MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JUNE 23, 2021
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 an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on June 23, 2021. The meeting took place remotely via Zoom and teleconference. This document provides a summary of the meeting, which focused on a variety of topics pertaining to COVID-19 vaccines, including an overview of myocarditis and pericarditis; an update on COVID-19 vaccine safety, including myocarditis after mRNA vaccines; a VaST WG assessment; benefit/risk of COVID-19 mRNA vaccines in adolescents and young adults; and an overview of data to inform recommendations for additional doses of COVID-19 vaccines.

WEDNESDAY: JUNE 23, 2021

WELCOME AND INTRODUCTIONS

Dr. José R. Romero (ACIP Chair) called to order and presided over the meeting. He welcomed everyone and thanked them for their attendance and the time they are dedicating to the COVID-19 effort.

Dr. Amanda Cohn (ACIP Executive Secretary) thanked everyone for their flexibility in the rescheduling of the meeting from the previous Friday in honor of Juneteenth, which is now a federal holiday. She indicated that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for ACIP voting members, ex officios, and liaisons. She indicated that there would be an oral public comment session at approximately 2:30 PM Eastern Time (ET). Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals who were not selected and any other individuals wishing to make written public comments may submit them through https://www.regulations.gov using Docket Number CDC-2021-0034. Further information on the written public comment process can be found on the ACIP website.

As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but are prohibited from participating in committee votes. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to that company. ACIP members stated COIs at the beginning of the meeting. No votes were taken during this emergency meeting.

ACIP is accepting applications and nominations for new members to fill upcoming vacancies. Applications should be submitted by August 1, 2021 for the 4-year term beginning July 1, 2022. The application and additional information can be found on the ACIP website at https://www.cdc.gov/vaccines/acip/apply-for-membership/index.html.

Dr. Rochelle P. Walensky (CDC Director) verbatim: I just wanted to briefly come in and say thank you for being here today. I know you have a lot of work ahead of you over the next 3 days, but I just wanted to take a minute and stop by and share my true gratitude and appreciation. We appreciate the expertise and guidance you have given CDC through this pandemic. I know my tenure here has only been 5 months. Your tenures have been longer, way longer than that. I know you've devoted countless hours to grappling really tough questions with us on vaccination, and for that, we are deeply grateful. I am deeply grateful. We particularly appreciate that on top of the additional meetings to discuss COVID-19 vaccination efforts, you have continued to look at a broader vaccination program and continue to advise us on vaccine considerations. We need to all be thinking about coming out of this pandemic, such as catching up on vaccinations that might have been missed. So, thank you for sticking with us during this critical moment, for dedicating your insights, wisdom, and feedback throughout this last year and a half and for many of you much, much longer. I know you will be combining both of those agendas in the next several days.

I want to just take a moment to thank Dr. Jose Romero who is nearing the end of his 7-year term of the committee, with the last 3 as chair. While I have not personally had the pleasure of meeting Dr. Romero—this is one of those challenges of remoteness— his leadership of this committee will be long-lasting in the US immunization program. His mentorship truly, of both CDC staff and all of the ACIP members, will benefit the agency and truly our country for years to come.

I want to thank you for your commitment to vaccine safety. I regularly speak now publicly about our agency's commitment, and my personal commitment, to ensuring that our vaccines are safe. I know that when I'm saying this that these are my words, but it is your actions that I'm relying on and that I'm referring to. So, I truly appreciate that you're going to continue today, as you have always done, to help us keep this commitment to safety and looking objectively at the potential risks and the potential benefits of our COVID-19 vaccines and truly of all vaccines in all ages. I also want to thank you for looking into the issue of vaccine boosters, and we'll very much be interested in your wisdom here. I'm particularly interested in hearing about your conversations on this topic and the critically important issue for the country as we move forward out of this pandemic. It would be helpful for me to know what data you think we might need to make an informed decision, guidance on how we might get there to receive those data, and what might be the thresholds of those data that would trigger the decision to boost. So, I really look forward to hearing this portion of your deliberations as with many others.

Lastly, I just want to take a moment to acknowledge that unbelievably, this is Dr. Anne Schuchat's last meeting with the committee as Principal Deputy of CDC. I have always looked to Anne as the voice of calm. In standing with many dignitaries over my entire career, I have had the great pleasure and gift of getting to know Anne over the last 5 months. I have deeply appreciated her wisdom, guidance, and friendship to me during this transition into CDC, and she has promised me I can use her cell phone number if I continue to need it after she has left. Anne has worked closely with many of you throughout the years through several past pandemics or epidemics, and I know you will feel it too when she transitions into retirement. We are all so sad to see her go. This week, we're celebrating her years of service, her leadership, and her incredible contributions to this agency, to the country, and truly to our overall health.

So, just to close, I want to thank you for being here today and for all you're doing on behalf of the public's health. I know we've asked a lot of you over the last many years, but particularly over the last year. So, I look forward to listening to your deliberations.

Dr. Amanda Cohn (ACIP Executive Secretary) verbatim: Dr. Schuchat, we also wanted to express, on behalf of ACIP, all of the committee's gratitude to you over the years. Since 2006, you have either, and even before then, you have either been at the helm of the ACIP meetings, or looking down on us from your office since you have been Principal Deputy, or attending. We are so grateful for your early recognition of the importance of an evidence-based recommendation process, which as all of you know has been so critical to us over the last 18 months—to the impact you've had personally on vaccine preventable diseases in this country, including your passion to increase pediatric and adult vaccination coverage with all of these new vaccines that have come to be used as tools over the last 15 years. Personally, I also want to express my gratitude for you. My early days of ACIP as a Meningococcal Work Group (WG) lead, a member of ACIP at the time told me that I would always have professional challenges because of three factors, and those factors were that I was female, I was short, and that I looked younger than my age. But I continued to be able to look at you, who have all three of those same characteristics as me, and see that, in fact, we are lucky enough to be living in a world where female, short, and young-looking women can be fierce, and kind, and empathetic leads. So, thank you on behalf of all of the ACIP. We will miss you greatly, but we look forward to your continued input from your retirement over the years.

Dr. Romero (ACIP Chair) thanked Dr. Walensky on behalf of all of the members of the ACIP, the liaisons, and the *ex officios* and offered his personal thanks for the very, very kind words that she offered regarding his tenure on the ACIP. He then conducted the roll call during which no conflicts were identified or declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Introduction

Dr. Matthew Daley (ACIP, WG Chair) introduced the COVID-19 Vaccines WG session, first providing a brief overview of the COVID pandemic and vaccines. In December 2020, there were approximately 250,000 cases and 3000 deaths each day in the United States (US) from COVID-19. In June 2021, there are approximately 13,000 cases and 300 deaths reported each day. There have been 3 vaccines against COVID-19 authorized under an Emergency Use Authorization (EUA) and recommended for use in the US. These vaccines have played a critical role in the extraordinary reduction in case counts and deaths occurring in the US. As of June 21st, 318 million vaccine doses have been administered, with approximately 150 million people in the US fully vaccinated. This translates to approximately 53% of the population 12 years of age and older who are fully vaccinated. Upwards of 63% of all persons 12 years of age and older in the US have received at least 1 vaccine dose. The epidemiologic curve of case counts stands in stark contrast to the epidemiologic curves in many other parts of the world where vaccines are scarce and waves of COVID-19 cases and deaths have continued unabated.

In the time since the last ACIP meeting, the COVID-19 Vaccines WG has been meeting weekly. The topics covered in these weekly meetings have included review of vaccines with respect to SARS-CoV-2 variants; review of data to inform discussions around additional doses of COVID-19 vaccines; review of a number of safety updates, including review of data regarding myocarditis following vaccination; and extensive discussion about the overall benefit/risk balance for the use of COVID-19 vaccines in adolescents and young adults.

The plan for this emergency ACIP meeting was to discuss cases of myocarditis and pericarditis that have been observed following receipt of mRNA COVID-19 vaccines. To frame the discussion about myocarditis, Dr. Daley highlighted several points related to vaccine safety. The safety monitoring system put in place to monitor COVID-19 vaccines in the US is the most rigorous system ever implemented to monitor any vaccine in the country, and there is an extensive list of potential adverse events (AEs) being monitored. To date, the COVID-19 vaccines authorized in the US have demonstrated a high degree of safety. However, nothing in life is absolutely risk free. It is known from decades of experience with other vaccines that rare and potentially serious adverse events (SAEs) can occur following vaccination. The extensive safety monitoring systems in the US should provide confidence that if a rare and potentially serious adverse event occurs following vaccination, the systems in place will identify that risk. Once a risk is identified, vaccine safety studies help to characterize and quantify the AE. Also, an understanding of risk factors helps to minimize AEs whenever possible. Finally, a critical aspect of vaccine safety is communication of vaccine risks, if identified, to the public, public health officials, and health care providers (HCP). In this circumstance, new knowledge about vaccine safety also is used in a reassessment of the benefit/risk balance of any vaccine in use.

Reassessment of the benefit/risk balance was part of the task during this session. The first reports of cases of myocarditis following vaccination with mRNA vaccines came from Israel. From December 2020-May of 2021 in Israel, 148 cases of myocarditis occurred around the time of vaccination. Most of these reports, although not all, were in younger men 16-19 years of age. This typically occured after the second dose. While most of these cases were hospitalized, 95% were characterized as mild cases. Israel determined that there was a possible link between the second vaccine dose and the onset of myocarditis in young men aged 16-30 years, but determined that the risk of complications of Coronavirus disease outweighed the risk imposed by the vaccine side effects. They stated that myocarditis cases observed among teenagers aged 16-19 years occurred at low rates and in most cases passed with no complications.

Since April 2021, there also have been cases of myocarditis and pericarditis reported in the US to the Vaccine Adverse Events Reporting System (VAERS). These reports and the reports from Israel led to the posting of additional information on CDC's website. In response to the report that myocarditis and pericarditis following mRNA vaccines, the Vaccine Safety Technical WG (VaST), reviewed data from Israel. In addition, VaST reviewed data from the US Department of Defense (DoD) and from other CDC and FDA safety surveillance systems. The COVID-19 Vaccines WG also reviewed these data and discussed the benefit/risk balance, which led to the convening of this June 23, 2021 public ACIP meeting to review these data and discuss a benefit-risk assessment.

After the discussion of myocarditis and pericarditis, the plan was for ACIP to begin discussion of the topic of booster doses of COVID-19 vaccines. The majority of Americans have received at least one dose of a COVID-19 vaccine. A great deal of planning is going to be required if booster doses of COVID-19 vaccines are needed. Discussions around planning need to occur well in advance of future recommendations. Dr. Daley emphasized that planning discussions are not meant to imply that the decision has already been made that booster doses will definitely be recommended. Instead, the intent was to discuss what additional data would be needed to inform these future recommendations.

Overview of Myocarditis and Pericarditis

Dr. Matthew Oster (CDC/NCBDDD) provided an overview of myocarditis and pericarditis, explaining that myocarditis is inflammation of the myocardium or the heart muscle. This is not myocardial infarction (MI) or heart attack, which typically affects the coronary arteries. Instead, it is an inflammatory process that involves the actual muscle of the heart. Pericarditis is a similar process, but instead of involving the heart muscle, it involves the pericardium, which is the lining around the heart. Often, these two entities can occur together and may have similar mechanisms. When they occur together, they are known as myopericarditis.

Myocarditis is not a new disease, but there have been some updates in how to recognize it. For the purposes of surveillance, CDC has drafted a definition for "Probable" and "Confirmed" cases. For the purpose of surveillance, both are counted. The following criteria are used to identify probable or confirmed cases:

Probable	Confirmed
1. Symptoms • Chest pain/pressure/discomfort • Dyspnea/shortness of breath • Palpitation 2. Abnormal testing • Elevated troponin • Electrocardiogram (ECG or EKG) findings • Decreased function on echo or MRI • MRI findings consistent with myocarditis 3. No other identified causes	1. Symptoms • Chest pain/pressure/discomfort • Dyspnea/shortness of breath • Palpitations 2. Abnormal testing • Biopsy • Elevated Troponin AND MRI findings consistent with myocarditis 3. No other identified causes

There can be other symptoms, especially gastrointestinal (GI) symptoms or fatigue, especially in younger children. It is important to make sure there are no other identified causes, such as a structural abnormality or MI that is leading to abnormal testing values. There is a well-established definition for pericarditis that CDC has been using, that states that someone must have any 2 of 4 symptoms of chest pain (a certain type is associated with pericarditis), pericardial rub that is audible by stethoscope on the physical exam, abnormal ECG findings (new ST-elevation or PR-depression), or pericardial effusion on ECG or magnetic resonance imaging (MRI). For the remainder of this talk, Dr. Oster focused primarily on myocarditis since it is the most concerning and most prominent that is occurring.

In children, the annual incidence of myocarditis on average is about 0.8 per 100,000. This has a a bimodal peak in that it tends to be seen a lot in infancy, there are some cases throughout childhood, and then there is an uptick in the number of cases as patients start reaching adolescence. The annual incidence in a recent study was about 1.8 hospitalizations for myocarditis per 100,000 in 2015 and 2016.[1] In traditional myocarditis, there is a predominance of this affecting males more than females and a length of about 6 days that can range from mild to severe.[2]

[1] Vasudeva et al. American J Cardiology. 2021
[2] Kyto et al. Heart. 2013

Traditionally, there are many types of causes of myocarditis. Most typical myocarditis is often from a viral trigger. A classic story would be someone who has mild viral symptoms for a few days, gets better, and then starts showing signs or symptoms of myocarditis a couple of weeks later as the immune system is ramped up. With traditional myocarditis, an exhaustive search is often undertaken to look for potential causes—especially viral causes. However, other causes can lead to myocarditis. For traditional myocarditis, supportive care has been the mainstay of therapy (e.g., oxygen, fluids) to support the body's response. That also has been the first line treatment for post-vaccine myocarditis, if needed. If there are effects on the heart (e.g., arrhythmias, decreased heart function, congestive heart failure), specific medicines or therapies can be implemented. A variety of anti-inflammatory medicines are often used and may vary by patient situation and age or by the hospital where they present. For post vaccine myocarditis, many children have been responding to minimal treatment with anti-inflammatory medicine. In traditional myocarditis and severe cases, mechanical support or heart transplant can be considered. In traditional myocarditis, exercise restriction is typically recommended while the heart recovers. The American Heart Association (AHA) and the American College of Cardiology (ACC) recommend restriction from competitive sports for 3 to 6 months until a patient can show documentation that the heart has recovered from this acute process. Many places are also implementing these same guidelines for post-vaccine myocarditis.

A few reports have been published in the literature about myocarditis after mRNA COVID-19 vaccines. In the US, a paper was published by Marshall et al[3] in *Pediatrics* that assessed 7 males 14-19 years of age who were previously healthy who developed myocarditis within 4 days of their second mRNA vaccine. All of these individuals had abnormal troponin levels, EKG findings, and MRI findings. Symptoms improved for 3 patients with nonsteroidal anti-inflammatory agents (NSAIDs) alone, while 4 patients received intravenous immune globulin (IVIG) and steroids. All of these patients were discharged to home after about 2 to 6 days in the hospital, with a median 4 days, and are currently being restricted from exercise.

Most recently, a paper was published by Rosner et al[4] in *Circulation* that looked primarily at adults. This paper reported 7 patients, 6 of whom received an mRNA vaccine. Among them were 5 males 19-39 years of who presented within 4 days of their second does and 1 male 24 years of age who presented about a week after his first dose. All patients had abnormal troponin and MRI findings, and there were some varying EKG findings. Treatment included NSAIDs or colchicine in 4 patients, beta blockers in 2 patients to help support the heart, and steroids in 1 patient. All patients were discharged home after 2 to 4 days in the hospital. One interesting finding for which the potential mechanisms are not yet known is that 1 patient who presented a week after the first dose had negative spike protein antibodies.

There also have been international reports of myocarditis after mRNA COVID-19 vaccine. Larson et al[5] studied 8 males 22-56 years of age, 4 in the US and 4 in Italy. Among them, 7 experienced onset within 4 days of their second dose and 1 had onset 2 days after his first dose. That patient had a history of prior SARS-CoV-2 infection. All of these patients also had abnormal troponin, EKGs, and MRIs. Of the 8, 7 had abnormal ECGs. Treatment included NSAIDs or colchicine in 4 patients, steroids in 2 patients, and no treatment in 3 patients. All 8 individuals were discharged home with resolution of symptoms and preserved ejection fraction (HFpEF). The Israeli Ministry of Health[6] reported 148 myocarditis cases occurring within 30

[3] Marshall et al. Pediatrics. 2021
[4] Rosner et al. Circulation 2021; Rosner et al. also reported a 28 year old with myocarditis after Johnson & Johnson's Janssen COVID-19 vaccine
[5] Larson et al. Circulation. 2021
[6] https://www.gov.il/en/departments/news/01062021-03

days of mRNA vaccine, 27 of which occurred after 5.4 million first doses and 121 that occured after the first 5 million second doses. Most were in males 16-30 years of age, particularly adolescents 16-19 years of age. Most were in the hospital up to 4 days, with 95% of cases considered to be mild.

To summarize, myocarditis is a rare disease though not new disease. Traditional triggers are thought to be viral, although there can be others. It appears that mRNA vaccine may be a new trigger for myocarditis, which has some different characteristics in presentation, particularly the course of how patients are doing. Treatment is largely supportive, which also has been the case for myocarditis after mRNA vaccine. Myocarditis after mRNA vaccine most commonly occurs in males, which is also the case for traditional myocarditis. It remains to be determined whether myocarditis after mRNA vaccine is more pronounced. It has been seen predominantly in those less 30 years of age, with typical onset within a few days after the second dose. Early data of acute outcomes of myocarditis after mRNA vaccine have been good. There is typically quick resolution, though there are exceptions. Patients are being followed long-term, but no long-term data are available yet. Patients are receiving standard recommendations with regard to exercise precautions.

Update on COVID-19 Vaccine Safety, Including Myocarditis after mRNA Vaccines

Dr. Tom Shimabukuro (CDC/NCEZID) presented early safety data on Pfizer BioNTech vaccination in persons 12-15 years of age and myocarditis and pericarditis following mRNA COVID-19 vaccination. Beginning with vaccine safety of Pfizer BioNTech vaccination in persons 12-15 years of age, v-safe[SM] is CDC's smartphone-based active surveillance system that uses text messaging and web surveys to monitor for AEs.[7] Monitoring during the first week post-vaccination is largely focused on local and systemic reactions with health impact assessment questions. On May 11, 2021, v-safe[SM] age limits were expanded to allow registration down to 12 years of age at Dose 1. As of June 13, 2021 for persons 12-15 years of age after the Pfizer vaccination, there were just over 57,000 with at least 1 health check-in during Days 0-7 after Dose 1 and almost 16,000 with at least 1 health check-in during Days 0-7 after Dose 2. Many of these health check-ins may be done by a parent or a caregiver who is responsible for registering the patient.

A side-by-side comparison of the top solicited reactions during Days 0-7 in individuals 12-15 years of age versus 16-25 years of age, the overall patterns were similar for Dose 1 versus Dose 2 for pre-specified and self-reported reactions. Notably, the 16-25 year-old comparator group was chosen because that is same comparator group that was used in the clinical trials. Injection site pain and certain systemic reactions are more common after Dose 2, at least for systemic reactions, than for Dose 1. If anything, there are slightly less self-reported solicited reactions in persons 12-15 years of age compared to persons 16-25 years of age.

In terms of the results of the health impact assessments, there are three categories: Unable to Work, Unable to do Normal Daily Activities, and Required Medical Care. Notably, the responses for Unable to Work may be influenced by the actual question as most persons 12-15 years of age are not working. The plan is to modify this question to include school attendance to make it more comparable. The categories of Unable to do Normal Daily Activities and Required Medical Care were quite comparable for the two groups. Unable to do Normal Daily Activities was reported more frequently after Dose 2 for both age groups. Required Medical Care was reported

[7] http://cdc.gov/vsafe

slightly more frequently after Dose 2. For both Dose 1 and Dose 2, Required Medical Care had very low rates for both groups.

VAERS is the nation's early warning system for vaccine safety, which is a spontaneous reporting or passive surveillance system that is comanaged by CDC and FDA. VAERS accepts all reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. There are specific reporting requirements for the COVID-19 vaccines under EUA. CDC encourages reporting of any clinically meaningful AE following immunization, although that does not necessarily mean that vaccination caused a health problem. The key strengths of VAERS are that it can rapidly detect potential safety problems and rare AEs. The key limitations are inconsistent data quality and completeness, reporting biases, and the general inability to determine cause and effect from VAERS data alone.

Regarding reports to VAERS after Pfizer COVID-19 vaccination in persons 12-15 years of age and using the same comparator of individuals 16-25 years of age, there were about 2500 VAERS reports in the 12-15 years age group and over 12,000 reports in the 16-25 years age group as of June 11, 2021. The crude reporting rates were fairly comparable, with 422 per million in persons 12-15 years of age and 592 per million in persons 16-25 years of age. The percent of non-serious SAEs also were very similar at about 96% non-serious and about 6% serious for both age groups. That is similar to other vaccines routinely given in these age groups. It is important to note that this vaccine had been authorized for use for a much longer period of time in the older age group. Approximately 6.0 million doses had been administered to persons 12-15 years of age from May 10-June 11, 2021, while about 21.6 million doses had been administered to persons 16-25 years of age from December 14, 2020-June 11, 2021. The same age groups were compared for the most commonly reported AEs to VAERS after the Pfizer BioNTech vaccination through June 11, 2021. The most common AEs were similar in both age groups and were associated with vasovagal or pre-syncope/syncope-type reactions plus some systemic reactions. The overall safety profile for persons 12-15 years of age is consistent with that observed in the pre-authorization clinical trials among persons 16-25 years of age, and is similar for both groups in post-authorization safety monitoring.

Pertaining to myocarditis and pericarditis following mRNA COVID-19 vaccination in the US, CDC's Clinical Immunization Safety Assessment (CISA) project participated in reviewing individual cases of myocarditis and pericarditis and also provided expertise on the development of the CDC working case definitions for myocarditis and pericarditis. Preliminary reports of myocarditis and pericarditis are identified through the VAERS database using Medical Dictionary for Regulatory Activities (MedDRA) code searches and pre-screened VAERs reports with signs and symptoms that are suggestive of myocarditis or pericarditis, such as reports that are brought to CDC's attention by HCPs. Follow-up, medical record review, application of CDC's working case definition, and adjudication are ongoing or pending.

There were 791 reports after receipt of Pfizer-BioNTech (150 after Dose 1; 563 after Dose 2) and 435 reports after Moderna (117 after Dose 1; 264 after Dose 2) as of June 11, 2021 after about 300 million mRNA doses had been administered. In terms of the characteristics of the reports, the general pattern was that there were more reports after Dose 2 than after Dose 1. There was a relatively small number of reports with an unknown dose. Moving forward, the plan is to focus on reports for which the dose number is available as that factors into the analysis. In the analysis of data through June 11, 2021, the median age of patients experiencing myocarditis or pericarditis following mRNA COVID-19 vaccination was younger for Dose 2 at 24 years compared to 30 years for Dose 1. The median time to symptom onset after Dose 2 was somewhat shorter at 3 Days for Dose 2 compared to 4 days for Dose 1. There was a stronger

male to female predominance of reports at 79% male to 20% female after Dose 2 compared to 66% male to 33% female after Dose 1.

Looking at vaccination by age and reports by age and dose number, the takeaway message is that most of the reports occurred in individuals in their late teens and early 20s, which were more pronounced for Dose 2 reports compared to Dose 1 reports. Looking at reports by dose number and time to symptom onset, there was a clear pattern of clustering for both doses in the several days after vaccination, with most of these occurring within a week of vaccination among individuals ≤ 29 years of age. Much of the analyses focused on the younger age groups because this is where most of the reports have occurred, especially the recent reports. Looking more closely at the 484 preliminary myocarditis and pericarditis reports among individuals ≤ 29 years of age through June 11, 2021, chest pain was the most common presenting symptom (N=416). Dyspnea was also common (N117), though less common than chest pain. As far as diagnostics, ST or T-wave changes on ECG (N=295) and elevated troponins (N=310) were commonly documented in the reports. A substantial number of reports documented abnormal echocardiography or imaging (N=81), which was often MRI noted in the reports.

Of these 484 reports in persons ≤ 29 years of age, 323 met the CDC working case definition of myocarditis, or pericarditis, or both. Of the total reports, 148 are under review. Notably, myocarditis and pericarditis are currently combined into the single category/outcome of myocarditis/pericarditis when they occur together. Of the 323 reports that met the case definition, 309 were hospitalized. Of those, 295 had been discharged and almost 80% of the 295 (N=218) known to have recovered from symptoms at the time of time of this analysis. A relatively small number N=14) were not hospitalized, but were seen in an emergency department (ED), urgent care facility, outpatient clinic, or unspecified setting.

Looking at myocarditis/pericarditis reports VAERS following Dose 2 with an observed or suspected analysis using a 7-day risk window, the expected was based on estimates generated from incidence rates in the published literature from an FDA/CDC literature review with an adjustment for male and female percentages. The takeaway message is that based on the reports received, myocarditis/pericarditis is occurring mainly in people in their teens and early 20s and in more males compared to females. However, differences in the observed versus expected in males versus females disappears in individuals 50 years of age and older. Looking at myocarditis/pericarditis reports per million mRNA vaccine doses administered by sex and dose number, with no restrictions on post-vaccination observation time, confirms these patterns.

The Vaccine Safety Datalink (VSD) system is CDC's population-based large, linked data system that is used for active surveillance and research. It is an electronic health record (EHR)-based system that includes 9 participating integrated health care organizations with data on over 12 million persons per year. The VSD has complete or near complete information from EHR records to include immunizations, outpatient and clinic visits, ED visits, procedures, birth and death certificate and information, and demographics all linked by unique study identifiers (IDs). CDC has rapid access to charts and EHRs through the VSD that enables for review of cases. The analysis done in the VSD is called Rapid Cycle Analysis (RCA), which is near real-time sequential monitoring. As data become available, the system monitors a limited set of pre-specified vaccine safety outcomes. This is a public health surveillance activity, which is not the same as an epidemiologic study. It is designed to detect statistically significant associations and statistical signals, which do not necessarily indicate a safety problem. When statistical signals are detected, they require further evaluation.

Through June 12, 2021 in VSD, there were about 4.5 million total doses of Moderna and about 5.8 million total doses of Pfizer. Broken down by age group, substantial doses were administered in persons 18-49 years of age because there were still a fairly limited number of doses administered among persons 12-15 years of age and 16-17 years of age. For the VSD RCA overall analysis for outcome events in the 21-day risk interval after either dose of any mRNA vaccine compared with outcome events in vaccinated comparators, there were no signals for myocarditis/pericarditis as of June 12, 2021. The adjusted rate ratio was just over 1 and has not yet statistically signaled. Given what was observed in VAERS, an age-stratified analysis was done in VSD for chart-confirmed events in persons 12-39 years of age in the 21-day risk interval. As more data accumulate, that age groups can probably be sliced a little finer. For any mRNA vaccination for both doses combined, the adjusted rate ratio was 3.5 and was statistically significant with a confidence interval of 1.1 to 15.0. The adjusted rate ratio was elevated for Dose 1, but was not statistically significant. It elevated for Dose 2 at 3.6 and was statistically significant. For the Pfizer BioNTech vaccine, the adjusted rate ratios were slightly elevated, but none of them reached statistical significance. The adjusted rate ratios were not estimable for the Moderna vaccine because at this point, there were no events in the control interval. The 95% confidence intervals for both doses and for Dose 2 were greater than 1. It is likely the Moderna findings are driving the overall analysis for any mRNA vaccine.

In the same analysis, the risk window was narrowed to 7 days because there is evidence to suggest that symptom onset occurs within that first week. There were similar findings in this combined analysis. The adjusted rate ratio for both doses for any vaccine was 10 and was statistically significant. It was elevated for Dose 1, but did not reach statistical significance. For Dose 2, the adjusted rate ratio was 10.8 and was statistically significant. For the Pfizer vaccine for Dose 2, the adjusted rate ratio was elevated and statistically significant. The findings were similar for the Moderna vaccine, with no events in the control window to date.
Looking at chart-confirmed myocarditis/pericarditis cases in the VSD by day of symptom onset since most recent vaccination in persons 12-39 years of age running a SaTScan™ analysis, the most likely clusters occurred in Days 0-5, 0-3, and 0-6. This offers clear evidence of onset for these vaccinated cases within the first week post-vaccination. This analysis includes cases on Day 0, while some of the other previous statistical testing did not. For straight-up rates among chart-confirmed rates in VSD in the 21-day risk interval in persons 12-39 years of age, there are two important features. First, there is a dose effect and the rates were higher for both vaccines after Dose 2 and in the combined analysis. However, this is still a rare event. For both vaccines combined, there were 12.6 cases per million doses administered. The highest rate was just under 20 per million doses administered for Dose 2 of the Moderna vaccine.

In terms of the care and status of the chart-confirmed myocarditis/pericarditis cases in the VSD, including cases with onset on the day of vaccination, there were 29 cases. Most of these cases were hospitalized either inpatient or in an intensive care unit (ICU). The median length of hospital stay was 1 day, with a range of 0 to 13. All were discharged home at the time of chart review, and a follow-up visit was noted in 27 of the 29 cases in the VSD in the 21 days following vaccination. As far as a qualitative summary, nearly all follow-up visit notes indicated resolution of symptoms at the time of follow-up. Of those who had a follow-up ECG /echo or other laboratory testing, most had returned to normal or baseline. As far as treatment plan, most follow-up visit notes indicated tapering of some medications, as well as maintenance of colchicine and activity limitations for 3 to 6 months.

Looking at all myocarditis/pericarditis rates based on ICD-10 coded cases, not just chart-confirmed cases, in the 21 days for persons 12-39 years of age, Dr. Shimabukuro focused on two findings here. In the overall analysis after Dose 2, the rate in the 21 days after vaccination was 4.7 cases per million doses administered for females and 32 per million for males. Again, there is a dose effect with Dose 2 rates being higher than Dose 1 rates. Returning to the VAERS reporting rates, the female reporting rates in the younger age groups were as high as 9 up to 25 years of age for Dose 2 and 1.8 for ages 30-39 years. Smoothing that out and thinking about the VSD rates, 4.7 is within the range seen in VAERS. For males, the VSD rate was 32. In VAERS that goes from 66.7 down to 10 for Dose 2 among males 12-39 years. Smoothing that out with the total age groups, it is probably within that range or reasonable estimate. These rates are thought to be comparable in terms of automated cases in VAERS or ICD-10 coded cases in VSD, which to CDC is indirect evidence that the capture of these cases in VAERS is probably pretty good. Therefore, the reporting efficiency of post-vaccination myocarditis/pericarditis to VAERS is probably pretty high, meaning that there is good capture of these cases by reporting primarily by HCPs.

In summary, the initial safety findings of the Pfizer BioNTech COVID-19 vaccination of persons 12-15 years of age from v-safe^{SM} and VAERS are consistent with the results from pre-authorization clinical trials. Analysis of VAERS preliminary reports is in progress, including follow-up. Applying the CDC working case definition and adjudicating cases, the preliminary findings suggest that the median age of reported patients is younger for reports after Dose 2 versus Dose 1. Symptom onset clusters within a week following vaccination. There is a predominance of male patients in younger age groups, especially after Dose 2. The observed reported cases exceed expected cases, especially after Dose 2 in younger age groups. The early VSD data in persons 12-39 years of age also suggests that there are more cases after mRNA COVID-19 vaccination with Dose 2 versus to Dose 1. There is a rate of 12.6 cases per million second-doses of any mRNA vaccination in the 21 days following vaccination. These rates appear to be higher in males and females. There is clustering of myocarditis/pericarditis within the week following vaccination, most likely within 0 to 5 days. Reassuringly, the available outcome data indicate that patients generally recover from symptoms and do well.

In terms of next steps, CDC will continue monitoring in VAERS. Follow-up will be done to obtain medical records, conduct case reviews, apply the CDC working case definition, and adjudicate case reports. A surveillance review focused on myocarditis and myopericarditis to describe the epidemiology and characterize clinical features of cases is in progress. Monitoring and assessment also will continue in the VSD to quantify risk and characterize the clinical features of cases. There are plans to conduct follow up on vaccine-associated cases to assess the longer-term outcomes of 3 to 6 months.

VaST Assessment

Dr. Grace Lee (ACIP, VaST Co-Chair) reminded everyone that the objectives of the VaST WG are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring; 3) advise on analyses, interpretation, and data presentation; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the ACIP on COVID-19 vaccine safety. Since December 21, 2020, VaST has had 25 independent meetings to review vaccine safety data and 5 joint meetings with the COVID-19 Vaccines WG focused on safety issues.

As a reminder, ACIP votes since December 2020 have included recommendations for use of Pfizer BioNTech vaccines in those 16 years of age and older on December 12, 2020; use of Moderna vaccines for adults 18 years of age and older on December 19, 2020; use of the Janssen vaccine for those 18 years of age and older on February 28, 2021, and use of the Pfizer vaccine for adolescents 12-15 years of age on May 12, 2021. As vaccine safety data have become available in real-time, VaST also has communicated their assessments in real-time through presentations during ACIP meetings or via the ACIP website. As a reminder, on January 27, 2021, VaST discussed anaphylaxis following mRNA vaccines. On March 1, 2020, VaST had updates on anaphylaxis and also reviewed pregnancy safety data, which were reassuring. On April 14, 2021, data on cases of cerebral venous sinus thrombosis (CVST) following the Janssen vaccine were shared. On April 23, 2021, updates on safety data regarding thrombosis with thrombocytopenia syndrome (TSS), including CVST, were shared to support decision-making by the ACIP and the Johnson vaccine was resumed with a warning. During the May 12, 2021 ACIP meeting, updates on TTS were again shared. Since the last ACIP meeting, VaST shared some early information about cases of myocarditis via the website in order to support early recognition and reporting of cases into VAERS. They just heard an extremely comprehensive review and update of the data on myocarditis following mRNA vaccination from Dr. Shimabukuro. This timeline of activities should ensure that there can be confidence in the systems that are in place and the processes, and that there is continuous and ongoing monitoring of vaccine safety for all vaccinations in the US.

To review the issue of myocarditis, the VaST WG met on May 17, 2021 at which time there were relatively few reports of myocarditis. However, they noted that the reports were predominantly in adolescents and young adults, more often in males than females, more often following Dose 2 than Dose 1, and typically within one week after vaccination. The majority of patients appeared to have transient symptoms, rapid resolution of laboratory abnormalities, and brief hospitalizations. Follow-up data were limited at that time. During the May 24th VaST meeting, the VaST WG reviewed updated data and noted a higher number of observed versus expected myocarditis/pericarditis cases in persons 16-24 years of age following Dose 2 of mRNA vaccines in VAERS using a 30-day window. During that meeting, VaST WG members discussed: 1) the need for continued vaccine safety monitoring through multiple surveillance systems; 2) the need for multidisciplinary collaboration as the vaccination rate started to increase in younger age groups to provide clinical guidance about early recognition, differential diagnosis to ensure that there are no other causes, diagnostic testing, and appropriate management of persons who develop myocarditis or pericarditis; and 3) the need for long-term follow-up of patients to understand the clinical course of these cases and the timing of resolution following both COVID-19 infection and COVID-19 vaccination. A few days later, CDC posted additional information about myocarditis and pericarditis following mRNA vaccines[8] in order to communicate transparently about what was known and what was not known on this topic. In addition, CDC posted clinical considerations for HCP to ensure that cases are reported in VAERS, which is critical to ensure robust monitoring of vaccine safety in the US and to ensure early detection, evaluation, and timely management of potential cases.

Moving onto the data just presented by Dr. Shimabukuro, the v-safe[SM] data indicate comparable local and systemic reactogenicity rates among persons 12-15 years of age and 16-25 years of age. Dizziness and syncope are the most common AEs reported among persons 12-15 years of age in VAERS. Partnerships and ongoing communication with clinician communities have enhanced vaccine safety efforts through their early recognition of potential AEs such as myocarditis. Based on the continued review of data, the risk of myocarditis/pericarditis following

[8] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html

mRNA vaccination in adolescents and young adults aged 12-39 years remains higher after Dose 2 and in males. To summarize the cases of myopericarditis per million vaccine doses administered in the VSD and VAERS on chart-confirmed cases, the overall estimated rate of myocarditis/ pericarditis is 4.4 per million first doses administered and 12.6 per million second doses administered. For context, published estimated background rates of myocarditis ranging from 1 to 10 cases per 100,000 persons annually. The rates following Dose 2 are noticeably higher for males, with estimates of 32 cases per million doses in VSD following Dose 2 using ICD-10 codes, compared to females at 4.7 cases per million post-Dose 2. The findings from VAERS are similar in nature to the findings from VSD by gender and across age groups within persons 12-39 years of age, which offers more confidence in these findings.

In summary, the VaST WG feels that the available data to date suggests a likely association of myocarditis/pericarditis with mRNA vaccination in adolescents and young adults. The clinical presentation of these myocarditis cases following vaccination have been distinct, occurring most often within one week after Dose 2 and with chest pain as the most common presentation. Further data are being compiled to understand potential risk factors, optimal management strategies, and long-term outcomes, which will continue to be needed to support ongoing decision-making. The VaST WG will continue to review data on myocarditis/pericarditis from available surveillance systems and ongoing safety evaluations; review and assess all safety data on all outcomes from these safety surveillance systems; and update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and the ACIP on a regular basis.

Summary of Discussion (Oster, Shimabukuro, & Lee)

- ACIP members applauded CDC for the transparency regarding the vaccine safety surveillance process, for putting clinicians on alert about reports of myocarditis, and for highlighting that anyone can submit a report to VAERS—not just HCP. This is an excellent illustration of the commitment to safety.

- The importance of using terms carefully, such as “rare” and “very rare” was emphasized. There is a difference in the definitions that clinicians might use in practice, versus the definitions that the general public may use in understanding risks, versus the definitions used when reviewing the overall safety of products that are used in medical practice and in making medical and public policy.

- ACIP members expressed interest in further information on the following topics related to myocarditis following COVID-19 vaccination with mRNA vaccines:

    - Breakdown of mild, moderate, and severe cases
    - Long-term prognosis and outcomes
    - Similarities between the pathophysiology of myocarditis after Dose 2 and the cardiac findings associated with Multisystem Inflammatory Syndrome in Children (MIS-C)
    - Myocarditis related to COVID-19 infection
    - Mechanisms for testing negative for spike protein and antibodies in patients who develop myocarditis after vaccine
    - Factors driving male predominance
    - Effort to proactively look for asymptomatic markers such elevated troponin levels or abnormal EKG findings in people who have been vaccinated but do not present for clinical care
    - Potential link between myocarditis/pericarditis and vigorous exercise or sports

- Possible geographic clustering of cases, if any, and whether there might be a biological or behavioral link
- Relationship of race and ethnicity on the potential for myocarditis/pericarditis
- Deeper information on understanding the burden of disease, the benefit-risk balance, symptomatic versus asymptomatic disease, et cetera in pediatrics, as vaccine trials continue in younger age groups and ACIP moves toward decision-making on children

COVID-19 mRNA Vaccines in Adolescents and Young Adults: Benefit-Risk Discussion

Dr. Megan Wallace (CDC/NCIRD) reminded everyone that the current COVID-19 mRNA vaccine policy is that COVID-19 vaccines are recommended for persons 12 years of age and older in the US under FDA's EUA. This presentation focused on the risks as well as the benefits after COVID-19 mRNA vaccines in adolescents and young adults. To frame this benefit-risk discussion, data were first presented on the public health problem, including COVID-19 infections and complications in adolescents and young adults, with a focus on epidemiology in adolescents and young adults 12-29 years of age; post-COVID conditions, including MIS-C and MIS-A, and myocarditis. This was followed by a benefit-risk assessment, including benefits of mRNA vaccines and risk of myocarditis after mRNA vaccines, and the WG's interpretation.

Since January 22, 2020, more than 33 million cases of COVID-19 have been reported to CDC. Overall, COVID-19 cases in the US have been declining since January 2021.[9] Based on projections of incident COVID-19 cases from the Scenario Modeling Hub depicting projections with models assuming 83% vaccination coverage and 68% vaccination coverage, cases may increase substantially in the setting of low vaccination rates and high variant transmissibility.[10] NOWCAST projections of the proportions of circulating SARS-CoV-2 variants from CDC's COVID Data Tracker provide timely estimates while accounting for limited sequence data availability. Based on recent NOWCAST data, variants of concern (VOC) are an increasing proportion of SARS-CoV-2 lineages circulating in the US. For the projections for the two weeks ending June 19th. B.1.1.7 (Alpha) remained the most frequent lineage, with a projected prevalence of 52%. P.1 (Gamma) increased to 16%, and B.1.617.2 (Delta) increased to 21%.[11]

Based on data showing cumulative COVID-19 incident rates by age and sex from April 1-June 11, 2021, adolescents and young adults have the highest COVID-19 incidence rates. Since the beginning of the pandemic, at least 7.7 million COVID-19 cases have been reported among persons aged 12-29 years. Therefore, the remainder of the presentation focused on this group.[12] In terms of the proportion of total COVID-19 cases by age group over time, as more older adults are vaccinated, adolescents and young adults make up a greater proportion of total cases. In May, 33% of cases reported were in persons aged 12-29 years compared with 28% last December.[13] Despite other age groups experiencing recent decreases in hospitalization rates, COVID-19-associated hospitalization rates have remained stable in adolescents and young adults.[14] In terms of cumulative COVID-19 mortality rates by age group and sex from April 1-June 11, 2021, looking at recent months when incident cases have been lower, COVID-19-associated deaths continue to occur in adolescents and young adults. Since the beginning of

[9] https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases
[10] COVID-19 Scenario Modeling Hub Round 5: https://covid19scenariomodelinghub.org/viz.html
[11] CDC COVID DATA TRACKER AS OF 6/14/21
[12] https://covid.cdc.gov/covid-data-tracker/#demographics
[13] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime
[14] https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

the pandemic, 2767 COVID-19 deaths have been reported among persons aged 12-29 years; 316 have been reported since April 1, 2021.
Post-COVID conditions also can occur after COVID-19. There is no standardized definition, but it is generally understood to be new or persisting symptoms from acute infection or exacerbation of a chronic condition 4 weeks or more after SARS-CoV-2 infection. Post-COVID conditions have been reported after infections ranging from asymptomatic to severe. There are currently limited data in adolescents and young adults,[15],[16] but recent cross-sectional studies have shown evidence of new or persisting COVID symptoms in this age group. In these studies, up to the one half of study participants had symptoms one month post-diagnosis. The symptoms reported included fatigue, insomnia, rhinorrhea, muscle pain, headache, lack of concentration, exercise intolerance, dyspnea, and chest pain.

MIS-C is a post-COVID condition. It is a severe hyperinflammatory syndrome occurring 2 to 6 weeks after acute SARS-CoV-2 infection among persons less than 21 years old, resulting in a wide range of manifestations and complications. Approximately 60% to 70% of patients are admitted to intensive care and 1% to 2% die.[17],[18] There have been over 4018 MIS-C cases reported as of June 2, 2021.[19] The estimated incidence of MIS-C cases is 1 per 3200 SARS-CoV-2 infections[20]; 36% of reported MIS-C cases occurred in persons aged 12-20 years; and 62% of reported cases have occurred in children who are Hispanic, Latino, or black/non-Hispanic. Lagging by a couple of weeks, MIS-C cases track with COVID-19 incidence. If COVID-19 cases were to increase, an increase also could be anticipated in MIS-C.[21]

MIS has also been reported in adults, though cases are less common. A single center retrospective cohort study[22] identified adults at risk of MIS-A from those hospitalized with a positive SARS-CoV-2 test result in which 15 (1.7%) hospitalized patients were diagnosed with MIS-A. Patients with MIS-A were younger and more likely to have evidence of SARS-CoV-2 infection documented by serologic testing compared to acute COVID-19 patients. Other demographic characteristics and comorbidities did not differ between MIS-A patients and acute COVID-19 patients. Of the 15 MIS-A patients, 8 had cardiovascular involvement. In a case series of 27 MIS-A patients,[23] antibody testing was required to identify SARS-CoV-2 infection in approximately 1/3 of cases. Patient ages ranged from 21-50 years, 96% of patients belonged to racial or ethnic minority groups, and 3 patients died.

Moving to epidemiology, myocarditis is inflammation of the heart muscle and pericarditis is inflammation of the outer lining of the heart as mentioned earlier. Myocarditis and pericarditis generally occur more frequently in young adults, men, and persons with certain underlying medical conditions or who have had recent medical procedures. They also can occur after SARS-CoV-2 infection, but data to estimate the frequency after COVID-19 are limited. There is a spectrum of disease, but for the purpose of the benefit-risk discussion, both myocarditis and pericarditis are referred to as myocarditis in this presentation.

[15] Buonsenso et al, Acta Paediatrica (2021)
[16] Walsh-Messinger et al, medRXiv (2020)
[17] Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091
[18] Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic [published online ahead of print, 2021 Apr 6]. JAMA Pediatr. 2021;e210630. doi:10.1001/jamapediatrics.2021.0630
[19] Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. https://www.cdc.gov/mis-c/cases/index.html
[20] Payne et al, JAMA Netw Open. 2021;4(6):e2116420. doi:10.1001/jamanetworkopen.2021.16420
[21] https://www.cdc.gov/mis-c/cases/index.html; accessed 06/08/2021
[22] Davogustto et al, JAMA Netw Open. 2021;4(5):e2110323. doi:10.1001/jamanetworkopen.2021.10323
[23] Morris SB et al, MMWR Morb Mortal Wkly Rep 2020;69:1450–1456. DOI:http://dx.doi.org/10.15585/mmwr.mm6940e

In a recent cohort study of 1597 collegiate athletes with recent SARS-CoV-2 infections who had cardiac MRI, 37 (2.3%) had abnormal MRI findings. However, 65% of the 37 had normal laboratory findings and no symptoms.[24] Another study suggested that some MRI findings may be related to remodeling from athletic training.[25] Studies also have highlighted differences between myocarditis related and unrelated to SARS-CoV-2. In a retrospective study that identified children with acute myocarditis treated at a single center from 2018-2020, 27 children 18 years of age and younger were identified.[26] Of the cases, 7 had evidence of prior SARS-CoV-2 infection or exposure and 6 were ultimately diagnosed with MIS-C. Individuals with myocarditis, or MIS-C-related to SARS-CoV-2 had a better clinical course than those with myocarditis due to other causes. None were diagnosed with acute fulminant myocarditis. There was a shorter duration of ionotropic drug support and ICU stay, and they did not require mechanical respiratory support.

As is discussed in presentations earlier in the day by Drs. Oster and Shimabukuro, there also have been cases of myocarditis after mRNA vaccines reported. These reports have been most commonly in males less than 30 years of age. Symptom onset clusters in the week following vaccination, and early data of acute outcomes have been good. Many of the cases have been hospitalized, but usually for a short duration. No long-term data are available yet, but continued monitoring is ongoing.[27]

In summary, COVID-19 incidence, hospitalization, and mortality rates are decreasing overall. However, variants continue to spread and scenarios exist in which cases increase in the fall. Adolescents are a growing proportion of cases, given vaccine coverage among adults. Post-COVID-19 conditions also impact adolescents and young adults. There have been 4018 MIS-C cases reported to national surveillance. Myocarditis is a disease marked by inflammation of the heart muscle, and risk factors include younger age and male sex. Myocarditis can be related to SARS-CoV-2 infection. Myocarditis after mRNA vaccines has been noted, with highest frequency in males aged 12-29 years following the second dose. Early outcomes have been encouraging, but no long-term data are available yet.

Moving on to benefits, the Phase 3 clinical trial data for the Pfizer-BioNTech COVID-19 vaccine demonstrated efficacy against thematic laboratory-confirmed illness among individuals 16 years of age and older, with an overall efficacy estimate of 95%. The VE against COVID-19-associated hospitalization was 100%. The Pfizer-BioNTech COVID-19 vaccine also demonstrated high efficacy against symptomatic laboratory-confirmed COVID-19 and adolescents aged 12-17 years. Overall efficacy was 100% and immunogenicity was non-inferior to persons 16-25 year of age. The Phase 3 clinical trial data for the Moderna COVID-19 vaccine demonstrated efficacy against symptomatic laboratory-confirmed COVID-19 among individuals 18 years of age and older. The overall efficacy estimate was 94%. The VE against COVID-19-associated hospitalization was 89%. Additionally, multiple real-world effectiveness studies from the US and other countries demonstrate that a 2-dose mRNA COVID-19 vaccination series in the age groups for which the vaccine is recommended is effective against SARS-CoV-2 infection, with an estimated range of 64% to 99%. It also is effective against COVID-19-associated hospitalization, with an estimated range of 87 to 97%. In terms of harms, there have been 133 million vaccine second doses administered, and 636 reported myocarditis cases as of

[24] Daniels CJ, et al. JAMA Cardiol. Pub online May 27, 2021. doi:10.1001/jamacardio.2021.2065
[25] Clark DE, et al. Circulation; 2021:143(6)
[26] Vukomanovic et al. PIDJ;2021:40(5):e173-e1782
[27] Marshall et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID- 19 vaccination. Pediatrics. 2021; Larson et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination; Mouch et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021 May 28;S0264-410X(21)00682-4

June 11, 2021. An individual-level benefit-risk analysis to evaluate the direct benefits and risks per million mRNA COVID-19 vaccine doses, which was used to examine the sex and age difference in risks and benefits. These calculations are based on recent COVID-19 case and hospitalization incidents, mRNA vaccine efficacy, number of mRNA vaccinations to date, number of persons already vaccinated, myocarditis risk within 7 days after Dose 2, and using a 120-day risk period. Benefits of vaccination are also described at the population level. Based on age-specific hospitalization rates as of May 22, 2021 and calculated over a 120-day risk window, when comparing COVID-19 hospitalizations prevented to risk of myocarditis, the benefits clearly outweigh the risk in the older populations, so the focus was on persons 12-29 years age.

For females aged 12-17 years, it is estimated that for every 1 million doses of mRNA given to complete the 2-dose series, 8500 COVID-19 cases, 183 hospitalizations, 38 ICU admissions, and 1 death would be prevented and that there would be an estimated 8-10 cases of myocarditis. For males aged 12-years, it is estimated that per-million second dose vaccinations, 5700 COVID-19 cases, 215 hospitalizations, 71 ICU admissions, and 2 deaths would be prevented and there might be 56-69 myocarditis cases. In persons aged 18-24 years, the benefit-risk balance is more favorable. For males, aged 18-24, for whom the risk is higher than females, it would be expected that 12,000 cases, 530 hospitalizations, 127 ICU admissions, and 3 deaths would be prevented and there might be 45-56 myocarditis cases. In persons aged 24 to 29 years, the benefit-risk balance is even more favorable and this trajectory continues with increased age. There are additional considerations for direct benefits that were not captured in the benefit-risk assessment, such as prevention of MIS-C, prevention of prolonged symptoms, and protection against variants.

For population-level considerations, there are no alternatives to mRNA vaccines for the foreseeable future in adolescents. Vaccination of students offers an additional layer of protection against COVID-19 and can be an important tool to return to normal. Higher levels of vaccination coverage can lead to less community transmission, which can protect against development and circulation of emerging variants. Racial and ethnic minority groups have higher rates of COVID-19 and severe disease. Potential changes in vaccine policy or anything that would impact vaccination coverage for adolescents and young adults may disproportionately impact those groups with the highest rates of poor COVID-19 outcomes.

The direct benefit-risk assessment shows a positive balance for all age and sex groups. It considers individual benefits of vaccination versus individual risks. The benefits presented are likely an underestimate because the analysis was performed using reported rates of cases and hospitalizations, which likely represent only a fraction of the true cases that have occurred in the population. There is still uncertainty in the rates of myocarditis after mRNA vaccines. Not all cases are verified, and the crude rates were used. The balance of risks and benefits varies by age and sex, and the balance could change with increasing or decreasing incidence. There is limited data currently on risk of myocarditis in persons 12-15 years of age due to the timing of recommendations and limited number of second doses given.

Clinical Considerations and the COVID-19 WG Interpretation

Dr. Sara Oliver (CDC/NCIRD) briefly described the draft clinical considerations around myocarditis and pericarditis and the WG interpretation, which are shown in the following table:

Vaccine Considerations in People with a History of Myocarditis or Pericarditis	
Scenario	**Recommendation**
Pericarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine.
Pericarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Proceed with a 2nd dose of mRNA COVID-19 vaccine after resolution of symptoms. Discuss with patient, guardian, and clinical team.
Myocarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Defer 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose under certain circumstances. Discuss with patient, guardian, and clinical team.

The clinical considerations website will be updated with additional language for each of these recommendations, but the WG wanted to share a brief summary.

The WG reviewed the data presented during this meeting on COVID-19 mRNA vaccines in adolescents and young adults and discussed the benefit-risk balance. Overall, they felt that the initial presentations are reassuring. However, continued monitoring of cases, the clinical course, and long-term outcomes of myocarditis after mRNA vaccines will be important. The WG also felt the need to follow the benefit-risk balance as more is learned around myocarditis, as well as updates to epidemiology (e.g., cases, variants, etc.). However, they felt that currently, the benefits still clearly outweigh the risks for COVID vaccination in adolescents and young adults. As a reminder, the current vaccine policy for COVID vaccines is that: “COVID-19 vaccines are recommended for persons 12 years of age and older in the United States under FDA’s Emergency Use Authorization.”

In closing, the following questions were posed for ACIP consideration and deliberation:

1. What does ACIP think about the benefit-risk balance of COVID-19 vaccines in adolescents and young adults, in the setting of the reports of myocarditis?
2. What additional information or analyses could inform these discussions as we continue to closely monitor the situation?

Summary of Discussion (Wallace & Oliver)

- The safety monitoring systems continue to be reassuring and the transparent communication is greatly appreciated. It was clear to ACIP members that based on current information, the benefits of vaccine clearly outweigh the risks related to the incidence of myocarditis.

- ACIP members emphasized the importance of being very upfront with parents and patients in terms of mentioning myocarditis/pericarditis as a potential risk of COVID messenger-RNA vaccinations and in updating the EUA fact sheets:

    - Dr. Fink, FDA, reported that the FDA has been working very closely with its partners at CDC in assessing the evolving data on this issue and interpreting the results. FDA and CDC are very much aligned with the information that was presented throughout the day and do agree that based on the available data, a warning statement in the fact sheets for both HCP, vaccine recipients, and caregivers. FDA thought it would be important to hear the discussion from the ACIP team meeting before finalizing the language on these anticipated warnings. The warning statements would likely include information stating that these events have occurred in some vaccine recipients, particularly following Dose 2 of the mRNA vaccines; onset of symptoms typically has been several days to a week following vaccination; based on limited follow-up, most cases appear to have been associated with resolution of symptoms; limited information is available about potential long-term sequelae; and symptoms suggestive of myocarditis or pericarditis should result in vaccine recipients seeking medical attention. Also anticipated is that warning statements would refer to CDC clinical guidance on use of mRNA COVID vaccines in individuals with a history of myocarditis or pericarditis, and that FDA would move rapidly to update the facts sheets with this information.

    - Dr. Cohn, CDC, indicated that CDC would coordinate closely with FDA after the language has been finalized and will update all CDC fact sheets and parent information sheets to reflect the same language, although potentially at the appropriate reading level for the documents.

- Regarding Slide 39 pertaining to vaccine consideration of people with a history of myocarditis or pericarditis, concern was expressed with the language in the fourth line reading, “myocarditis after the first dose prior to second.” It is not clear how easily interpretable or user-friendly that language might be because one can have myocarditis with pericarditis at the same time and it is not always easy to differentiate in the clinic setting. Perhaps the language could be revised to reduce the potential for confusion.

- In terms of consideration for people with a history of myocarditis and pericarditis, Dr. Long indicated that she is an Associate Editor of the *Journal of Pediatrics* and that they received a single case that did get through to publication and is now on the journal’s website. The first author’s last name is Minocha. This is a case from Manhattan that she accepted because it was so beautifully proven. This was a 17-year-old boy who had traditional myocarditis in January 2012, with a lot of investigation, including SARS PCR and antibody, both of which were negative in January. He recovered and had normal findings in cardiac follow-up within a month of discharge. In April, he received Pfizer Dose 1 without difficulty. Two days after Pfizer Dose 2 given at the appropriate interval, he had sudden onset of severe chest pain going to his left shoulder, and again was investigated very thoroughly. He had all of the findings that would confirm myocarditis, including a cardiac MRI. He had no PCR positivity, but IgM antibody at the time he presented with the myocarditis. While this is a single case, it is well-documented and raised some uncertainty about what a clinician should do with a patient in front of them.

- Dr. Oster indicated that he quickly reviewed the Minocha paper that Dr. Long described and had some comments with regard to the guidance that was given. First, a timeline of about 3 months from myocarditis to vaccine will be included with the clinical considerations. This gets at long-term follow-up in that they want to see resolution of the myocarditis and full heart recovery. As Dr. Oliver mentioned, there is other verbiage that will be in this content. A lot of it is taken from the guidance of the AHA and ACC, which recommend about 3- to 6-month window for allowing the heart to recover. Second, it is especially important to follow-up on abnormal findings. He was struck that in the Minocha paper, the distribution of inflammation in the follow-up myocarditis was identical to the MRI in the acute phase of the earlier myocarditis. It does not appear that there was an intervening MRI to show that that had resolved. While Dr. Long's thoughts are very well-taken, it is important to emphasize that people who have ongoing concerns and ongoing considerations are still followed. It was meant more for those who have a remote history of myocarditis that have essentially recovered, are off of cardiac medications, and have been discharged from cardiology care.

Public Comment

The floor was opened for public comment during the June 23, 2021 ACIP meeting at 2:30 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC–2021–0034. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Ms. Susie Olsen Corgan
Concerned Individual

Thank you for the opportunity to speak today. Today, as I listened to the committee discuss the cases of myocarditis and pericarditis following COVID-19 vaccinations in adolescents and young adults, I was alarmed. As we all know and has been documented, adolescents and young adults have zero relative risk of dying from COVID-19 infection and very low risk of having severe adverse events. But as we have heard today and have seen from the Vaccine Adverse Event Reporting System, there have been several severe adverse events reported after receiving COVID-19 injections. As of June 11, looking at myocarditis and pericarditis alone, there have been 197 reports in 30-39-year-olds, 392 reports in 19 to 29-year-olds, and 279 reports in 18 years and younger. Looking at the Harvard Pilgrim study, which states that less than 1% of adverse events were reported to VAERS, it is reasonable to assume that these numbers are much higher than are being reported. From the meeting here today, we heard that there have been more than 1200 cases of myocarditis or pericarditis, mostly in people under 30. The numbers are growing quickly. This should ring the alarm for all of you. It certainly does for me. With information on myocarditis or pericarditis being just two of the effects being reported and no long-term safety data on these vaccines, how can you, the ACIP committee who were entrusted by the citizens of this country to provide the safest recommendations, continue to recommend any COVID-19 vaccines for adolescents or young adult populations? Furthermore, since we know that many of the deaths stated to be caused by COVID-19 infection in adolescents and young adults have underlying health conditions such as obesity and diabetes, why aren't we talking about how to live a healthy lifestyle? Simple guidance on eating a diversified whole foods diet, getting outside and exercising regularly—how much could we reduce negative outcomes in the entire population with just these few simple recommendations? A report came out several months ago saying that 90% of COVID-19 deaths could have been

prevented if the individual had adequate levels of vitamin D. Why is this not being discussed further? Why is the vaccine the only option being given when we do not yet know what the long-term effects are going to be on our children? Why aren't you, our public health regulatory agency, looking at other options that carry zero risk for most individuals? I brought several concerns up to you many months ago prior to the emergency use authorization of any COVID-19 vaccines. I warned you that if this rush through of COVID vaccines continued, the supply of that vaccine would not be your primary issue, but that demand would be. We are seeing that now. Even with the many courses of tax incentives given millions in lotteries, free beer, joints, donuts, scholarships, etc., hesitancy is still growing. The only way that you may begin to regain any confidence from the public is to completely stop administration of the COVID-19 vaccines in adolescent young adult populations until the safety studies have been done. Please take these comments into consideration. Thank you for your time.

Mr. William Huston
Terra Vigilate (Earth Watch)

My name is William Huston. I'm associated with Terra Vigilate, a public interest research organization focused on public health and safety. Thank you to the committee for letting me speak today. I just want to start by saying that technical experts with a lot more credentials and knowledge than I were denied a right to speak today, and I was denied the ability to cede my time to the technical experts. So, if the ACIP is truly wanting to engage the public and have a robust conversation about the safety and efficacy of these vaccines, I would suggest an additional public comment session that's open to anyone and it should be taken as long as needed to get everybody heard. These COVID-19 vaccine trials must be halted immediately and the emergency use authorization withdrawn, because it's causing massive, massive injuries and deaths. These vaccines are unnecessary for a purported infectious disease with a case fatality rate comparable with a common flu. The EUA was issued using scientific and medical fraud due to violations of the criteria for issuance of authorization, including that the infectious agent is serious. It's not. The benefits of the product must outweigh the risk, and that's highly questionable, and that there's no adequate alternative, yet existing prophylactics and therapeutics known to be effective against coronavirus infections were banned for off-label use by the FDA. The testing and surveillance program is an unmitigated disaster. All testing including PCR and antigen and antibody are non-specific to the SARS-CoV-2 virus, which is purported to be the pathogen which causes COVID-19, yet that simple fact is unproven. RT-PCR is utterly unsuitable for the diagnosis of clinical disease, and that comes from Kary Mullis. He's the guy that won a Nobel Prize for inventing the thing. The FDA recalled 255 test kits, tens of millions, due to contamination at a cost of billions. The VAERS database is known to be underreported by a factor of between 10x and 100x. This is according to the Harvard study. There's also what I call the VAERS data lag, and other people are calling it the backloading of data. The CDC is apparently withholding and delaying submitted adverse event reports from the published data by a factor of at least 3x and could be as high as 14x. And when you combine these two factors together, we can say that the number of deaths in the US is not 6000, but it could be 180,000, and the upper bound might be 6 million. So, you know, this is the 20th anniversary of 9/11 when 3000 people died. So this vaccine program is like two 9/11s . . . [time expired].

Thomas Perry, MD
Phoenix Allies for Community Health

My name is Thomas Perry. I'm a retired cardiologist from Phoenix. Thank you for inviting me to speak. My written comment is much more detailed and with references. There is a large sector of the population which does not trust the scientific integrity of the vaccine program. This was especially notable before the mask requirement for fully vaccinated people was removed. I believe in universal vaccination based on scientific proof that vaccines are 20 times stronger than placebo to prevent COVID. No such finding is available for recovered COVID patients. The WHO states that 11 billion vaccines will be needed. Perhaps 2 billion have already been distributed. The CDC continues to target recovered COVID victims who are already immune. If large numbers of vaccine are wasted on the already immune population, the overall vaccine strategy is slowed down, allowing more time for the evolution of variants. Scientific assessment of the durability of COVID immunity is a key to the formation and reformation of vaccination policy. This includes boosters and second generation vaccine development. The results of 4837 COVID-recovered victims randomized in the Moderna and J&J trials, Phase 3, are pending. The available scientific studies on vaccine durability warrant more critical scrutiny. In my written comment, I examine four excellent studies on reinfection of already infected people. These show 180,000 patient years with a reinfection rate of less than 1 per 100-person years, hospitalization rate less than 0.15, and mortality rate of 0. Natural immunity shows itself to be good and durable. By contrast, there are studies which claim that the reinfection rate is high so that transient immunity should be the working hypothesis. Most commonly, such claims are based on waning IgG levels in neglect of T and B cell immunity, which may be more important. Others omit antibody data using only PCR swab results. A report in *Lancet* from Denmark uses twisted tables of PCR results to claim only 82% immune protection in the first year of recovery, and an extremely low 47% for the 65-year-old and over group. The serious flaws in this study includes omission of all data on clinical severity. Vaccine resistors have a sharp eye on the logical and scientific integrity . . . [time expired].

Ms. Sarah Barry
Ms. Independent Pro-Vaccine Advocate
Hello, ACIP. My name is Sarah Barry. I am an independent pro-vaccine advocate from Ohio, and I thank you for the continued transparent and thorough discussions of the safety data. I have previously given comment before about the rampant abuse of autistic children within the anti-vax community and how anti-vax lobbyists in Ohio made efforts to censor my testimony in a government committee. I also wanted to give testimony these past few weeks on Ohio House Bill 248, which would make it illegal for hospitals, nursing homes, and any business or school to require any vaccine—not just the COVID vaccine. However, the testimony protocol was changed and the anti-vax Chair of the Health Committee did not select me to give testimony. So today I will use this time to give it to you all now: Chairman Lipps, Vice Chair Holmes, Ranking Member Liston, and Members of the Ohio House Health Committee, thank you for the opportunity to give opponent testimony for House Bill 248. We all saw Sherri Tenpenny come before this committee and turn Ohio into a national embarrassment. Tenpenny is, in fact, one of the founding members of Ohio Advocates For Medical Freedom who are the anti-vax lobbyists that worked with the sponsor to write the bill. Health Freedom Ohio, the anti-vax lobbyist group that previously tried to censor my testimony in this building, is responsible for the amendments. That makes this bill an anti-vax bill. You cannot continue to hide behind the rhetoric of freedom as cute as the attempt is. You can call this a "freedom bill" if you want, but everybody knows it is a freedom to be anti-vax bill. If you have cancer and you want to go to get your normal checkup, you have to worry that the people who are treating you might not be vaccinated against measles. Sherri Tenpenny, in addition, is a grifter who not only is embarrassing for the

statements she made in front of this committee, but made statements about mental illness and vaccines and implied that vaccines caused the Sandy Hook shooting. She also, her clinic that she runs in Ohio, offers homeoprophylaxis. Homeoprophylaxis is a non-FDA approved alternative to a vaccine. It is absolutely disgusting to me that these are the experts that you would listen to and these are the groups that you would listen to in the construction of this bill. I am ashamed to be an Ohioan when I think of the corruption that is going on behind closed doors. I question the testimony protocol changes that have been made, and I urge a "no" vote on House Bill 248 as it is an anti-vax bill. Thank you for your time, ACIP, and thank you for the time of the Ohio House Health Committee that did not select my testimony.

Ms. Cathy Margolin
Acupuncturist and Herbalist

My name is Kathy Margolin. I'm a nationally licensed acupuncturist and herbalist and myself, along with my colleagues of East Asian medicine, have suddenly noticed a startling difference in our new patient population. As a small piece of background, I communicate directly with thousands of traditional Chinese medicine practitioners from all over the world in various online Meetup bulletin boards, social, and university groups. We are all experiencing a trend we've never seen before. New patients are arriving with complaints that they attribute to the vaccinations. Some of these pathologies happen within days. Others within a few weeks. But the common theme is patients never had these symptoms and they have all received vaccinations. Acupuncturists like myself are having some very good success with menstrual disorders, Bell's palsy, respiratory issues, palpitations, generalized malaise, a wide variety of GI disorders, shingles, and now more common than ever, skin and eye disorders, along with extreme anxiety and depression. We can and are treating all of them. But one of the most frightening symptoms acupuncturists worldwide are experiencing with their patients are immediate changes in patients' radial artery wrist pulses after vaccination. Pulse analysis is a major assessment of health in TCM. This has never been seen before, certainly not in the volume where we are seeing. Clearly, heart mechanics are being affected by these vaccinations. Two days ago, the World Health Organization revised the recommendations, as you know, for children 18 and younger—no COVID vaccinations for this group. I commend them for this action and would go further to say pause all vaccinations in the US until the current reports from the government's VAERS website are thoroughly investigated, tracked, and reviewed. Pause until we know for sure that vaccinations are safe for all. As a health practitioner, I'm alarmed at what I'm seeing. As a mom, I'm scared for the next generation. I have a pediatric focus in my TCM practice, and this last year, I've seen a colossal amount of depression, anxiety, and suicidal thoughts in the under 18 age group, in fact, for all age groups. China has been treating COVID with herbal formulations since the onset of the epidemic. The acupuncture community in the US has been able to learn these treatment protocols since February 2020. We have learned from some of the very first Chinese medicine doctors in Wuhan what botanical combinations work best for COVID-19 patients. We, the acupuncture community here, have been treating COVID patients successfully for more than a year without long-term side effects. We have adapted to virtual consultations and mailing herbal formulas, keeping people out of the hospitals, and now we are being perversely rewarded with patients who have taken the vaccine. I implore you, review the risks of these vaccinations for all ages. Benefits should never . . . [time expired]. Isn't the rule of medicine and the oath I took "first do no harm?"

Mrs. Barbara Loeppke
Loeppke Professional Services

Hi. My name is Barbara Loeppki. I'm a parent and a parent advocate. After attending a February 2019 ACIP meeting, I've had concerns about the rigor of the ACIP recommendations. My takeaway from that meeting was hearing the phrase numerous times, "don't let the lack of data keep you from voting." My takeaway from today's meeting is that this will still occur. How can you look people in the eye and say that you voted without all the data? We're told that the mechanism of the cardiac problems isn't known and that there is no data about the long-term effects. We're told that the prior current COVID infection is being looked at, but the presence of the vaccine spike protein is not. We're told the background rate for myocarditis has been used for 12- to 15-year-olds from 2015-2016, but that's 5- to 6-year-old data. Why is that year's entire numbers being compared to the vaccine numbers when these kids have only had it for 32 days? In fact, the background rate used in every meeting is very vague. This does not show transparency, nor does it build trust. Why are the different reporting systems using different age group ranges? The discussion is that myo- and pericarditis is mostly occurring in young participants, yet the VSD presentation diluted the results by using data from ages up to 39 years. Parents are very concerned about VAERS data. Medical professionals have stated that the forms are time consuming, cumbersome, and often they are penalized by their healthcare systems for reporting. What are you doing to make sure that all vaccine reactions are being reported? Parents are watching. Parents are relying on you to get the correct info before their children are injured for life. The events are not mild to them. Parents feel minimalized. How do you even begin to think you'll be able to address vaccine hesitancy when you do this? The very fact that the ACIP scheduled an emergency meeting to address heart problems and then postponed it to take a holiday speaks volumes. In December, the Committee met numerous times on the weekend when the manufacturers wanted approval. An emergency, yet you postponed for 5 days. This brings up three possible scenarios. Either you thought it wasn't really an emergency; or you really don't care about children, which I don't think is the case; or most likely answer, which the public believes is the outcome, was already determined before the meeting was going to be held. Vaccine hesitancy is not about having a needle poke the skin. It's about the lack of trust in you, the ones who are responsible for the recommendations. Will you do the right thing? Thank you for your time.

Leslie Moore, MD
Mother & Physician

My name is Leslie Moore. I am a mother and a physician. I'm not a virologist, but I can read data, and I cannot fathom why this mass vaccination program has not been halted yet and why the consideration to extend it to younger ages because the data is atrocious and frightening. First, let's acknowledge that these experimental vaccine products are still investigational. Yet, there is no comprehensive monitoring and data collection. People get shot up and left to deal with the consequences on their own. All we have is the VAERS system, which is voluntary self-reporting. We know VAERS only captures 1% to 10% of all adverse events. Adverse events are grossly underreported for a variety of reasons. I looked at OpenVAERS this morning. These products have amassed 6,000 deaths and 20,000 hospitalizations in the US alone, which is more than the other 70 vaccines for the last 30 years combined. That is with gross under-reporting and a 2-month backlog. Let's face it. These vaccine products are not safe. Now let's consider these products for children. What is the risk-benefit analysis? Children are at a statistically insignificant risk from COVID-19, so there is no benefit to vaccination. And you can't vaccinate them to protect others. These shots don't work that way. They don't prevent infection or transmission. Your shot at best protects you from severe symptoms. No one else. Children

have no benefit, only risk from these products. Any child injured or killed by the shot likely would have done fine with the virus and received broad and lasting natural immunity. Natural immunity is always better than vaccine immunity. Anyone who says otherwise needs to go back to medical school. Finally, these risks and injuries are all short-term data. We have no long-term data. But one extremely concerning signal is the biodistribution study from Japan that showed that the lipid nanoparticle did not stay in the shoulder as intended but traveled throughout the body and then concentrated in the ovary. That should set off alarm bells that more study is needed before we inject our youth. In conclusion, I believe available data and common sense justifies a halt to the mass vaccination of our children. Thank you.

Mrs. Christina Dietrich
Delaware Medical Freedom Alliance

My name is Christina Dietrich and I represent Delaware Medical Freedom Alliance. I have 4 children, including 14-year-old twins. I live in a low-income majority-minority neighborhood in Middletown, Delaware. I also work in home healthcare. I've had a patient for 9 years who has a neuromuscular disease and a tracheotomy and is obviously at very high risk for COVID complications. My family, therefore, took extreme precautions to avoid me bringing the infection to work, including homeschooling. I even made my husband, an Amazon worker, shave his beloved beard. My parents were both hospitalized with COVID in April 2020. The high effectiveness rate of the vaccines seemed very exciting. After the vulnerable people in my life had been vaccinated, I allowed my children back to normal life. As their mom, I decided the socioemotional benefits clearly outweigh the incredibly low morbidity and mortality from COVID-19 in healthy kids. As I began to consider vaccinating my children, I called the CDC mid-May to inquire about myocarditis and other adverse events. I asked if an emergency ACIP meeting might be called before children 12 to 15 started getting their second doses. Why can we not wait for a BLA. As Dr. Cody Meisner pointed out at the SBA meeting on June 10, the current COVID pediatric hospitalization rate of 4 per million certainly does not constitute an emergency. Nearly half these children had a positive test that was only incidental to their hospitalization, and 7 in 10 hospitalized for COVID had at least one comorbidity. Your own charter states that you will advise on population groups and/or circumstances in which a vaccine is recommended. Healthy children are not the same as kids with risk factors. I fear that your risk-benefit balance fails to take this into account. I'm also not compelled by the argument that we need to use kids to constrain community spread. It is unconscionable to ask a child to risk his health in order to protect adults. Human beings hold the welfare of our children and the health of human future generations paramount. The WHO, UK, Germany and others have all declined to recommend this vaccine for all children. I thought the USA was the standard bearer for safety and evidence-based medicine. The prevalence for COVID-19 antibodies in children is 27%. Why ignore natural immunity? How can universities mandate a vaccine under EUA when the federal government is barred from such a mandate? Would young people be as willing to use this product if they knew, for example, the odds of winning a serious adverse event exceeded the odds of winning a state-won lottery prize? Is it ethical for the CDC Director to use out-of-date and improperly contextualized hospitalization data to frighten parents into vaccinating their children? "Primum non nocere. First, do no harm." In other words, don't just do something—stand there. Recommendations should not be based on conjecture, nor should they be political, made to protect pharmaceutical companies, or to manipulate public opinion. Trust in our public health apparatus has declined precipitously. Any risk has been downplayed by government officials with the slogan of "safe and effective," which violates the spirit of informed consent, if not the letter . . . [time expired] Updating your guidance in light of the adverse events in mRNA vaccines in young Americans will go a long way towards increasing trust in the future. Thank you very much for the opportunity to speak.

Kelly Moore, MD
Deputy Director
Immunization Action Coalition

I'm Dr. Kelly Moore, Deputy Director of the Immunization Action Coalition (IAC), the nation's leading non-profit focused on supporting frontline immunization providers. Thank you to the committee for your ongoing work. I want to add my personal thanks to Drs. Ann Schuchat, Nancy Messonnier, and Jose Romero for their years of leadership of CDC and ACIP, especially the past 18 months. With my time, I'd like to recognize another person who's been essential to the work of ACIP. Next week, Dr. Deborah Wexler retires as the Founder and Executive Director of IAC. Although not a voting member of the ACIP, she served on several working groups and has been a constant presence at meetings and the public comment microphone for many years. In the late 1980s, Dr. Wexler first began helping clinicians understand and implement ACIP recommendations. She started out writing a local hepatitis B vaccination newsletter in St. Paul, Minnesota, then went national, creating 3 major print publications: *Needle Tips*, *Vaccinate Adults*, and *Vaccinate Women* mailed free of charge to the offices of thousands of healthcare providers. In 1993, Deborah founded IAC and created one of the first websites dedicated to immunization, our online home, immunize.org. In 1997, Deborah founded *IAC Express*, a free weekly e-newsletter featuring the latest CDC immunization news. This morning, the 1574th edition went out to nearly 53,000 subscribers. Twenty-five years ago, Deborah and her CDC collaborators created *Ask the Experts*, now an online repository of more than 1100 up-to-date answers to common questions from immunization providers about how to apply ACIP's recommendations in specific situations. Deborah has inspired many other vaccine champions. In 2005, she conceived of Voices For Vaccines, the first national immunization advocacy group for parents, recruiting and mentoring its leader Karen Ernst. In 2012, she founded the National Network of Immunization Coalitions to facilitate ongoing collaboration among over 100 state and local immunization coalitions. IAC also is the home of the National Adult and Influenza Immunization Summit, Co-Chaired by IAC's Dr. LJ Tan, in partnership with CDC and HHS. Thanks to the tireless educational efforts of Dr. Deborah Wexler, the recommendations of the ACIP have been implemented more effectively by thousands of immunization providers, preventing untold suffering. Thank you for the opportunity to acknowledge her vital contributions to the work of the ACIP today on the occasion of her well-earned retirement.

Mrs. Heidi Johnson-Sandall
Mother & Grandmother

I am a mother of 5, I am a grandmother to 8 little ones, and I am very concerned with the adverse events reporting worldwide with these vaccines. They include bleeding, clotting issues, immune system issues, neurological problems, loss of sight, hearing, speech, smell, pregnancy loss, heart inflammation, and the list keeps going on. It is one thing for the ACIP, and the NIH, and our government to target adults with these vaccines, but to target children when there is such a very low risk of complications with this virus, it makes my heart hurt. I'm literally shaking right now. I feel like the ACIP and all the government regulatory agencies are not taking into consideration natural infection—the rates of infection for children. I would implore this agency to look at this a little bit more carefully since there are no long-term studies whatsoever with any of this. We have no idea what this is going to look like in a year—what kind of illnesses this is going to create for our children and our next generation. Please, I implore you.

Data to Inform Recommendations for Additional Doses of COVID-19 Vaccines

Dr. Oliver (CDC/NCIRD) presented a COVID-19 WG overview of the data to inform recommendations for booster doses of COVID-19 vaccine. This will include data currently available, as well as data needed before recommendations can be made. The main policy question and other questions to be addressed include the following:

Are booster doses of COVID-19 vaccines needed for those previously vaccinated with a primary series?

- Are booster doses needed for all persons or only in specific populations?
- What is the optimal timing of booster doses after a primary series?
- Can these be given as a "mixed dose" or do they need to be matched to a primary series?

Note that decisions around strains for vaccine productions are likely to be made separately. The focus of this session was on data to inform the overall decisions around the use for boosters. Policy on booster doses will need to be coordinated with the FDA for possible amendments to the EUA and ACIP for recommendations around use in specific populations. Both FDA and ACIP will require data on safety, immunogenicity, and the public health need. By definition, the term "booster dose" refers to vaccine doses after a primary series, which could be 1 or 2 doses in the case of COVID vaccines, that are needed to increase immunity after waning of the initial immune response. However, it is important to note that if there was a specific subset of individuals who may not have mounted a sufficient immune response after an initial 1- or 2-dose primary series and could need an additional dose to reach protective immunity, this would not meet the technical definition of a booster dose. However, for the purposes of this presentation, they were all referred to as "booster doses."

To inform recommendations on the initial doses of COVID-19 vaccine, ACIP used the ethical framework as well as data on the risk of COVID-19 complications and risk of COVID-19 exposure. Balancing these two risks led to the populations recommended for allocation of initial supplies of COVID vaccine for LTCF residents, HCP, persons 65 years of age and older, persons 16-64 years of age with high-risk medical conditions, frontline essential workers, and other essential workers. However, data to inform recommendations for booster doses will require even more information. To inform recommendations around booster doses of COVID-19 vaccine, information will be needed on the risk of COVID complications, risk of exposure, risk of waning immunity, and risk of COVID variants.

As was done previously, COVID-19 epidemiology will be closely monitored in terms of cases; hospitalizations; and deaths by age, settings, and medical conditions. The risk of waning immunity after the primary series also will have to be factored in. The ability to boost after additional doses also will have to be assessed. VE studies will have to be monitored and vaccine breakthrough cases will have to be assessed. Data will need to be monitored by time since vaccination, age, settings, and medical conditions. Information on correlates of protection would be very important to interpret data around the risk of waning immunity. Risk of COVID variants, variant proportions, antibody response, and effectiveness for each variant and vaccine will have to be monitored as well.

To inform these discussions on booster doses, it is important to understand what is currently known. Booster doses would apply only to those individuals who already have received a primary series. As of June 21, there have been over 318 million doses of COVID vaccines administered, which means that at least 62% of those 12 years of age and over, 65% of those 18 years of age and over, and 87% of those 65 years of age and over have received at least one dose.[28] For data around immunogenicity and antibody response, first, to discuss what is known around a correlate of protection. A correlate of protection is the immune response that allows prediction of the degree of protection against infection or disease. This work is ongoing and no official correlate has been established yet. Available information will be reviewed on duration of protection, including the kinetics, of the antibody responses and efficacy from early phase clinical trials. In addition, preliminary information on antibody responses to variant vaccines will be reviewed.

While there have not yet been established correlates of protection, two studies have demonstrated robust correlations between vaccine efficacy and mean neutralizing antibody titers across vaccines. The study by Khoury et al[29] estimated 54 IU/ml as a correlate of protection against detectable SARS-CoV-2 infection, which was estimated to be around 20% of the mean convalescent titers and noted this threshold for protection against severe disease may be lower and less likely to be affected by vaccine differences. For variants where declines have been in neutralization titer, the authors estimate that a 5-fold lower neutralization titer was predicted to reduce efficacy from 95% to 77% in a high efficacy vaccine or from 70% to 32% for a vaccine that starts out with lower efficacy. The same paper illustrates that initial efficacy may be useful in predicting time until boosting may be needed. For example, a vaccine starting with an initial efficacy of 95% is expected to maintain 77% efficacy by 250 days or 8 months. An initial efficacy of 70% may be predicted to drop to 33% efficacy within the same period. However, it is important to note in interpretation of all of this information that this model assumes that neutralization is the only major mechanism of protection. These numbers may be an underestimate where neutralization and cell-mediated immunity (CMI) both play a role in protection.

Another important consideration is the duration of protection against severe disease. Studies of antibody responses to many vaccines shows that after an initial period of rapid exponential decline, antibody levels generally stabilize into a slow linear decline with half-lives of over 10 years. Depending on when this transition occurs, this model predicts that even without immune boosting, a significant proportion of individuals may maintain long-term protection from severe infection by an antigenically similar strain, even though they may become susceptible to mild infection. In terms of what is known around duration of immunity, antibody persistence has been demonstrated up to 8 months after COVID infection and up to 6 months after the second mRNA vaccine dose so far. Two studies were conducted around 6 months after receiving the Moderna vaccine. These studies showed lower neutralization titers and higher proportions with undetectable titers against a B.1.351 and P.1 variant compared with an ancestral strain. However, many studies have shown larger decreases in variant neutralization for convalescent sera than for post-vaccine sera.[30]

[28] https://covid.cdc.gov/covid-data-tracker
[29] https://www.nature.com/articles/s41591-021-01377-8
[30] Gaebler, C. et al. Evolution of antibody immunity to SARS-CoV-2. Nature 591, 639–644 (2021); Dan, J. M. et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371, eabf4063 (2021); Choe et al. Antibody Responses 8 Months after Asymptomatic or Mild SARS-CoV-2 Infection. Emerg Infect Dis. 2021;27(3):928-931; Doria-Rose et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. N Engl J Med 2021; 384:2259-226; https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious; Khoury et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01377-8 ; Pegu et al. bioRxiv preprint (May 16 2021): https://doi.org/10.1101/2021.05.13.444010; Wu et al. medRxiv preprint (2021): https://doi.org/10.1101/2021.05.05.21256716; Luo, Hu, Letterio, medRxiv preprint (4 2021): medRxiv preprint doi: https://doi.org/10.1101/2021.05.04.21256537

Preliminary data were published by preprint evaluating the safety and immunogenicity of a SARS-CoV-2 variant vaccine booster after a 50 µg booster dose of mRNA-1273 vaccine and a B.1.351 specific booster. Two weeks after booster vaccination, titers against the wild-type original strain, D614G, as well as titers against the B.1.351 and P.1 variants all increased to level similar to or higher than peak titers after the primary series. Overall, both vaccines demonstrated broad antibody boosting across all variants detected. There may be a slight advantage for B.1.351 with a B.1.351 specific boost, but the preliminary study documented that both vaccines demonstrated broad boosting for a variety of variants.[31]

Turning to what is known around VE in terms of overall real-world VE in the general population, efficacy and effectiveness against the variants and effectiveness in specific populations are illustrated by several published studies.[32] In a real-world VE in a fully vaccinated adult population, studies looking at symptomatic infections had a range of 82% to 97% VE compared to infection, which had greater variation with a range of 65% to 95%. Overall, a higher VE is generally observed for symptomatic disease where assessed. Many variants showed reduced antibody neutralization activity relative to the wild-type or ancestral strain. The largest fold reductions have been in the B.1.351 or beta variants, among others.

The best way to get specific impact of a vaccine and only a single variant is through laboratory-based neutralization studies. However, VE in specific geographic locations can be assessed to determine the dominant strain or strains at the time a study was conducted. Overall, VE remains fairly high, even where the dominant strain has been a VOC. VE is slightly lower for the B.1.351 or beta variants. But even for this variant of concern, VE is higher for the prevention of severe disease.[33]

To highlight what is known around the newest variant of concern, Delta or B.1.617.2 variant, there are 3 studies.[34] A study from Scotland, which highlights the Delta-specific VE for PCR-confirmed infections, estimates 79%. A study from England shows that VE is higher for symptomatic infection at 88% and 96% for hospitalization. This increase in VE for symptomatic disease and severe disease has been observed in both the clinical trials and for other variants. There are 4 antibody neutralization studies[35] in which 2 doses of a Pfizer vaccine lead to somewhere between a 1.4- and 5.8-fold reduction compared to a wild-type virus. A recent study from the UK[36] showed a resurgence driven by a replacement of a B.1.1.7 with B.1.617.2, which has a higher transmission rate and infections driven by younger unvaccinated people.

Boosters may be required for a broad population. However, it could also be that the need for boosters of COVID vaccines may only be demonstrated in some populations. Populations to monitor include residents of LTCF, adults 65 years of age and older, HCP, and immunocompromised persons.

[31] https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1
[32] See reference list at end of slide presentation
[33] CDC Science Brief : https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html; Abu-Radad and Butt. NEJM (2021); Sandoff et al. NEJM (2021); Chung et al. medRxiv preprint (May 28 2021); Yassi et al. medRxiv preprint (May 25 2021))
[34] Sheikh et al. Lancet (2021): https://doi.org/10.1016/S0140-6736(21)01358-1; Lopez Bernal et al. medRxiv preprint (May 26 2001); https://doi.org/10.1101/2021.05.22.21257658
[35] Stowe et al. PHE preprint: https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266 ; Planas et al. bioRxiv preprint (May 27 2021); https://doi.org/10.1101/2021.05.26.445838 ; Wall et al. Lancet (2021). https://doi.org/10.1016/ S0140-6736(21)01290-3: Liu et al. Cell (2021). https://doi.org/10.1016/j.cell.2021.06.020
[36] Riley et al. medRxiv (June 21 2021): https://doi.org/10.1101/2021.06.17.21259103 ; Liu et al. Nature (2021); https://doi.org/10.1038/s41586-021-03693-y

Looking at 2-dose mRNA VE for SARS-CoV-2 infections in older adults 60 years of age and older and adults in LTCFs,[37] VE initially has been high, although with some variability among studies and populations. The range among residents of LTCFs was 64% to 92%. For adults 60 years of age and older, VE ranged from 70 to 95%.[38] Given that HCP were a group prioritized for initial vaccination, there are several studies[39] evaluating VEs specifically in this population. To date, VE has been high for both SARS-CoV-2 infection and symptomatic COVID in this population.

Moving to people with clinically or therapeutically suppressed immunity, the immunocompromised population represents around 2.7% of US adults and includes a broad variation of conditions. It is known that immunocompromised adults are more likely to get severely ill from COVID and may be at higher risk for prolonged infection, viral evolution, and may be more susceptible to infection from variants. This variety of conditions for immunocompromised populations may also impact how they respond to a vaccine.[40] Among populations identified as immunocompromised, there are additional factors that can impact that response, including host factors such as older age, decreased kidney function and degree of immunocompromise as well as type of immunosuppressive medications.

Information is beginning to become available around VE among these immunocompromised populations. One study found that 2 doses of an mRNA vaccine was 71% effective compared to 90% overall, but the VE was slightly higher for symptomatic infection. There was also lower protection with increasing age group.[41] Another study estimated 2 doses of mRNA vaccines were 80% effective against SARS-CoV-2 infection among people with inflammatory bowel disease on various immunosuppressive medications. The VE after the first dose was low, highlighting the need to complete the recommended series in this population. No differences were noted in effectiveness between the two mRNA vaccines.[42]

Looking at percent antibody response after two mRNA vaccine doses by different types of immunocompromising conditions. Studies of people with cancers ranged from 45 to 95%, with larger impact seen among the people with hematologic cancers. Studies of people on dialysis ranged from 45% to 88%. Studies of people with solid organ transplant had the largest effects and antibody response, ranging from 3% to 58%. Studies of people being treated for autoimmune or inflammatory disorders ranged from 40% to 87%. For reference, the healthy controls included in all of these studies ranged from 95% to 100%. Almost all studies that assessed response after the first and second doses demonstrated poor response of people who are immunosuppressed to a single mRNA vaccine dose.[43] For antibody titers observed in different studies of immunocompromised groups, shown as full reduction of healthy controls, the largest full decreases were observed among some of the hematologic cancers, but some studies of people with cancer, on hemodialysis, or with solid organ transplants observed more than a 5-fold reduction in antibody titers compared to healthy controls. However, an important question to address is if the situation regards whether immunocompromised persons would mount a sufficient immune response if given a booster or third dose if they did not mount one after the first two doses.[44]

[37] Cabezas et al, Emorg et al, Canvanaugh et al, Mousten-Helms
[38] Dagan et al, PHE (5.20.21), Lopez-Bernal et al, Aran, Mason et al
[39] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
[40] See list of references on slide 29
[41] Chodick et al. Clinical Infectious Diseases, ciab438, https://doi.org/10.1093/cid/ciab438
[42] Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf
[43] See references at the end of the slide set
[44] See references at the end of the slide set

There is evidence on providing a third COVID-19 vaccine dose to immunosuppressed people with suboptimal response. One study[45] looked at solid organ transplant recipients who had suboptimal responses to standard vaccination and subsequently received a third dose. Among these individuals, 80% had negative antibody titers and 20% had low positive titers after a primary series. These individuals received a third dose, a median of 67 days after their second dose. After this third dose, over half of those individuals remained antibody negative. Another study[46] assessed persons on hemodialysis vaccinated with up to three doses among whom 83% seroconverted after a second dose. Of those who were negative after the second dose, nearly 60% remained negative after a third dose. As there is no correlate of protection, it is not clear how these antibody test results relate to clinical protection for disease, so additional studies are needed. There is at least one trial looking at additional doses in transplant recipients.

To recap, there are plans to monitor data across all populations. However, the WG has highlighted the populations to monitor closely: LTCF residents, adults ≥65 years of age, HCP, and immunocompromised persons. For LTCF residents and ≥65 years of age, the VE is encouraging. However, these individuals were vaccinated in the early phase of COVID vaccine rollout. In addition, this is a population that in the past has needed special considerations for other vaccines, including additional booster doses or higher dose vaccine. HCP also were vaccinated in the early phase of the COVID vaccine rollout. They also will have continued exposure to SARS-CoV-2, even as community transmission rates improve. For immunocompromised persons, emerging literature is suggesting a reduced antibody response after a primary series. In addition, by definition, this is a population with an impaired immune response. Because of the concern regarding the ability of this population to mount an immune response after additional vaccine doses, consideration will have to be given to whether this is a population that needs additional vaccine doses or a population that may need other prevention measures, such as monoclonal antibodies.

The WG also highlighted the issue of mix-and-match, or more formally, a heterologous primary series and booster vaccine. Recent studies from Europe[47] have assessed heterologous primary series with a Pfizer and AstraZeneca (AZ) vaccine with reassuring results. Information can definitely be learned from these studies. Evidence also is needed regarding the ability to use different vaccines as a booster than what was used in the primary series, including studies specific to US-authorized vaccine.

To highlight additional data that may be forthcoming,[48] there will be data from the Phase 1, 2, and 3 clinical trials. This will include kinetics and duration of the antibody response, as well as efficacy from the early phase clinical trials. In addition, the Biologics License Application (BLA) submissions should include efficacy for approximately 6 months. To inform the heterologous boost, defined as a primary series followed by a different boost vaccine, there is an NIH-sponsored study that is looking to address this, with the results expected late Summer 2021. In terms of the booster-specific studies, Moderna published preliminary results in May that were

[45] Werbel et al. Annals of Internal Medicine. https://www.acpjournals.org/doi/pdf/10.7326/L21-0282

[46] Longlune et al.. Nephrology Dialysis Transplantation, gfab193, https://doi.org/10.1093/ndt/gfab193 https://clinicaltrials.gov/ct2/show/NCT04885907

[47] Borobia et. Al Reactogenicity and Immunogenicity of BNT162b2 in Subjects Having Received a First Dose of ChAdOx1s: Initial Results of a Randomized, Adaptive, Phase 2 Trial (CombiVacS). Available at SSRN: https://ssrn.com/abstract=3854768; Shaw et. al Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(21)01115-6; Hillus D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunization with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv; 2021. DOI: 10.1101/2021.05.19.21257334.Schmidt et al. medRxiv preprint (June 15 2021): https://doi.org/10.1101/2021.06.13.21258859

[48] https://www.nih.gov/news-events/news-releases/nih-clinical-trial-evaluating-mixed-covid-19-vaccine-schedules-begins

described earlier in this presentation. Additional data on mRNA-1273 vaccine and other variant vaccines as boosters is expected late Summer or early Fall of 2021. Pfizer's data on their BNT162b2 (30µg) vaccine and variant booster studies is expected during the same timeframe as well.

To highlight data from CDC, vaccine breakthrough cases will be tracked and severity of disease and genomic sequences specifically to monitor for variants of concern will continue to be monitored. VE studies over time will continue to be monitored to stratify by age, time since vaccination, setting, and medical conditions. It is important to note that the ability to track waning VE could be impacted by the declining incidence and changes in variant prevalence. In addition, over time, individuals who are vaccinated may become increasingly less comparable to the unvaccinated population. This will need to be considered in terms of both study design and study interpretation.

There are many studies ongoing to assess the VE and vaccine breakthrough cases, three of which Dr. Oliver highlighted. The Healthcare, Emergency Response, and Other Essential Workers Surveillance Study-Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (HEROES-RECOVER) study is following around 5000 essential workers with weekly SARS-CoV-2 testing and quarterly serology. To date, they have fully vaccinated populations that have been followed for around 4 months post-vaccination, and they plan to assess neutralizing antibodies at 6 months post-vaccination to inform duration of protection. The VISION VE Network is a multi-state network of 8 integrated care systems and research centers. They assess COVID disease by confirmed molecular assays and vaccination documented by EHRs and registries. The network plans to assess waning effectiveness using a test-negative VE design. The Influenza and Other Viruses in the Acutely Ill Network (IVY VE Network) is a collaboration of hospital-based investigators through 18 tertiary academic medical centers in 16 states. They plan to assess duration of protection by adapting prior methods used for influenza. This is not a comprehensive list of studies, but highlights some of the larger studies as a representation of upcoming data that are expected.

Attempting to put everything together, later this Summer and early Fall, CDC expects to receive manufacturer data on safety and immunogenicity of booster doses, longer-term trial follow-up, and results from the mix-and-match studies. In early Fall, COVID epidemiology will be monitored closely for any possible increase in cases, COVID variants, VE studies, and assessment of vaccine breakthrough cases. There will continue to be ACIP meetings during which updates will be provided on all of these data as they become available. A vote to recommend boosters in any population could occur whenever data support updating policy. These data were reviewed with the workgroup as well. Their interpretation was that recommendations for booster doses would occur only: 1) After evidence of declining protection against illness, such as declines in VE, not only waning antibody response; and/or 2) An escape variant, VOC, is substantially impacting vaccine protection. There are not sufficient data to support recommendations for booster doses currently, but this will continue to be closely monitored. The WG felt that global vaccine availability should be considered in these discussions as well.

The following questions were posed for ACIP consideration and deliberation:

1. What does ACIP feel would be needed to move forward with booster recommendations?
2. Is the risk of disease enough to warrant a recommendation for boosters, before additional data may be available, or would ACIP need to see the data around waning VE and breakthrough cases prior to a recommendation for boosters?

Summary of Discussion

- Dr. Fink commented that in the past when the FDA has contemplated the addition of a booster dose to a vaccine that has been previously authorized for use as a primary series, they have assessed the safety profile of the primary series, including in clinical trials and post-authorization use. In addition, they have assessed the safety profile of the booster dose as studied in clinical trials. The overall safety database from clinical trials that have supported approval of a booster dose typically has not been nearly as large as the size of the safety database that would be expected to support initial approval as the primary series for a number of reasons. The primary reason is because they are relying on and leveraging the vast experience that they typically would have available with post-authorization use of the primary series. Unless there is a reason to suspect or be concerned about a specific safety issue with an additional dose, the FDA typically would characterize reactogenicity to the booster dose. Given that evaluation for much less common adverse reactions would be outside the realm of what is feasible, the FDA would need to look carefully at the safety profiles from clinical trials and post-authorization use for COVID vaccines and the reactogenicity profile from clinical trials that typically could be characterized with several hundred or slightly more booster dose recipients. If there are specific safety concerns that could feasibly be evaluated with a somewhat larger safety database, they would take that under consideration as well.

- ACIP members raised some concerns and expressed interest in further information on a variety of topics related to data needed to move forward with booster recommendations for COVID-19 vaccines and/or whether to recommend boosters, before additional data may be available:

    - Boosters should not become a distraction for the US. Many parts of the US have incredibly low vaccination rates, which poses a risk for homegrown variants that may spread rapidly across the US when introduced. Before focusing efforts on giving everyone boosters, improvement is needed in the overall vaccination rate—especially for those who continue to be at risk.

    - Extensive vaccine education continues to be needed for families, friends, co-workers, and religious attendees to emphasize that they must be vaccinated themselves to protect those who are immunocompromised, frail, and or live in nursing homes/LTCFs. It is critical for people to have their questions answered, to have geographic access to vaccines, and to clearly understand that even though they are immunized they may still be vulnerable and should consider continuing other countermeasures (e.g., masks, social distancing, sanitizer).

    - It is important to communicate and share with the world. While ACIP is a US-focused committee, the world is very small world thanks to air travel and other luxuries. Variants are surging and causing large numbers of deaths across the world. To prevent further evolution of these variants, the US should provide vaccines to these countries. While there has been discussion about sending doses to the rest of the world, that is not enough. More needs to be done and there is extra vaccine in this country that needs to be distributed to help stop the suffering and the evolution of more variants.

- The relatively heterogeneous immunocompromised populations represent a common theme, given the devastating number of breakthrough infections seen even in fully vaccinated individuals. While additional information would be beneficial, this population should be offered a booster dose as soon as there is good science on which to base a decision to recommend.

- As Dr. Fink highlighted, the safety profile should be one of the considerations for boosters.

- The basic research laboratory data are needed from long-term memory B cell and T cell studies and CMI studies.

- In the absence of sufficient data to make a recommendation for booster or third doses, perhaps a cue that might trigger ACIP to move quickly to make a recommendation would be if an uptick is observed in reinfections or new infections among people who are considered to be fully vaccinated with the primary series. An exception may be making a recommendation for a booster vaccine against a variant for which a booster vaccine is not available, though ACIP should be able to make a recommendation for a booster of the primary vaccines that were given against wild-type virus.

- There are years of experience on the safety and epidemiology of influenza vaccine, but the US does not wait until disease is full-blown or there is an outbreak before beginning a new vaccine with a different combination of vaccine viruses. Much has been learned from the Delta variant that certainly will inform ACIP on whether to begin considering a decision on the use of a booster ahead of outbreaks throughout the US or the world. This consideration should begin before there is evidence of disease from variants if this continues to be an ongoing virus with periodic recirculation. While they certainly want to mitigate the risk of severe breakthrough disease, breakthrough cases appear to be milder at this time. Perhaps consideration should be given to a trigger threshold for a booster dose.

- It may be a mistake to administer a booster dose in someone who is elderly or immunocompromised without additional safety data, especially given that there have been issues with the second dose of mRNA vaccines.

- It is important to note that people are already requesting and receiving booster doses even though there is not a recommendation.

CERTIFICATION

Upon reviewing the foregoing version of the June 23, 2021 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACC	American College of Cardiology
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
AGS	American Geriatric Society
AHA	American Heart Association
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
CVST	Cerebral Venous Sinus Thrombosis
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVRPA	Division of Vaccines and Related Product Applications
DVT	Deep Vein Thrombosis
ECG/EKG	Electrocardiogram
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent
EMA	European Medicines Agency
EtR Framework	Evidence to Recommendations Framework
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHCs	Federally Qualified Health Center

GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAN	Health Alert Network
HCP	Health Care Personnel / Provider / Professional
HCW	Health Care Workers
HEROES-RECOVER	Healthcare, Emergency Response, and Other Essential Workers Surveillance Study-Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel
HFpEF	Ejection Fraction
HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-Induced Thrombocytopenia
HRSA	Health Resources and Services Administration
IAC	Immunization Action Coalition
ICU	Intensive Care Unit
ID	Identifier
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
IVIG	Intravenous Immune Globulin
IVY VE Network	Influenza and Other Viruses in the Acutely Ill Network
J&J	Johnson & Johnson
MASO	Management Analysis and Services Office
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	*Morbidity and Mortality Weekly Report*
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	New England Journal of Medicine
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NSAIDS	Nonsteroidal Anti-Inflammatory Agents
OB-GYN	Obstetrics and Gynecology
PE	Pulmonary Embolism
PF4	Platelet Factor 4
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PIDS	Pediatric Infectious Disease Society
RCA	Rapid Cycle Analysis

RCT	Randomized Controlled Trial
RR	Relative Risk
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHEA	Society for Healthcare Epidemiology of America
SMEs	Subject Matter Experts
TCM	Traditional Chinese Medicine
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Work Group
VOC	Variant of Concern
VOHC	Variant of High Consequence
VOI	Variant of Interest
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization