna vaccine received full approval from the FDA. Among unvaccinated respondents, 20% said they would continue waiting to see if COVID-19 vaccines were safe, 52% said they would definitely not get vaccinated or would only do so if it was required, 11% said that they would wait a few more weeks to get a COVID vaccine after the Moderna vaccine received full approval but were open or unsure about getting the vaccine, and 11% said they would wait more than a year to get a COVID vaccine after the Moderna vaccine received full approval.

The WG felt that the overall population felt the desirable effects were large relative to undesirable effects. However, there was probably important uncertainty or variability in how people value the outcome.

Moving to the domain of acceptability, over 200 million doses of the Moderna vaccine had already been administered and implemented as of February 2, 2022 in a wide variety of settings, including state and local health departments, mass vaccination clinics, long-term care facilities (LTCF), and retail pharmacies.[37] Vaccination with the Moderna COVID vaccine already was highly acceptable to stakeholders under FDA's EUA and ACIP interim recommendations. Vaccination may be more acceptable under full FDA approval and standard ACIP recommendations. The WG felt that the Moderna vaccine is acceptable to key stakeholders.

Moving to the domain of feasibility, possible barriers to implementation that have been mentioned in previous EtRs complexity of recommendations, vaccine storage and handling requirements, financial barriers, and supply barriers. The Moderna vaccine will be the second vaccine with the BLA. The BLA has only been issued for some indications, which could add complexity. The BLA is issued for the primary series in those 18 years of age and over, while the EUA recommendations remain for the additional dose and booster dose recommendations. Recommendations made under COVID-19 Vaccine Emergency Use Instructions (EUI) only allow for vaccines with a BLA. The BLA will allow these recommendations to be extended to include the Moderna vaccine. There have been a variety of updates and improvements to the vaccine storage and handling requirements since the initial EUA.[38] Now, the vaccine can be stored frozen and refrigerated for up to 30 days prior to the first use. As throughout the pandemic, all COVID vaccines are provided to the US free of charge. However, health systems or health departments can incur costs for vaccine implementations, clinics, and outreach. Financial hardships may arise if vaccine recipients need to take time off of work or could experience post-vaccination reactogenicity that would keep them from working. Supply barriers are not anticipated. Vaccine supply in the US is sufficient for implementation of the intervention. As of February 2, over 200 million doses have been administered in the US, demonstrating that the vaccine is feasible to implement broadly.[39] In terms of the feasibility domain, the WG felt that the vaccine is feasible to implement.

[37] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed February 3, 2022.
[38] Moderna. Storage & Handling. Storage & Handling | Moderna COVID-19 Vaccine (EUA) (modernatx.com). Accessed January 18, 2022
[39] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed February 3, 2022.

Moving to the resource use domain, a KFF analysis estimated the cost of preventable COVID-19 hospitalizations among unvaccinated adults in the US.[40] From June - November 2021, preventable COVID hospitalizations among unvaccinated adults were estimated to cost over $13 billion. Vaccine doses purchased with US taxpayer funds will be given to people living in the US at no cost.[41] Several published modeling studies have found that COVID vaccines are likely to be of reasonable economic value and may also be cost-saving under many circumstances.[42] While not a primary driver of decision-making in the pandemic, the WG still felt that the Moderna vaccine was a reasonable and efficient allocation of resources.

For the domain of equity, the cumulative COVID-19-associated hospitalizations in the US by race and ethnicity for March 7, 2020 through March 22, 2022 showed that AI/AN, Black, and Hispanic populations have consistently had the highest rates of COVID-19-associated hospitalizations in the US.[43] In terms of the percentage of people 18 years of age and over who have received at least one dose of COVID-19 vaccine by race and ethnicity over time, AI/AN populations have consistently had the highest percentage of those receiving at least one dose of COVID-19 vaccine.[44] Looking at COVID-19 vaccination coverage by geography, only 20% of US counties report 70% or more of the population 18 years of age and over who are fully vaccinated.[45] Vaccine uptake lags in adults living in rural and suburban areas compared to urban areas. As of November 2021, 8 in 10 urban residents said that they have received at least one dose of a COVID vaccine, compared to 7 in 10 suburban adults and 67% of rural adults. Of those living in rural areas, 1 in 5 say they will “definitely not” get a COVID-19 vaccine and 1 in 6 of those living in suburban areas say they will “definitely not” get a COVID vaccine. This is at least twice the share of urban residents who say the same.[46]

An *MMWR* published earlier in the week assessed COVID-19 vaccination coverage among LGBT adults 18 years of age and older by sexual orientation. Gay or lesbian adults reported higher vaccination coverage overall than heterosexual adults. There were no significant differences in vaccination coverage among persons based on gender identity. Vaccination coverage was lowest among non-Hispanic Black LGBT persons across all categories of sexual orientation and gender identity.[47] While there was considerable variability in the interpretation of the equity domain, overall the WG felt that the approval of the Moderna vaccine probably would have no impact on health equity.

[40] Peterson-KFF Health System Tracker. https://www.healthsystemtracker.org/brief/unvaccinated-covid-patients-cost-the-u-s-health-system-billions-of-dollars/ Accessed January 25, 2022
[41] CDC COVID-19. COVID-19 Vaccines Are Free to the Public. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/no-cost.html
[42] a) Padula et al. 2021. J Med Econ; b) Bartsch et al. 2021 J Inf Dis; c) Gupta et al. 2021 Health Aff; d) Kohli et al 2021 Vaccine
[43] CDC. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network Accessed February 3, 2022
[44] CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends as of February 2, 2022, and US Census Bureau National Population Estimates
[45] CDC COVID-19 County Integrated County View. https://covid.cdc.gov/covid-data-tracker/#vaccinations-county-view Accessed January 20, 2022
[46] KFF COVID-19 Vaccine Monitor: Differences in Vaccine Attitudes Between Rural, Suburban and Urban Areas. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-vaccine-attitudes-rural-suburban-urban/ Accessed January 18, 2022
[47] McNaghten A, Brewer NT, Hung M, et al. COVID-19 Vaccination Coverage and Vaccine Confidence by Sexual Orientation and Gender Identity — United States, August 29–October 30, 2021. MMWR Morb Mortal Wkly Rep 2022;71:171–176. DOI: http://dx.doi.org/10.15585/mmwr.mm7105a3

This table summarizes the WG's judgments for each of the EtR domains:

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Large
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention (Moderna COVID-19 vaccine)
	What is the overall certainty of the evidence for the critical outcomes?	High to Moderate
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Large
	Is there important variability in how patients value the outcomes?	Probably important uncertainty or variability
Acceptability	Is the Moderna COVID-19 vaccine acceptable to key stakeholders?	Yes
Feasibility	Is the Moderna COVID-19 vaccine feasible to implement?	Yes
Resource Use	Is Moderna COVID-19 vaccine a reasonable and efficient allocation of resources?	Yes
Equity	What would be the impact of the intervention on health equity?	Probably no impact

For both of the primary series and additional booster doses and for all 3 COVID vaccines used in the US, there are EUAs in place. The primary series for Pfizer in those 16 and over and the primary series for Moderna in those 18 and over have full FDA approval with the BLA. Dr. Oliver emphasized that the authorization in any vote by the ACIP during this session would not override any existing recommendations for the EUAs. The ACIP will continue to review data as additional vaccines and indications move from EUA to BLA. The WG's interpretation is that overall, COVID-19 vaccines have been a critical tool in this pandemic, preventing millions of COVID-19-associated hospitalizations and deaths. To date, hundreds of millions of doses of the Moderna COVID-19 vaccine have been given with over a year of incredibly closely monitored real-world safety and effectiveness data. Vaccinating the unvaccinated with a primary series continues to be important. Additional protection from all recommended COVID-19 vaccine doses is important over the course of an evolving pandemic. In summary of the WG's interpretations with the balance of consequences, the WG felt that the desirable consequences clearly outweigh undesirable consequences in most settings. In terms of the type of recommendation, the WG recommended the intervention.

Discussion Summary

Dr. Hahn (CSTE) said she came to fully understand something in the last week or so that she wanted to bring forward. CSTE continues to get questions about case rates, particularly for hospitalization rates among people who are partially vaccinated. CSTE has responded that they continue to consider these individuals to be unvaccinated because that is where they show up in the data. It was not until recent conversations with continued queries from members of the public that she realized that the perception, rumor, or theory is that partially vaccinated people who had a single dose or have just gotten their second dose make up a large percentage of the group being identified as "unvaccinated" in hospitals and hospitals are filling up with people who got a dose of the vaccine and that maybe that somehow gave them COVID-19 from the vaccine itself or from some sort of immune suppression after the vaccine. CSTE has begun to produce data showing this as a separate group. Perhaps ACIP should show this group separately in the data. CSTE was able to demonstrate that a very small percentage of people in the hospital currently had a single dose or had recently been vaccinated.

Regarding the resource use allocation, Dr. Lee recognized that the mandate of ACIP is the health of the US population. However, she also highlighted that the estimated impact or economic burden does not reflect the true cost of the pandemic in the US society. It is not just the cost of the hospitalizations. It is the cost of the work missed, businesses closed, wages lost, and the worsening of the already existing educational disparities in the in this country which also have long-term economic consequences on this generation of children directly impacted by the pandemic. While she recognized that it is nearly impossible to capture all of that in the resource assessment, it is important to acknowledge in some way because this goes well beyond the way ACIP vaccine deliberations are typically thought of.

Dr. Poehling expressed gratitude to Dr. Oliver for a fantastic presentation that was very clear. She asked for additional input about whether there was much diversity in the opinion of the WG in voting for this recommendation?

Dr. Oliver indicated that there was not. The WG overwhelmingly agreed that they would recommend the intervention of the 2-dose Moderna primary series among those ≥18 years of age.

Vote: Moderna COVID-19 Vaccine for Individuals ≥18 Years of Age

Dr. Sara Oliver (CDC/NCIRD) presented the proposed recommendations for Moderna COVID-19 vaccine for individuals ≥18 years of age, which follows:

> "The Moderna COVID-19 BLA-approved vaccine (Spikevax®, 2-dose primary series) is recommended for persons 18 years of age and older."

Though not included in the vote language, Dr. Oliver clarified that the ACIP recommendations addressing the EUA uses of the Moderna vaccine will remain in effect. This is the only change that would move the recommendation for the 2-dose primary series from the interim recommendation under EUA to a full recommendation. The other EUA votes would remain in effect.

Motion/Vote: COVID-19 Vaccine Booster Doses for Individuals ≥18 Years of Age

Dr. Poehling made a motion for ACIP to adopt the verbiage of the recommendation stating that, "The Moderna COVID-19 BLA approved vaccine (Spikevax®, 2-dose primary series) is recommended for persons 18 years of age and older." Dr. Ault seconded the motion. No COIs were declared. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

Dr. Daley expressed his sense of wonder at what had been accomplished, along with his deep sense of gratitude. There are now 2 vaccines against COVID-19 that are fully licensed in the US. These vaccines were authorized and then licensed along a rapid timeline while still following all of the well-established regulatory processes in place before the pandemic. As he mentioned earlier in the day, an estimated 1.1 million deaths have been averted through vaccination in the US and countless more globally. This cannot be taken for granted and it should not be assumed that this was an inevitable outcome. To put this in a more personal context, everyone has individuals in their lives—parents, grandparents, children, friends—who may have gotten sick and/or died from COVID who did not because of vaccination. For that, he is very grateful. That said, he acknowledged that many have lost their lives to COVID-19 and everyone is still vulnerable, particularly the very young, the very old, the unvaccinated, and those with immunocompromise. While he realizes that there is still a lot of work to do and a lot of challenges ahead with respect to the pandemic and the role that vaccines play, on this day he was just very appreciative of all that has been accomplished.

Dr. Lee thanked Dr. Daley and expressed everyone's appreciation of his leadership of the COVID-19 Vaccines WG, which has been quite busy.

Dr. Bell commented on a corollary to what Dr. Daley said. One of the things that the ACIP values the most is transparency. Therefore, one of the things she thought they could see from the process throughout the day was the broad context of evaluating risks and benefits using scientific evidence that has been accumulated over a long period of time with millions of people vaccinated. It is possible to see the power and the value of vaccination. Given that the biggest risk continues to be to individuals not getting vaccinated, she hoped that this transparent process would encourage at least some people who are still thinking about whether they should get vaccinated to do the most important thing that they can do to protect themselves and their family, which is to get a vaccine.

Dr. Duchin (NACCHO) said he wanted to reinforce the importance of the booster dose. While they had rightly been talking about the primary series, there are many people in many communities throughout the country who have received the primary series who are eligible but yet have not received a booster dose. It is critical to understand how necessary that booster dose is in terms of receiving the full protection that these vaccines can offer against serious disease, hospitalizations, and deaths. For people who wonder whether an Omicron-specific vaccine will be needed, perhaps one of the one of the experts could talk about what is on the horizon with respect to the potential need and development of such a vaccine.

Updates to Clinical Considerations

Elisha Hall, PhD (CDC/NCIRD) presented on anticipated updates to the Interim Clinical Considerations for use of COVID-19 Vaccines. Anticipated updates will include clarification and updates on guidance for people who are moderately or severely immunocompromised, updates to recommendations on passive antibody products, and reduction in reorganization for ease of use.

Beginning with the guidance for people who are moderately or severely immunocompromised, all guidance in this section will apply only to this population. As a reminder, recommendations for people who are immunocompromised at the time of vaccination are already different than recommendations for most people. This is because this group is at increased risk for severe COVID-19 and more likely to have serious breakthrough infections. They may not mount a protective immune response after a 2-dose primary series, in general have lower VE than people who are not immunocompromised, and have waning protection over time. In terms of the current COVID-19 vaccination schedule for people who are moderately or severely immunocompromised, similar to the recommendation for the general population, mRNA COVID-19 vaccines are preferred for all doses over Janssen COVID-19 vaccine. For those in this population who choose an mRNA COVID-19 vaccine 2-dose primary series, 1 additional dose and 1 booster dose are recommended for people aged 12 years and older for a total of 4 doses. This is not indicated for people who are immunocompetent. For those who choose Janssen, this includes 1 primary dose and 1 booster dose.

There has been recent confusion about the recommendations for this population, including reports of people who choose mRNA COVID-19 vaccines being denied their fourth dose. In addition to communication efforts, more clarification is being added in the clinical considerations to emphasize that this population should receive 3 doses for a primary series and 1 booster dose if they are aged 12 years and older. There are no changes in the number of doses. It is simply clarification to address the challenges being reported.

The next few changes are possible through use of EUI. EUI are allowed under the Pandemic and All Hazards Preparedness Reauthorization Act (PAHPRA). EUI provides information about emergency use of FDA-approved medical products that may not be included or may differ from the information provided in the FDA approved labeling package insert. Since EUI are only for FDA-approved products, this only applies to the 2 approved COVID-19 vaccines Spikevax® (Moderna) for which guidance would apply to people 18 years and older, and Comirnity® (Pfizer-BioNTech), for which guidance would apply to people 12 years and older. EUI materials include fact sheets for HCP, fact sheets for recipients and caregivers, and FAQs and can be found on the CDC website.[48] Revisions utilizing the EUI mechanism for people who are moderately or severely immunocompromised include a shorter booster interval after an mRNA COVID-19 vaccine primary series, an additional dose after a Janssen COVID-19 vaccine primary series, and case-by-case clinical decision-making.

Currently, people who are moderately or severely immunocompromised who received an mRNA COVID-19 vaccine primary series are recommended to receive a booster dose at least 5 months after completion of the series. This 5-month booster interval will be revised to at least 3 months after completion of the mRNA primary series. The rationale for this decision was out of an abundance of caution to help this population who may not be as well-protected get their booster dose sooner, particularly with concerns about initial immune response, loss of protection over time, and high community transmission due to the Omicron variant. To support this change, small studies demonstrate immunogenicity of a fourth dose when administered 1 to 3 months after the third dose. Among participants with seronegative or low positive responses after 3 doses, 42% to 66% were seropositive after 4 doses. Additionally, multiple studies demonstrate immunogenicity of a booster dose as early as 3 months in the general population following a 2-dose primary series. Multiple countries have implemented booster doses as early as 3 months in the general population following a 2-dose primary series. To support this change, small studies demonstrate immunogenicity of a fourth dose when administered 1 to 3

[48] https://www.cdc.gov/vaccines/covid-19/eui/index.html

months after the third dose. Among participants with seronegative or low positive responses after 3 doses, 42% to 66% were seropositive after 4 doses. Additionally, multiple studies demonstrate immunogenicity of a booster dose as early as 3 months in the general population following a 2-dose primary series. Multiple countries have implemented booster doses as early as 3 months in the general population following a 2-dose primary series.[49]

Guidance will be added on the schedule for people who are moderately or severely immunocompromised who received a Janssen COVID-19 vaccine primary series. These people are currently recommended to receive 1 booster dose at least 2 months after completion of the primary dose. An mRNA COVID-19 vaccine is preferred for the booster dose, but Janssen COVID-19 vaccine can be used provided that the patient is educated on the risks and symptoms of thrombosis with thrombocytopenia syndrome (TTS), the need to seek medical care should such symptoms develop, and the availability of mRNA COVID-19 vaccines. The revised guidance will add an additional dose to this schedule. People who are moderately or severely immunocompromised would be recommended to receive 1 additional dose at least 28 days after the primary Janssen COVID-19 vaccine dose, and 1 booster dose at least 2 months after completion of the additional dose for a total of 3 doses. Recognizing that many people may already have received 2 doses—their primary dose and booster dose. The guidance will address what to do if someone already has received a booster dose. There is not guidance for more than 3 doses.

Language will be added that on a case-by-case basis, providers who care for moderately or severely immunocompromised patients may administer mRNA COVID-19 vaccines outside of the FDA and CDC dosing intervals based on clinical judgment when the benefits of vaccination with a different schedule or dosage are deemed to outweigh the potential and unknown risks. However, providers should not routinely administer additional doses of COVID-19 vaccine beyond those recommended in this guidance. Additionally, antibody testing is not currently recommended to assess the need for vaccination or assess immunity following vaccination.

Passive antibody products guidance applies to everyone, not just those who are immunocompromised. Currently, for people who have received passive antibody products for COVID-19, there is a recommended deferral period before vaccination. People should defer vaccination for 30 days if the product was used for post-exposure prophylaxis (PEP) and 90 days if it was used for treatment. With the revised guidance, people who previously received antibody products such as anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma as part of COVID-19 treatment PEP or pre-exposure prophylaxis (PrEP) can be vaccinated at any time. There is no longer a recommended deferral period for COVID-19 vaccination following receipt of anti-SARS-CoV-2 antibody product. In people who previously received a COVID-19 vaccine, EVUSHELD™ for PrEP should be deferred for at least 2 weeks after vaccination per the product EUA.

[49] a) Kamar, N., Abravanel, F., Martion, O. (2021). Assessment of 4 Doses of SARS-CoV-2 Messenger RNA–Based Vaccine in Recipients of a Solid Organ Transplant. Infectious Diseases, 4(11), e2136030; b) Benotmane, I., Bruel, T., Planas, D., et al. (2021). A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the delta variant in kidney transplant recipients. medRxiv. Preprint. doi.org/10.1101/2021.11.25.21266704; c) Alejo, J.L., Mitchell, J., Chiang, T., et al. (2021). Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Transplantation, 105(12), e280-281; d) Munro, A., Janani, L., Cornelius, V. (2021). Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet, 398, 2258-76; and e) Atmar, R.L., Lyke, K.E., Deming, M.E. (2021). Heterologous SARS-CoV-2 booster vaccinations-preliminary report. medRxiv. Preprint. doi: 10.1101/2021.10.10.21264827

The reason for removing the deferral period is based on a balance of benefits and risks. A study among nursing home residents and staff demonstrated that recipients of the monoclonal antibody bamlanivimab mounted a robust immune response to mRNA vaccination regardless of age, risk category, or vaccine type. This suggests that an interval dose does not need to be tailored to particular subgroups. Although antibody response was numerically lower in people who received monoclonal antibodies, it was still considered to be high and the clinical significance of the reduction is unknown. Most notably, there was no correlation between interval to COVID-19 vaccination and neutralizing titers. Programmatically, there can be challenges to current intervals between receipt of monoclonal antibodies and COVID-19 vaccination, which may reduce the likelihood of getting vaccinated. In the current setting of the COVID-19 pandemic, getting people vaccinated, including booster vaccination, is a priority and the benefits likely outweigh any potential risks for immune interference for monoclonal antibodies.[50]

CDC is in the process of streamlining the content and layout of the Interim Clinical Considerations for increased usability. The Interim Clinical Considerations can be found on the CDC website.[51]

Discussion Summary

Dr. Lee noted that the changes were very much welcome for those of who are providing care or recommendations on the frontline. This is helpful, practical implementation information that should make a huge difference to many patients.

Dr. Kotton agreed that the updates will dramatically help immunocompromised patients. In the past 2 months, she has seen many of these immunocompromised patients who followed all of the rules still have significant breakthrough infections.

Dr. Brooks observed that the J&J guideline for immunocompromised showed that for the second dose, only an mRNA vaccine should be used but that for the booster, any vaccine could be used. He asked for further explanation for that difference in the recommendation.

Dr. Hall acknowledged that it is confusing and explained that the main reason for this is due to legal limitations. The recommendations that have been added for moderately or severely immunocompromised, including this recommendation, are possible through the EUI that can only be used for licensed vaccines. The additional dose added on must be Pfizer or Moderna because those are the only vaccines allowed through the EUI. The booster continues to be preferred for Moderna and Pfizer due to the risk for TTS with the J&J vaccine.

Dr. Sanchez emphasized that the datasets are strong in that it has to be at least 2 months and the other one has to be 3 months, especially if the second dose is a Pfizer or Moderna. He asked whether this could be harmonized to say that all booster doses are to be given 3 months or later rather than grappling with 21, 28, 1 month, 2 months.

Dr. Hall acknowledged that it is confusing to have different intervals. She clarified that the 2 months is currently allowed under the EUA for the booster and consideration has not been given to extending that interval for the mRNA. They want people to get it sooner. The Janssen vaccine

[50] Benschop, et al. (2021). The effect of anti-SARS-CoV-2 monoclonal antibody, bamlanivimab, on endogenous immune response to COVID-19 vaccination. medRxiv. Preprint. doi: https://doi.org/10.1101/2021.12.15.21267605
[51] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#CoV-19-vaccination

is already sitting with that 2-month interval, so consideration would have to be given to whether it would be possible to actually extend that. However, they would not necessarily want anyone to get the booster later.

Given that the ACIP just voted to expand the BLA for the primary series for Moderna, it seemed to Dr. Loehr that the clinical considerations were going past that to make suggestions that still fall into the EUA. It was not clear to him whether it was appropriate to do that. His sense in the past had been the EUA was a strict guideline and those rules should not be bent at all.

Dr. Hall stressed that this is being done through an EUI not an EUA. CDC is allowed to issue EUIs that go outside of what is indicated in the package insert. That is the reason they were able to do that and still be covered.

Dr. Fryhofer (AMA) noted that Slide 7 said that this applied only to use of Spikevax® that is approved for persons 18 years of age and older and Comirnaty® for persons 12 years of age and older. She thought that the Comirnaty® vaccine was FDA-approved with the BLA for persons 16 years of age and older.

Dr. Hall confirmed that Comirnaty® is licensed for the 2-dose primary series for persons 16 years of age and older. Essentially, the EUI allows for use of approved vaccines. Comirnaty® has gray cap and purple cap vials, which means that they would be called BLA-compliant vials. Anything in the EUI can apply to those vials. Since they can be used for ages 12 years and older, that is why the EUI can apply down to that age. However, it cannot go down to 5-11 years of age.

Dr. Mbaeyi added that EUI are a new pathway that many people are hearing about for the first time. CDC is using these in close coordination with FDA, not going outside of FDA, to determine the best way forward that legally would allow CDC to make some necessary changes to the clinical considerations. It is through mutual consultation that CDC has sometimes made the decision that it is more appropriate to use an EUI for certain guidance versus other regulatory mechanisms.

Canadian Experience and Evidence with COVID-19 Vaccine Primary Series Extended Intervals

Dr. Matthew Tunis (Public Health Agency of Canada) presented on the Canadian program context and highlighted some of the evidence that has informed Canadian recommendations in terms of 1-dose effectiveness and duration between doses, immunogenicity with longer intervals, effectiveness with longer intervals, and safety with the longer intervals. Canada's National Advisory Committee on Immunization (NACI) has been providing advice on the COVID-19 vaccine intervals since 2020. It is important to note some of the structural differences throughout the pandemic between the Canadian and US context. Under the Terms of Reference, even under a regulatory Interim Order (roughly comparable to an EUA) through most of the pandemic, NACI was permitted to issue off-label advice on COVID-19 vaccines as per usual. There have been a number of off-label recommendations from the beginning of COVID-19 vaccines, for which there have been no issues. NACI has provided several updates on extended intervals for the primary series as evidence has evolved.

There has been an evolving story in Canada around intervals. From the beginning with the COVID-19 vaccines in December 2020, NACI recommended an alternate interval of 28 days for Pfizer-BioNTech versus the 21-day authorized interval. In early in December 2020, Quebec's Provincial Immunization Committee (CIQ), which has a strong linkage with NACI, recommended first doses to all priority groups before second doses. On December 30, 2020, the Joint Committee on Vaccination and Immunisation (JCVI) in the United Kingdom (UK) recommended a 3-12 interval for Pfizer-BioNTech and a 4-12 week interval for AstraZeneca to maximize first-dose priority groups. An alternate interval was recommended by NACI in January 2021 moving to six 6 or 42 days for mRNA vaccines based on the clinical trial data and the efficacy estimates that included up to 42 days. The purpose of that alternate interval was to maximize first doses to priority groups. The big shift in Canada occurred in March 2021 when NACI recommended up to a 4-month interval for all COVID-19 vaccines. There was a full statement with all of the evidence and rationale in April 2021. In October 2021, the interval was refined further to an optimal interval of 8 weeks for adolescents and adults. In November 2022 when the pediatric program for children 5-11 years of age came through, NACI recommended an interval of at least 8 weeks. Notably in January 2022, WHO and its Strategic Advisory Group of Experts on Immunization (SAGE) recommended an interval of 4–8 weeks, with a preferential 8-week interval. The settling place does seem to be around 8 weeks.

The core principles that have informed NACI interval recommendations have been fairly diverse. The extended interval recommendation for up to 16 weeks in March 2021 was initially informed by a trigger for limited supply. There were early VE assessments of strong 1-dose protection from mRNA clinical trials and from Israel, and later from Canada and UK research and surveillance. AstraZeneca 2-dose clinical trials showed that longer intervals yield better vaccine efficacy. There was modeling to optimize program impact in the context of limited supply. In addition, there were immunology and vaccinology principles and ethics, equity, feasibility, and acceptability. The subsequent move in the fall toward an 8-week interval was additionally informed by Canadian and UK VE data demonstrating increased protection with longer intervals, which plateaued around 8 weeks; immunological data on the breadth and duration of immune response with longer intervals; Canadian safety surveillance showing lower rates of myocarditis with a longer interval; and ethics, equity, feasibility, and acceptability. While safety and myocarditis have been an emerging part of the story, it actually is a latecomer to the Canadian interval story that originally was driven more by other vaccine principles. Now safety and myocarditis rates also have additionally augmented and informed the interval story.

To recap some immunological principles regarding longer intervals, it is known that affinity maturation can be improved. The longer interval between primary and secondary antigen exposures will allow immune memory cells more cycles of affinity maturation to develop higher affinity. This may increase the breadth and/or neutralizing activity of the response. There also is less potential for immune interference also with longer intervals. Circulating antibodies may interfere with the immune responses of the subsequent exposures due to: 1) epitope masking in which circulating antibodies may occupy antigen binding sites on the surface of the vaccine antigen; and 2) reduced antigen availability in which antibodies can form immune complexes and be cleared through the liver and spleen to reduce the pool of available antigen if the antigen is reintroduced too soon.

Dr. Bryna Warshawsky (Public Health Agency of Canada) indicated that the first area explored when Canada considered an extended interval was VE with regard to 1 dose. NACI reviewed the literature that was available at the time and published a statement on April 7, 2021 that summarized the literature to that point.[52] Based on that summary, 1 dose of mRNA vaccine was shown to be effective against symptomatic disease and infection at about 60% to 80%. That was somewhat lower than expected based on the 1-dose efficacy from the clinical trial, which was 92% and lower than the effectiveness and efficacy with 2 doses. Very reassuringly, 1-dose protection against serious outcomes was higher than against symptomatic disease and infection at around 80% or more. Regarding the question of how long the protection would be from that 1 dose, NACI turned to its colleagues from the UK who already had started the extended interval. JCVI presented to NACI on a regular basis. A summary of the data that JCVI has on VE following the first dose over time[53] shows that for adults 50-64 years of age who have had 1 dose of the Pfizer-BioNTech vaccine, VE is about 60%. About 8 weeks after the first dose, VE decreases to 40% to 50%. This was similar for persons 65-79 years of age at about 60% out to 10 weeks, followed by a decrease.

Knowing that there is VE after 1 dose and that it lasts 8-10 weeks, NACI also was interested in the principle from immunology that the longer the interval between the first and second dose, the higher the immune response that might be expected after a second dose. This was borne out in trials from the UK. These data come from the CONSENSUS Trial in the UK that followed a cohort of 750 people ≥50 years of age who had periodic serological testing. Based on the interval between their first and second doses, the geometric mean titers (GMTs) achieved after the second dose were lower when the interval was shorter. As the interval was increased between the first and second dose, the GMTs were higher after the second dose. There also were subsequent studies from the UK group showing that extending the interval between the second dose and the booster dose also results in higher titers. This immunologic information suggests that this may translate as well into VE.

Data from the UK also examined VE after the second dose of the Pfizer-BioNTech vaccine. Among persons 65-79 years of age, when the interval was shorter at 19-29 days between the first and second dose, VE was around 75%. With longer intervals between doses of 6 weeks or more, VE became higher at up to 90%. This was observed in other age groups as well. Notably, those who had a shorter interval also were likely to have a longer period of time from their second dose to when the study was completed. The longer interval between the second dose and the time of the study also affected VE. Those 2 concepts, the interval between first and second dose and the time from second dose to the study end can be conflated.

Studies from Canada helped to tease those 2 concepts apart. A study by Skowronski and Arel from Canada[54] examined mRNA VE in British Columbia and Quebec against infection and hospitalization by interval. Looking at Quebec, when the interval was short at 3-4 weeks, there was 79% VE against infection. When the interval was longer at 7-8 weeks between the first and second dose, VE after the second dose was 89% or about a 10% difference with the longer and the shorter interval. This was similar with hospitalizations. With an interval of 3-4 week, VE against hospitalization was 87%. With a longer interval, VE against hospitalization increased to 97% to 98%. Again, there was about a 10% VE difference moving from a shorter interval to a

[52] https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html

[53] Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications

[54] Skowronski et al, 2021 (Preprint) Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada https://www.medrxiv.org/content/10.1101/2021.10.26.21265397v1

longer interval. The findings were similar in British Columbia, thought the difference was about 6% difference between the shorter interval and the longer interval. The investigators also assessed this over time. In Quebec, the lower VE with the shorter intervals and the higher VE with the longer intervals persisted over time. A study from Kwong and colleagues[55] examined VE over time in Ontario during various parts of the outbreak. In the Delta wave, they examined a longer interval of ≥8 weeks, an intermediate interval of 5 to <8 weeks, and a shorter interval of 2 to <5 weeks. Again in this study, VE was lower if the interval was shorter and higher if the interval was longer. Though the difference was not as large in this study, it was still 5% and that persisted over time.

To summarize this portion of the Canadian journey through the extended interval, 1-dose provides good protection against symptomatic disease and infection at about 60% to 70% that lasts between 8-10 weeks. The protection for serious infection is higher at about 80% or more compared to protection against infection. One a second dose has been received, the longer interval in the primary series results in a higher antibody response. That higher antibody response also translates to somewhat higher VE.

Canada has some varying intervals over the time. Based on data on fully vaccinated people to mid-August 2021, about 52% of the Canadian population who have been fully vaccinated had an interval between 50-77 days. Only 4% had a shorter interval of 28 days or less. This varies somewhat depending on provinces and territories. Particularly notable are 3 territories that are smaller and Northern that received higher allocations of doses originally and used a shorter interval between the first and second dose. The rest of the provinces had a range of intervals for their populations over time.

What Canada did not expect was that there also would be a benefit from prolonged intervals based on safety that emerged. When the safety signal for myocarditis and pericarditis with the mRNA vaccines was first identified, colleagues in Ontario and nationally began to assess whether the difference in the interval might impact the rate of myocarditis and pericarditis. A study by Buchan and colleagues[56] conducted in Ontario looked at myocarditis and pericarditis rates based on vaccine product, schedule, and interval using a 7-day risk period between vaccination and the onset of myocarditis and pericarditis and a Brighton Collaboration level of 1-3. This study showed that the reported rates of myocarditis and pericarditis were higher after the second dose of an mRNA vaccine than after the first, which has been seen in a number of other studies. This was particularly for individuals who received Moderna as their second dose. The highest reporting rate was for myocarditis and pericarditis in males 18-24 years of age following Moderna as their second dose. Males 18-24 years of age had a 5 times higher rate of myocarditis and pericarditis compared to Pfizer after the second dose. An interesting finding of this study was that for both vaccines, the longer interval resulted in lower myocarditis rates and the shorter interval had higher myocarditis and pericarditis rates. The study also showed that among individuals who received a heterologous schedule with Pfizer as their first dose and Moderna as their second dose, the rates of myocarditis and pericarditis were higher than those who received a homologous schedule of either Pfizer-Pfizer or Moderna-Moderna. In conclusion, this study supports the identified age and sex risks for myocarditis and pericarditis and shows that vaccine product, schedule, and interval also may have an impact on the rates of myocarditis and pericarditis.

[55] Kwong et al. Effectiveness of COVID-19 vaccines over time in Ontario. Presentation January 24, 2022
[56] Buchan et al, Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval | medRxiv

Ongoing analyses of national passive surveillance from the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS), which includes the Ontario dataset and information from other provinces and territories, supports the same interval trend. The CAEFISS analysis found that the interval makes a difference with regard to myocarditis and pericarditis rates, with shorter interval/higher rates and longer intervals/lower rates of myocarditis and pericarditis. To explore the Buchan et al study further by vaccine product, schedule, interval, 7-day risk period, there were 297 cases of myocarditis and pericarditis. In a sub-analysis of 202 cases from June onwards who received 2 doses, those with a heterologous schedule of Pfizer followed by Moderna had a higher rate of myocarditis than the other schedules. Also notable was the difference in myocarditis rates between the shorter interval and the longer interval. For both the homologous Moderna schedule and the homologous Pfizer schedule, comparing a shorter interval of 30 days or less to a longer interval of 56 days or more, there was a 5-fold or greater rate of myocarditis with the shorter interval compared to the longer interval.

To summarize the myocarditis/pericarditis story, Canada is seeing the same risk profile with regard to younger males being at greater risk after the second dose. Myocarditis is higher after Moderna for the second dose, particularly with the heterologous schedule. The shorter interval seems to result in a higher rate of myocarditis and pericarditis compared to a lower rate with a longer interval.

Discussion Summary

Dr. Lee commented that a silver lining of this pandemic has been that it has strengthened the US's collaboration with its international partners such as Canada, Israel, and others. That has created a focus on what countries can share and learn together to improve the health of their respective populations. She expressed appreciation for Canada sharing this information with ACIP.

Dr. Poehling asked whether Canada has learned anything about the resolution of myocarditis in terms of shorter intervals versus longer intervals.

Dr. Tunis said that to his knowledge, they have not yet been able to ascertain any differences in severity or resolution based on intervals.

Ms. Ogunnaike-Cooke from the surveillance group at PHAC added that this is an area of active interest and they are working with external partners to put in place some outcome monitoring studies that will help to look in more detail. They data they get with this surveillance does not have that ongoing monitoring components to give them that richness of information at this time.

Dr. Daley asked whether they have any sense about whether the individuals who got a shorter interval were different in any of systematic way from the individuals who received doses at a longer interval.

Dr. Tunis said that in broad strokes, they did see a difference in terms of territorial populations where there was more complete allocation pushed to those territories early on that allowed shorter intervals before the preference toward extended intervals was implemented.

Ms. Ogunnaike-Cooke added that this is an interesting and tough question. This analysis is complicated because the interval does have some kind of age component to it, because that is because the vaccine rollout plan used an age-based component. The surveillance data do not necessarily have that depth of clinical information to be able to dig deep into the clinical

presentations by age. While there was a shorter interval than the territories, the populations are so small that there were not enough cases to assess and differentiate between what the pattern of myocarditis was for that group compared to the other populations.

Dr. Sanchez observed that the Canadian data had some important implications that may impact ACIP's ultimate recommendations. It is interesting that the Moderna booster after the Pfizer was associated with more myocarditis. This would suggest that perhaps ACIP should recommend a preference to Pfizer versus Moderna, at least in the highest risk group of younger males. The data also speak to pathogenesis, because the longer interval was associated with higher GMTs but less myocarditis. Moderna is a higher dose than the Pfizer, so maybe it is not all related to an immune antibody-mediated process.

Ms. Stinchfield (NAPNAP) asked whether Canada was seeing data for people who have not completed the series as the intervals are lengthened or if they have any concerns about that.

Dr. Tunis said he had not seen anything in the data to be able to tease apart those who are receiving incomplete series in terms of whether there was a temporal association between them not being able to receive the second dose for a number of months like early in the rollout and then giving up.

Dr. Warshawsky added that she also was not aware of any data regarding the interval impacting people getting their second dose or a booster. She thought this may be driven more by the context of the outbreak. If the outbreak is settling down, people may be less enthusiastic about their vaccines. But as the outbreak ramps up, they become more so.

Ms. Ogunnaike-Cooke added that Canada has been very fortunate to have high coverage overall. The latest information shows that almost 83% of the population is fully vaccinated. She thinks Omicron had a lot to do with that in terms of motivating stragglers to get their primary series, complete their schedules, and/or get their boosters.

Dr. Lee commented that the data presented were convincing that an extended interval is not only potentially safer from a myocarditis standpoint, but also potentially more effective. She asked whether it is also more durable or if they have noticed that in provinces that had shorter vaccination intervals the need for a booster is greater than in areas where there are extended vaccination intervals. There is not only the immediate question around this series, but also the potential question about the need for future boosters in terms of whether the need for ongoing boosters can be mitigated. Every time there is a booster, it carries both benefits and risks. The cumulative benefit-risk profile over time does change.

Dr. Tunis indicated that Canada has been very preoccupied with this excellent point as well. Various countries have been trying to compare notes with other countries throughout the pandemic. Canada has been closely watching what happens in Israel, understanding that Israel has been using the authorized interval. Everything has been short and quick as things rolled out there, which he supposed is often the case in the US. There is a sense that the booster programs in Canada were held off somewhat longer than in other countries. Part of their understanding is that that was due to the longer intervals. However, that is somewhat confounded because those who got longer intervals over the summer also had a shorter time since their second dose. If worried about time since second dose, Canada was at an advantage in that respect going into the fall compared to some other countries. That was perhaps compounded also by the longer intervals that afforded more durable immunity. There has been some research around the breadth of response and the longer time between exposures in terms

of whether vaccine or viral exposures could allow affinity maturation to improve the breadth of response against variants. Part of the rationale that NACI is articulating in some of their statements regards durability, higher effectiveness, and possibly the breadth against variants that has been of interest to the committee. Not only has this been seen with the primary series, but also NACI continues to recommend a 6-month interval for boosters, although many jurisdictions have gone a little bit shorter that that.

Dr. Warshawsky added that Canada was still seeing high VE against infection and severe disease as they headed into the Delta period, which she thinks is because their interval was longer. There were some populations for which a shorter interval was used, particularly at the beginning of the outbreak when they were vaccinating older adults in LTCF. In that population, there was a more rapid decline in VE. In the general population, a sustained higher level of protection was observed against both infection and severe disease into the Delta period. They did not need the booster as quickly because they were still seeing sustained protection in the Canadian data. The other population is healthcare workers (HCW) who dominantly received a short interval, except in the province of Quebec where a longer interval was used. HCW had a short interval because they were prioritized early for boosters due to concern about potential waning of protection occurring earlier.

Dr. Sanchez asked what vaccines are being used in Canada and whether they have any preferential recommendations for use of one versus the other based on their data, especially as it relates to the myocarditis.

Dr. Tunis indicated that the program in Canada has used predominantly mRNA vaccine. AstraZeneca viral vector vaccine was also used in the Winter/Spring of 2021, but it accounts for a very small proportion at about 4% viral vector, and then the vast majority has been mRNA. Janssen vaccine supply was made available to some Canadian provinces and territories in the past few months, but it has been a relatively small amount. The program has used over 90% mRNA. Since Spring/Winter of 2021, NACI has been preferentially recommending mRNA over viral vector vaccines. As TTS emerged, that strengthened the preferential position even further for the committee. Similar to ACIP who have now also preferentially recommended mRNA over viral vector vaccines, that position has been longstanding in Canada and he thought was part of what pushed toward the predominantly mRNA program. Based on the myocarditis signals that have been observed within the mRNA category, NACI has preferentially recommended Pfizer over Moderna for persons 12-29 years of age for both primary series and booster doses.

Dr. Warshawsky added that Canada has had some mixed schedules in which people who started with AstraZeneca vaccine finished with an mRNA vaccine. Most of the heterologous vaccination is Pfizer as the first dose and Moderna as the second dose. About 12% of people have received either heterologous AstraZeneca with an mRNA or heterologous mRNA schedules.

Dr. Tunis pointed out that a theme Canada has been trying to communicate is that the strength of this surveillance system and the research that has been conducted has allowed Canada iterate and refine the program to improve the safety of already safe vaccines. That has been a nice lesson learned in a pandemic. It can be a challenging communication message at times as things evolve, but Canada is quite pleased that they have been able to evolve in a positive direction to iterate on over time.

VSD: Myocarditis after Moderna and Pfizer/BioNTech COVID-19 Vaccine

Nicola Klein, MD, PhD (KPNC) presented the results of a myocarditis analysis monitoring COVID-19 vaccine safety conducted by the VSD and head-to-head product comparisons, with a focus was on myocarditis and pericarditis during the Day 0-7 window after mRNA vaccination in terms of the risk among competitors who were 22-42 days after vaccination and direct head-to-head comparisons of Moderna vaccine versus Pfizer vaccine. As a reminder, the aims of the VSD RCA are to: 1) monitor the safety of 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. Myocarditis/pericarditis in the first 60 days after vaccine is one of the pre-specific RCA outcomes. Surveillance began in December 2020 and the pre-specified outcomes are monitored weekly.

The codes in the left column in the following table initially were used for early surveillance, but based on some feedback and discussions internally with the VSD investigators, the ICD code list was expanded within the past few months to include the ICD codes listed in the right column. All of the data and analyses Dr. Klein shared were based on the codes in the right column:

Initial Code List (based on consultation with cardiologist)	Revised Code List (based on VSD feedback)
• B33.22 Viral myocarditis • B33.23 Viral pericarditis • I30.* Acute pericarditis • I40.* Acute myocarditis	• B33.22 Viral myocarditis • B33.23 Viral pericarditis • I30.* Acute pericarditis • I40.* Acute myocarditis • I51.4 Myocarditis, unspecified • I31.9 Disease of the pericardium, unspecified

As of January 15, 2022 in the VSD, nearly 15 million total doses of COVID-19 vaccines had been administered and 73% of the age-eligible population was fully vaccinated. The vast majority of vaccines that have been administered through the VSD are mRNA vaccines, with somewhat more Pfizer-BioNTech than Moderna vaccine. Substantial numbers of each mRNA vaccine have been administered compared to Janssen vaccines.

For the analytic strategy, the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccine were compared to the number expected. The expected number was derived from “vaccinated concurrent comparators” who were in a comparison interval (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.

This presentation focused on a subgroup of persons 18-39 years of age who were verified to be myocarditis/pericarditis patients after mRNA vaccine through January 15, 2022. At this time, the total number of doses administered to data included the following: Moderna Dose 1: 923,711; Moderna Dose 2: 901,393; Pfizer Dose 1: 1,479,596; Pfizer Dose 2: 1,432.447. In terms of dates and intervals between Dose 1 and Dose 2 in this age group, all most all Pfizer doses were given 21 days between Dose 1 and Dose 2. There was some variation on either side of Day 21, but not much. For Moderna, nearly all doses were given on Day 28, with some doses given a couple of days later or earlier than that.

For myocarditis and pericarditis, chart reviews are performed for all cases identified. Chart review has been completed for 297 cases since January 15, 2022. There are 19 charts pending review for persons under 18 years of age. Cases amongst individuals 5-39 years of age are identified anytime post-vaccination. After initial chart review, they are adjudicated either by an infectious disease clinician and/or cardiologist to confirm that the case is an incident following vaccination, that the case meets the CDC case definition (myocarditis, pericarditis, or myopericarditis), and to evaluate the level of certainty for myocarditis. Adjudication has verified 213/297 (71%) of myocarditis and pericarditis cases. Of those, 79 (16 after Dose 1 and 63 after Dose 2) have been verified amongst persons 18-39 years of age, all of whom experienced onset in the Day 0-7 risk interval—the risk interval of focus for the rest of analyses, the selection of which was based on earlier findings of significant clustering of cases in the first week after vaccination.

In the vaccinated concurrent analyses comparing myocarditis and pericarditis in the Day 0-7 risk interval among persons 18-39 years of age by product and dose, all adjusted rate ratios were elevated for all vaccinees after both doses. Focusing on Dose 2, the adjusted rate ratio for Pfizer was 14.3 with 22.4 excess cases. The adjusted rate ratio for Moderna was 18.75 with 31.2 excess cases. This suggests indirectly that the rate ratio after Moderna appears to be higher than after Pfizer, but that they are both very elevated. The excess cases in the risk period are roughly 31.2 versus 22.4. Notably, these are indirect calculations and indirect comparisons. This table shows what was in the charts for verified myocarditis/pericarditis cases in the 0-7 days after any dose of either mRNA vaccine:

Level of Care and Status	18–39-Year-Olds (Pfizer) N=41	18-39–Year-Olds (Moderna) N=38
Highest level of care		
Outpatient	1 (2%)	1 (3%)
Emergency department	5 (12%)	7 (18%)
Admitted to hospital	35 (85%)	30 (79%)
Admitted to ICU	0 (0%)	0 (0%)
Length of hospital stay, median (range)	1 day (0–2 days)	1 day (0–13 days)
0 days (same day discharge)	8 (20%)	7 (18%)
1 day	18 (44%)	19 (50%)
2 days	15 (37%)	9 (25%)
3 days	0 (0%)	2 (5%)
4 days	0 (0%)	0 (0%)
5 days	0 (0%)	0 (0%)
6+ days	0 (0%)	1 (3%)
Discharged to home	41 (100%)	38 (100%)
At least one follow-up visit noted at the time of chart review	37 (90%)	34 (90%)

Based on the chart review of cases only, there do not appear to be any obvious differences in the clinical cases of myocarditis/pericarditis between persons 18-39 years of age for Pfizer or Moderna.

In terms of whether there is any difference in the risk of myocarditis and pericarditis between mRNA vaccines, analyses with vaccinated concurrent comparators indicate that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in persons 18-39 years of age. Analyses with vaccinated concurrent comparators indirectly suggest that Moderna may be associated with more risk of myocarditis/pericarditis than Pfizer. To directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, a head-to-head comparison was conducted among persons 18-39 years of age.

Based on data through January 15, 2022, the interval between Dose 1 and Dose 2 was fairly consistent between Pfizer and Moderna vaccines and with what was seen in the overall population at about 21 days for Pfizer and about 28 days for Moderna. In terms of symptom onset of verified cases, there was very strong clustering of cases after both vaccines in the first week after vaccination. Temporal clustering scan statistics show that the clustering is highly statistically significant in the first 3-5 days after Moderna vaccine and 0-4 days after Pfizer vaccine. In the head-to-head comparison, the Moderna and Pfizer vaccinees were directly compared during the risk interval within groups. The groups were comprised of individuals inside the risk interval (Days 0-7 post-vaccination); individuals of the same age group, sex, and race/ethnicity and from the same VSD site; and on a calendar day when an mRNA vaccinee had myocarditis/pericarditis. The rate ratios were estimated with 95% confidence intervals (rate post-Moderna / rate post-Pfizer). The null hypothesis was tested that the rate of myocarditis and pericarditis after vaccination does not differ between Moderna and Pfizer.

Following either dose in both sexes, there was an elevated rate ratio of 1.61 that was statistically significant, and excess cases of 8 per 1 million doses. The other analyses trended similarly, although none of them met statistical significance. Looking at Dose 2 comparing Moderna versus Pfizer, there were excess case of 10.7. In the analysis with pericarditis excluded, the adjusted rate ratios were similar in terms of the level of the increased point estimates, although none of these analyses meet statistical significance.

In summary, among persons 18-39 years of age, both mRNA vaccines were associated with increased risk of myocarditis and pericarditis in the 0-7 days post-vaccination, particularly after Dose 2. There were an estimated 22.4 excess cases per million second doses after Pfizer and 31.2 excess cases per million second doses after Moderna. Among persons 18-39 years of age, there were no noticeable clinical differences between cases after Moderna and those after Pfizer. Most had a hospital length of stay of 0-1 days and none were admitted to the ICU. Direct head-to-head comparisons provided evidence that the risk of myocarditis and pericarditis may be higher after Moderna than after Pfizer. Comparing Moderna versus Pfizer, it was estimated that Moderna was associated with an additional 10.7 cases of myocarditis and pericarditis per million second doses. Both mRNA vaccines were associated with increased risk of myocarditis and pericarditis for individuals aged 18-39 years.

Discussion Summary

Dr. Zimmerman (APRT) asked whether there are any data from this study on the background rates from COVID disease-induced myocarditis.

Dr. Klein indicated that this was not part of this study.

Dr. Duchin (NACCHO) inquired as to whether any analyses were performed for the risk window through 21 days and whether cases in that window were adjudicated to determine whether they might be vaccine-associated.

Dr. Klein indicated that all cases of myocarditis/pericarditis after vaccination are adjudicated. Referring to Slide 36 showing the results of the primary analysis of the 21-day risk interval, the adjusted rate ratios were numerically lower than for the Day 0-7 interval, which is remarkable. The excess cases following Dose 2 after both Pfizer and Moderna was 22.6 and 31.3, respectively. That suggests that all of the excess risk is in the Day 0-7 risk window because it is the same as seen in the 21-day risk interval.

Myocarditis and COVID-19 Vaccine Intervals: International Data and Policies

Danielle Moulia, MPH (CDC/NCIRD) presented an examination of international data and policies on preferential recommendations of an mRNA vaccine product or extended primary series interval as they relate to myocarditis and/or pericarditis. This included a review of data on the risk of myocarditis by mRNA vaccine product, focusing on the highest risk group: younger males post second dose; a review of data on an extended primary series interval, specifically how that relates to myocarditis risk and VE; and presentation of international policies related to preferential recommendations or extended primary series intervals. Throughout this presentation, myocarditis and/or pericarditis were generally referred to as myocarditis unless a specific study was being referenced. As a reminder, in the VAERS data among males aged 18-24 years, the observed myocarditis reporting rate within a 7-day risk interval after a second dose of Moderna was 40 per million doses. In the VSD data among males 18-39 years of age, the rate for myocarditis in the 7 days after a Moderna vaccine was 1.5 times the rate for the 7 days after Pfizer vaccine. However, the adjusted rate ratio of 1.5 was not statistically significant.

To review key findings from Canada heard earlier in the day,[57] in a study of passive and enhanced surveillance, the myocarditis and/or pericarditis reporting rate among males 18-29 years of age in the 7 days after a second dose of Moderna vaccine was 140 per million doses, which was almost 5 times higher than the Pfizer reporting rate of 25 per million doses. In Ontario during the period of enhanced passive surveillance, among males 18-24 years of age, the myocarditis and/or pericarditis reporting rate after a second dose of Moderna was over 5 times the Pfizer reporting rate. The reporting rates included all reports during the length of the study.

The UK's Yellow Card reporting scheme is a national passive and active surveillance system. Among all persons aged 18-29 years of age, the myocarditis and pericarditis reporting rate after a second dose of Moderna was 71 per million doses, roughly 2.5 times higher than the Pfizer reporting rate of 24 per million doses. In a self-controlled case series of myocarditis hospitalizations in the UK, among males younger than 40 years of age after a second dose of Moderna, there were 101 additional events of myocarditis per million doses compared to 12 additional events of myocarditis per million doses of Pfizer.[58]

The Nordic Collaboration (includes Denmark, Finland, Norway, and Sweden) presented the results of their study of all 23 million residents aged 12 years and older to VaST on January 10, 2022. While these data are not publicly available, within a 7-day risk period, the rate ratio for myocarditis after either dose of Moderna vaccine versus an unvaccinated comparator was higher than Pfizer. The highest rate ratios observed were among those receiving a second dose

[57] Sources: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3988612 Accessed 1/23/2022; and https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1.article-metrics Accessed 1/23/2022

[58] Sources: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#yellow-card-reports Accessed 1/22/2022; and Patone M. 2021 MedRxiv preprint. https://www.medrxiv.org/content/10.1101/2021.12.23.21268276v1.full.pdf Accessed 1/22/2022

of Moderna in a heterologous mRNA primary series.[59] A retrospective cohort of all 5 million residents of Denmark ages 12 years and older[60] had a case definition of hospital diagnosis of myocarditis or pericarditis, increased troponin levels, and the hospital state lasting more than 24 hours within 28-day risk period. Analysis was done using a Cox proportional hazard model with covariates for age, sex, vaccine priority group, season, and clinical comorbidities. The absolute rate of myocarditis was per 100,000 doses and the adjusted hazard ratio with an unvaccinated comparator for those aged 12-39 years. By gender after any dose, the rates were about 3-fold to 4-fold higher for those vaccinated with Moderna compared to Pfizer. In a post-hoc analysis of males ages 12-39 years, the rate of myocarditis was 9.4 per 100,000 or 94 per million post-Dose 2 of Moderna. Using an unvaccinated comparator, the adjusted hazard ratio of myocarditis was 9.8 for Moderna and 1.5 for Pfizer.

Looking to France and Germany, in both national AE surveillance systems, the highest reporting rates of myocarditis were among young males. In Germany, among males ages 18-29 years, the myocarditis and pericarditis reporting rate after any dose of Moderna was 117 per million doses, roughly 2.5 times higher than that of Pfizer. In France, among males ages 18-24 years, the myocarditis reporting rate after a second dose of Moderna was 139 per million doses, roughly 3 times higher than that of Pfizer.[61]

Summarizing the myocarditis rate ratios comparing Moderna to Pfizer by country, subpopulation, and dose number looking across the studies, there is a 1.5-fold to 5-fold increase in myocarditis after a second dose of Moderna vaccine compared to a second dose of Pfizer among younger males. Direct comparisons of rate ratio should be interpreted with caution due to differences in subpopulation, study design, modeling, national setting, and implementation factors.[62]

In summary of the findings for myocarditis risk by mRNA product, global data suggests that the risk of myocarditis may be higher for Moderna than Pfizer vaccine. There are limitations to this review. Absolute rates are not readily comparable due to differences in case definition and risk period, subpopulation, case ascertainment, calendar time, and vaccine implementation factors including extended primary series intervals. A limited number of geographic locations are administering both Moderna and Pfizer and had data available.

Turning now to the risk of myocarditis by primary series interval or the time between the first and second doses, this assessment returned to the work of Bouken and colleagues out of Ontario, examining rates of myocarditis by dosing intervals of less than 4 weeks, 5-7 weeks, and greater than 8 weeks among adults ages 18 years and older. Across the three schedules of primary series, rates of myocarditis decreased as the intervals between Dose 1 and Dose 2 lengthened. Within each vaccine schedule, the lowest rates of myocarditis were observed among those with the longest time between Dose 1 and Dose 2. The highest rate was observed among persons who received Pfizer for their first dose and Moderna for their second dose within the

[59] Source: Hovi et al., Slides not publicly available
[60] Source: Husby et al., SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study BMJ 2021; 375 :e068665 doi:10.1136/bmj-2021-068665
[61] Sources: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/46_21.pdf. Accessed 1/23/2022; https://www.omedit-auvergne-rhone-alpes.ars.sante.fr/index.php/system/files/2021-10/ANSM_Rapport_CRPV_Moderna_22102021.pdf Accessed 1/23/2022; https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf Accessed 1/23/2022
[62] Sources: Husby et al., SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study. BMJ 2021; 375:e068665 doi:10.1136/bmj-2021-068665 https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf Accessed 1/23/2022; Klein, N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons. Slides. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3988612 Accessed 1/23/2022 https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1.article-metrics Accessed 1/23/2022

shortest interval of 4 weeks or less between doses. In summary, limited data suggest the rates of myocarditis may be lower with an extended interval between Dose 1 and Dose 2 of a primary series. These observed rates were observed both with Moderna and Pfizer vaccine.

Looking now to data on VE with an extended primary series interval, results from a test-negative case control study from May to October 2021 among 1.2 million community-dwelling adults aged 18 years and older in British Columbia and Quebec, adjusted VE estimates against SARS-CoV-2 infection and hospitalization was 5% to 10% higher with an extended interval of 7 to 8 weeks compared to a standard interval of 3 to 4 weeks. Increases in VE can be observed to level off at around the 7- to 8-week interval. The overall VE against hospitalization and infection for a 2-dose mRNA series with an extending dosing interval of 7 weeks or greater was 94% to 97% for hospitalization and 89% to 91% for infection.[63]

Turning to England, there was a test-negative case control study of VE from October 2020 to June 2021 among adults aged 50 and older attending community testing, across all age groups starting at age 50, estimated Pfizer VE against SARS-CoV-2 infection was higher with extended intervals of greater than 6 weeks compared to the standard 3- to 4-week interval.[64] Looking at immunogenicity with an extended primary series interval in a study by Payne and colleagues out of the UK that examined SARS-CoV-2 infection-naïve persons. Serological responses were higher after an extending dosing interval of 6 to 14 weeks compared to a standard interval of 3 to 4 weeks. Among persons with an extended interval, there were higher antibody and B cell responses, as well as sustained B and T cell responses compared to a standard interval. An extended interval may promote efficient T cell expansion and long-term memory cell persistence.[65] Three additional studies found that neutralizing antibody titers were higher following an extended dosing interval of 6 to 14 weeks with an mRNA vaccine compared to a standard interval of 3 to 4 weeks.[66]

In summary, global data suggest that an extended primary series interval may improve immunogenicity and VE. Neutralizing antibody titers were higher following an extended dosing interval of 6 to 14 weeks with an mRNA vaccine compared to a standard interval of 3 to 4 weeks. VE against infection and hospitalization was higher with an extended interval of 7 to 8 weeks compared to a standard interval of 3 to 4 weeks. One limitation to note is that these studies were conducted prior to the Omicron surge, during which the absolute VE may be lower.

Turning finally to global policies, Canada's NACI[67] strongly recommends a complete mRNA series for all persons aged 12 years and older. Among persons 12-29 years of age, Pfizer is preferred for the primary series. For all mRNA primary series, the optimal interval is 8 weeks. In the UK, there is a preferential recommendation for the use of Pfizer over Moderna in persons aged 12-17 years. The UK's JCVI[68] has advises a minimum interval of 8 weeks between first and second doses for all persons over 18 years of age. For children and adolescents aged 12-17 years who are at higher risk of COVID due to underlying conditions, living accommodations, or who are contacts of immunocompromised persons, the recommended interval is 8 weeks.

[63] Skowronski DM. 2021, MedRxiv preprint
[64] Amirthalingam G. 2021, Nat Commun
[65] Payne R. 2021, Cell
[66] Amirthalingam G. 2021, Nat Commun.; Parry H. 2022, Npj Vaccines.; Grunau B. 2022, Clin Inf Dis
[67] Sources: National Advisory Committee on Immunization: Updated Guidance on the use of COVID-19 Vaccines (slides) https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/vaccines/safety-side-effects.html#myocarditis-and-pericarditis Accessed 1/23/2022; https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html#a5.4. Accessed 2/1/2022.
[68] Source: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045852/Greenbook-chapter-14a-11Jan22.pdf. Accessed 1/22/2022

However, for children and adolescents who do not fall into these high-risk groups, a 12-week interval is preferred. The guidance does go on to note that in periods of high incidence or concern over a new variant, the interval can be shortened to eight weeks.

Looking now to the Nordic countries. In Sweden, Pfizer is recommended over Moderna for persons aged 12-30 years. The recommended interval for both vaccines is 3 to 4 weeks. In Norway, Pfizer should be offered to persons aged 12-30 years. Children and adolescents aged 5-15 years without severe underlying conditions may receive 1 or 2 doses based on their parents' decision. Persons aged 16 years and older should receive 2 doses. The recommended interval for persons aged 18 years and older is 3-12 weeks. For adolescents aged 16-18 years, the recommended interval is 8-12 weeks. For children and adolescents aged 5-15 years with severe underlying conditions, the recommended interval is 8-12 weeks. However, this can be adapted down to 3 weeks based on medical assessment. In Finland, boys and men aged 12-30 years are only offered Pfizer. Girls and women aged 12 years and older are offered Moderna or Pfizer. The recommended interval is 6 to 12 weeks for all persons aged 5 years and older. In Denmark, both Moderna and Pfizer vaccine are approved for persons aged 12 years and older. The primary series interval is 3 to 6 weeks, and studies have shown that the median interval between Dose 1 and Dose 2 is 5 weeks.[69]

In Singapore, children and adolescents ages 18 years and younger should receive Pfizer vaccine. The recommended interval is at least 21 days. Guidance notes myocarditis risk may decrease with a longer interval, but encourages a second dose at 21 days due to Omicron. In Taiwan, both Pfizer and Moderna vaccines are approved for persons aged12 and older, and the recommended interval between first and second dose is at least 12 weeks.[70] In Australia, the recommended interval is at least 3 weeks for Pfizer or 4 weeks for Moderna. Among children aged 5-11 years, the recommended interval is 8 weeks. Guidance notes that the interval can be shortened in special circumstances to a minimum of 3 weeks, such as in an outbreak response prior to the initiation of significant immunosuppression or international travel.[71] In France, Haute Autorité de Santé (HAS) recommends persons under the age of 30 be given Pfizer over Moderna when available. The recommended interval is 6 weeks. And in Germany, the recommendation is for persons under the age of 30 to be given Pfizer over Moderna. The recommended interval is 3 to 6 weeks.[72]

This review has a number of limitations. It was not a systematic review and the studies presented are biased toward findings that influence national vaccine policy. Caution should be used when comparing myocarditis rates across studies as surveillance systems, case definitions, risk intervals, subpopulation, age ranges, and vaccine implementation differ substantially. National vaccines policies are constantly evolving. Some policies extending the primary series interval evolved from implementation strategies to reach the most people with a first dose.

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[69] Source: https://www.fhi.no/en/id/vaccines/coronavirus-immunisation-programme/coronavirus-vaccine/#vaccination-of-children-and-adolescents. Accessed 1/22/2022 https://www.lakemedelsverket.se/en/coronavirus/covid-19-vaccine. Accessed 1/23/2022 https://thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronavirus-covid-19-latest-updates/vaccines-and-coronavirus/getting-vaccinated-against-covid-19-how-why-and-whenhttps://www.sst.dk/en/English/Corona-eng/Vaccination-against-covid-19/COVID-19-vaccines-in-Denmark

[70] Source: https://www.cdc.gov.tw/En/Bulletin/Detail/YPIDZwC4HjqBMtGi4jynHQ?typeid=158. Accessed 1/31/22; https://www.moh.gov.sg/covid-19/vaccination/faqs---children-related-vaccination-matters. Accessed 1/31/22

[71] Source: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/doses-and administration. Accessed 1/30/2022; https://www.health.gov.au/sites/default/files/documents/2021/12/atagi-recommendations-on-pfizer-covid-19-vaccine-use-in-children-aged-5-to-11-years_0.pdf Accessed 1/30/2022

[72] Source: https://www.nitag-resource.org/sites/default/files/2021-12/48_21.pdf. Accessed 1/23/2022; https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/46/Art_03.htm Accessed 1/23/2022; https://www.reuters.com/business/healthcare-pharmaceuticals/french-health-authority-advises-against-moderna-covid-19-vaccine-under-30s-2021-11-09/ Accessed 1/23/2022

In conclusion, observational data suggests that myocarditis may be associated with receipt of Moderna mRNA vaccine in persons aged 18-29 years, especially males and with shorter primary series intervals. Extended primary series intervals may improve VE and several countries have implemented policies or recommendations to lengthen the interval between doses in the primary series, which may improve VE and mitigate myocarditis risk. Some have preferentially recommended use of Pfizer among males and/or persons aged 30 years or younger, which may mitigate the risk of myocarditis.

Discussion Summary

Dr. Lee expressed gratitude for the comprehensive overview of the various policies. Much of the tension over the course of the past year for ACIP has been to try to simplify the message to make it more straightforward for implementation. From a global perspective, she recognizes how confusing this must be going from country-to-country but also recognizing that everyone is trying to do the right thing—optimize health and mitigate risk.

Ms. Bahta noted that in the summary of US findings, the reporting rate after a second dose of Moderna was 42 million, but there was not a rate for the second dose of Pfizer.

Dr. Shimabukura clarified that the reporting rates for Moderna in males after Dose 2 in 0-7 days was 40 per million. The corresponding rate for Pfizer was 37 per million. For persons 25-29 years of age, Moderna after Dose 2 in 0-7 days was 18.3 per million and Pfizer was 11.7 per million. After those ages, there is not much of a difference between these vaccines.

Dr. Sanchez noted that these presentations raised a lot of questions and issues in his mind as ACIP tries to refine vaccine policy, recommendations, and the pursuit of safety and efficacy. It seemed to him that it was not just a matter of saying that Pfizer is recommended over Moderna. Based on the data, Pfizer has been associated with lower myocarditis. However, to try to minimize myopericarditis occurrence, ACIP also will have to deal with the intervals. Perhaps a preferential recommendation should be for the vaccine and the interval, which has a lot of implications for boosters as well.

Summary and WG Interpretation: Extended Intervals for mRNA COVID-19 Vaccines

Sara Oliver, MD, MSPH (CDC/NCIRD) provided a summary and WG interpretation of the data on extended intervals for mRNA COVID-19 vaccines. As a reminder, the policy question for the ACIP voted was, “Should vaccination with the Moderna COVID-19 vaccine (Spikevax®, 2-dose primary series) be recommended for persons 18 years of age and older?” comparing the Moderna vaccine to no vaccine. This presentation focused on an additional question for discussion based on new and emerging data heard throughout the afternoon, “Based on new and emerging data, should CDC consider guidance around the interval between Dose 1 and 2 for mRNA COVID-19 vaccines?” This discussion addressed both Moderna and the Pfizer COVID-19 vaccines.

VaST reviewed the most recent data from 3 US safety monitoring systems, as well as data from international partners. Reported rates of myocarditis following the mRNA vaccines are higher than background, highest after Dose 2, and higher in adolescent young adult males. In most safety monitoring systems, myocarditis risk is somewhat higher after Dose 2 of Moderna vaccine than Dose 2 of Pfizer vaccine. The data are limited but emerging around myocarditis risk following different Dose 1 and Dose 2 intervals.

Summarizing the international data around myocarditis after the mRNA vaccines, the risk of myocarditis was higher for Moderna than Pfizer and highest after the second dose among younger males. However, the rates of myocarditis were lower with an extended interval between the first and second doses of the mRNA vaccine primary series.

To summarize the extended primary series interval data around immunogenicity and VE, an extended primary series interval may improve immunogenicity and VE. Antibody responses were higher following an extended interval between the first and second doses of the mRNA vaccines compared to a standard interval. VE against infection and hospitalization were higher with an extended interval compared to a standard interval.

Considering the benefit-risk balance for mRNA COVID-19 vaccines looking specifically in adults 18-39 years of age but comparing vaccine-specific benefits to vaccine-specific harms with the mRNA vaccines, the benefit-risk assessment used the same methods as those previously described, but now includes vaccine-specific VE and myocarditis inputs for both the Moderna and Pfizer vaccines. In terms of vaccine-specific estimates for effectiveness against COVID-19 hospitalization from both IVY and VISION, the pooled VE estimate was 92% for Moderna and 87% for Pfizer. In terms of vaccine-specific rates of myocarditis per million second doses administered among persons 18-39 years from VSD, the rates were the highest in males at 67.5 per million second doses for Moderna and 46.8 per million second doses for Pfizer.

Regarding COVID-associated hospitalizations prevented compared with myocarditis cases expected from the vaccine, over the course of 5 months, the benefits of receiving either mRNA vaccine far outweigh the risks. More myocarditis cases would be expected among the Moderna COVID-19 vaccine recipients than Pfizer, but more COVID hospitalizations would be prevented among the Moderna recipients compared to Pfizer as well. For males aged 18-39 years for whom the myocarditis rates are the highest, the benefits for the mRNA vaccines still far outweigh the potential risk. Again, more myocarditis cases would be expected among the Moderna vaccine recipients compared to Pfizer. But again, more COVID hospitalizations would be prevented among the Moderna recipients than the Pfizer recipients.

To highlight the limitations, the benefit-risk analysis focuses on individuals 18-39 years of age, considers direct benefits and risk over a 150-day period, and compares vaccine vs. no vaccine. VE assumptions used in the model do not yet include Omicron-specific VE estimates. The model assumes static hospitalization rate over 5 months. The benefit-risk profile might change as hospitalization rates change. The model does not account for booster doses or prior infection.

To summarize the benefit-risk balance for mRNA COVID-19 vaccines, COVID hospitalizations averted by the Moderna COVID-19 vaccine are greater than for the Pfizer BioNTech COVID-19 vaccine. On the risk side, myocarditis after the Moderna COVID-19 vaccine are likely greater than for the Pfizer BioNTech COVID-19 vaccine. The benefits for both mRNA vaccines far outweigh the risk of myocarditis compared to no vaccine. When compared to the benefit risk balance for Pfizer, Moderna prevents more hospitalization, but more myocarditis cases would be expected. Rates of myocarditis were lower with extended intervals between the first and second dose of the mRNA vaccine, and the extended vaccine primary series may improve immunogenicity and VE.

In terms of the additional question regarding the possibility of an extended interval, consideration must be given to how such a recommendation would be applied. Overall, there are around 33 million unvaccinated individuals. If there is a focus on those aged 12-39 years, the population with no vaccine at all is lower in the older age groups. Then there are several considerations regarding extended intervals between the first and second doses of mRNA vaccines. Thinking through the possible benefits specifically for safety, the extended interval appears to reduce the risk of myocarditis, with the lowest rates of myocarditis with an interval at least 8 weeks. Extending the interval also appears to increase the VE for the primary series, although this benefit may level out at about 8 weeks. For implementation, it is possible that uptake of the COVID-19 vaccine primary series could increase if individuals or parents desire an action that they could take that would lower their risk for myocarditis. Thinking through possible risk with regard to effectiveness, there will be a longer duration of time where individuals would only have the benefit of a single dose of an mRNA vaccine. Regarding implementation, for aspects that require being fully vaccinated (e.g., quarantine, travel, or restaurants), extending an interval would extend the time before somebody would be considered fully vaccinated.

Overall, the WG had several thoughts about an extended interval. An individual's risk of getting COVID-19 likely increases the longer they are only partially vaccinated with a single dose. That risk needs to be balanced with the benefits of lowering rates of myocarditis and optimizing the long-term VE. This balance is influenced by the trajectory of the pandemic and recent epidemiology of COVID-19, which can change over time. Early in the pandemic, the priority was for individuals to have optimum protection from the primary series as quickly as possible. However, guidance around COVID vaccines can be updated as new data become available, and the focus expands to also look to the future of the COVID-19 vaccine program. The WG emphasized that clear communication for COVID-19 vaccines and preferred intervals is important. Being specific for what interval is desired and for whom will be critical for those and is needed to implement any updated guidance. Also, there may be populations for whom the benefits of the earlier interval at 3 or 4 weeks would outweigh any possible risks of myocarditis. The licensed interval of 3 weeks for Pfizer or 4 weeks for Moderna would continue to be recommended, especially in circumstances where early protection is desired. Overall, after having discussions, the WG supported a preferred interval of 8 weeks between the first and second doses of an mRNA COVID-19 vaccine primary series.

Discussion Summary

Dr. Poehling expressed appreciation to everybody on the ACIP for putting together these presentations and pulling information from around the world. She found the data presented from their Canadian colleagues and from around the world very persuasive that an extended interval, particularly in younger persons at increased risk of myocarditis, would be particularly beneficial. She also appreciated the caveat the WG included because it appeared that the US was beyond the peak of Omicron. When the pandemic is receding is a particularly good time to do a prolonged interval, but there may be cases and circumstances in which a shorter interval would be recommended. She liked the extended interval of 8 weeks, which seems ideal according to Canadian data.

Dr. Daley said he was in favor of extending intervals as doing so would provide benefits to the recipients of Pfizer vaccine or Moderna vaccine. He also appreciated the desire for clear communication, which is why he would prefer an 8-week interval, but with flexibility for those who need to achieve protection sooner.

Thinking from the frontline and the knowledge that extended time seems to provide a better immune response, Ms. Bahta would support the proposed extension.

Dr. Sanchez agreed and would favor an extended interval, especially among the younger male individuals because of the association with myocarditis. This is an age group that in general does not have severe infection, but still should be protected. Trying to optimize vaccine safety in that group is important. He would support a recommendation for an extended interval in that group. In the extended interval, the difference in occurrence of myocarditis between the Pfizer versus the Moderna vaccine seem less significant. With respect to making a recommendation for one versus the other product, particularly in those who are at highest risk for myocarditis, with a shorter interval it should be the Pfizer product if needed and somebody wants quicker protection. Certainly, he would favor the longer duration of 8 weeks.

Dr. Oliver noted that especially around that kind of clear communication, the thought was that any recommendations around an extended interval would be best to be applied to both mRNA vaccines. There would not be an extended interval for one or the other. Based on the data from other countries regarding myocarditis concerns, it seems that the extended interval could be a potential mitigation measure for myocarditis concerns. Looking at the totality of the benefit-risk in terms of VE and myocarditis, it was felt that the extended interval may lower the risk of myocarditis, which hopefully would negate the need for a preferential recommendation. Certainly, individual clinicians could make a choice around which vaccine they thought would be best in any specific circumstance. As a nationwide public health policy, the extended interval would be a good way to mitigate the myocarditis risk.

Dr. Sanchez clarified that he did not mean to imply or suggest that there should be a different interval between the two vaccines, but they may need to harmonize it. His understanding of the Canadian data was that with the extended interval, the differences in myocarditis with Moderna versus Pfizer was not so significant. If that was not the correct interpretation, then they would want a preferential product.

Dr. Kotton requested information on the thoughts of the WG about the people to whom this would apply who are still unvaccinated in terms of how a change in the interval might impact their desire or ability to get vaccinated.

Dr. Daley agreed that people who are not currently vaccinated have some reluctance for which there may be multiple reasons. Vaccine safety is a concern that has been raised repeatedly. As always, these are complicated issues that are nuanced and hard to communicate. Communication that there are highly effective vaccines that have a high degree of safety, but there is a way to make them even safer and the risk of myocarditis, could convince some who are reluctant to get vaccinated.

Dr. Loehr agreed with the proposed extended interval and supported the 8-week recommendations.

Ms. Hayes (ACNM) requested a reminder of the original clinical trials for the mRNA vaccines the number of times the frequency between the 2 doses was studied. She recalled that multiple schedules were tested.

Dr. Oliver emphasized that early in the pandemic, the goal was to get optimum protection as quickly as possible, so the early clinical trials for both mRNA vaccines had 3- or 4-week intervals.

Dr. Das added that by and large, the participants in the Moderna vaccine trial were extremely compliant with a 4-week interval. But they have data out to 6-week intervals showing the same level of efficacy.

Dr. Lee said she thought an extended interval would be a win-win in terms of the reduction of AEs and improvement in immunogenicity. As they approach new variants, the higher the antibodies and the more diverse these antibodies are, the better protected people will be.

As a member of the WG, Dr. Bell noted that she had the opportunity to have a very robust discussion about this already, which Dr. Oliver reflected very accurately. She was very taken with the consistency of the WG members feelings about this issue of the extended interval and the overwhelming agreement that an extended interval makes sense for both safety and efficacy reasons. She certainly supported this and thought at the end of the day, picking an8-week interval, but recognizing the need for flexibility would be the best way to keep things as simple as possible.

Dr. Ault pointed out that one of the potential problems during the 8-week gap would be that people will be vulnerable to getting infected, which would be important to address in the Clinical Considerations. Going back through his copy of the slides to see if that was specifically addressed, it appeared to be addressed tangentially.

Dr. Daley indicated that the WG did discuss that. It is a risk to be sure, but as Dr. Poehling said, if this is implemented at a timeframe when case counts are falling, that is a benefit. It is still a fairly short period of time of a 4-week or 5-week difference. The WG felt comfortable with the idea that there would be some protection from a first dose, even if the second dose was delayed somewhat. He emphasized that how this is communicated will be very important. Since many parents express concern about vaccine safety of often bring up myocarditis, perhaps they would be best service to start with that.

Dr. Brooks said that the benefit of greater immunogenicity and decrease in the rates of myocarditis made it clear to him that this would be a good recommendation. Based on the Canadian study, the level of coverage did not drop off appreciably. Concern about lowering immunity over time by only one dose is not a major worry of his. He thinks it affords a level of safety and also demonstrates to the public that ACIP is very focused on doing this in the right way and making these adjustments that are overall beneficial.

Dr. Duchin (NACCHO) agreed with the rationales around improving vaccine safety and improving VE. The type of graphics that were shown earlier may be very helpful in communicating to the public around any changes that may be made in the vaccine schedule. He asked whether someone could comment on any implications for timing of booster doses if an extended primary series interval is adopted.

Dr. Oliver indicated that booster recommendations are based on timing since completion of the primary series, so that recommendation would stay the same and the clock would start counting after the second dose. It would be 5 months after someone is fully vaccinated, and that would not change. If they have learned anything throughout the pandemic, it is that their crystal balls are not always great at predicting what the future will be. They are aware that there are studies

ongoing for Omicron-specific vaccines. As they learn what is going on with the pandemic, as the pandemic evolves, and as additional data become available, the WG will review the information and will bring it to ACIP.

Dr. Lee said that recognizing that the current authorization either sits at 21 or 28 days, she appreciated the flexibility. In terms of whether a full recommendation is needed versus clinical guidance, this felt to her like a good opportunity to use the Clinical Guidance from a timeliness perspective and because they have an opportunity to optimize the immune response in young children, many of whom remain unvaccinated. The hope is that this will continue to improve vaccination rates over time. She recognize that there seemed to be generally supportive comments in favor of an extended interval, and now they needed to understand the regulatory allowance for these comments to be incorporated into the Clinical Guidance. Regarding the question of Moderna versus Pfizer, and also recognizing and acknowledging the variable vaccination policies that are occurring in different countries, she was not yet personally sure that there was sufficient evidence to make a preferential recommendation for two reasons. First, some people decide that they would like Moderna, such as people who have a suboptimal immune response. Allowing flexibility to be available to individual patients and clinicians to think about the benefit-risk balance for the individual would be important to reflect. That may be more difficult with a preferential recommendation. Second, the Moderna vaccine is now fully approved for persons 18 years of age and older.

Dr. Sanchez said that as much as he agreed with that statement, if there is a higher risk of myocarditis in the highest risk group of males and now one of the vaccines is associated with lower risk, he thought there should be a preferential recommendation for that vaccine in that age group in males. His current preference was that somebody in the highest risk group for myocarditis who received either Moderna or Pfizer as the first dose should get the Pfizer vaccine for their second dose.

Dr. Daley pointed out that the ACIP COVID-19 Vaccines WG discussed all of the issues that had been discussed throughout the day and they felt like an extended interval was a strategy to increase safety and decrease myocarditis risk for both mRNA COVID-19 vaccines, and did not find that there was compelling evidence at this time to have a preferential recommendation for one mRNA vaccine over another.

Dr. Fryhofer (AMA) said that speaking as a practicing physician, she greatly appreciated all of the data that had been presented throughout the day about ways to make the vaccines work better and make them safer. She also greatly appreciated what Dr. Lee mentioned about increasing flexibility for the doctors who care for these patients to help patients make decisions. By adding some flexibility there, physicians know what the points are that patients are concerned about and what might make them go ahead and get a vaccine now or wait. In previous conversations, they heard that Moderna seemed to be more durable. Now on the downward curve of Omicron, the myocarditis concern was a big one. She liked the concept of giving guidance, but also giving some flexibility. She also looks forward to more details in the Clinical Guidance about immunocompromised patients and expanding who that group of patients is for those new booster recommendations.

Dr. Loehr emphasized that one thing which came out in the presentations was that there is a higher risk of myocarditis from Moderna, but there also is a benefit in terms of hospitalization. He did not want that to get lost. In terms of a preferential recommendation, he thought they needed to look at the whole picture. Hospitalizations might be just as important as the myocarditis.

CERTIFICATION

Upon reviewing the foregoing version of the February 4, 2022 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
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
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
AR	Adverse Reaction
ASTHO	Association of State and Territorial Health Officers
BEST	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CAEFISS	Canadian Adverse Event Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention
CIQ	Quebec's Provincial Immunization Committee
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COVE Trial	Coronavirus Efficacy Trial
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ECG/EKG	Electrocardiogram
ED	Emergency Department
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
EUI	COVID-19 Vaccine Emergency Use Instructions
FDA	Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers

HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
ICD	International Classification of Disease
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IVAC	International Vaccine Access Center
J&J	Johnson & Johnson
JCVI	Joint Committee on Vaccination and Immunisation
KFF	Kaiser Family Foundation
LTCF	Long-Term Care Facilities
MAAE	Medically Attended Adverse Events
MMF	Mycophenolate Mofetil
MMWR	*Morbidity and Mortality Weekly Report*
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCIRD	National Center for Immunization and Respiratory Diseases
NCL	National Consumers League
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NP	Nasopharyngeal
PAHPRA	Pandemic and All Hazards Preparedness Reauthorization Act
PCP	Primary Care Provider/Practitioner
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PIDS	Pediatric Infectious Disease Society
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SOC	System Organ Class
TRAIPAG	Transplant and Immunocompromised Patient Advocacy Group
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
USG	United States Government
VA	(US Department of) Veteran’s Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	Vaccine Safety Technical Subgroup
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines for Children

VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization