MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

AUGUST 30, 2021
SUMMARY MINUTES

TABLE OF CONTENTS

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on August 30, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on the BNT-162b2 COVID-19 vaccine Biologics License Application (BLA) safety and efficacy data; COVID-19 vaccine safety updates; Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Pfizer-BioNTech COVID-19 vaccine for persons 16 years of age and older; Evidence to Recommendations (EtR) Framework for Pfizer-BioNTech COVID-19 vaccine for persons 16 years of age and older; and the framework for COVID-19 vaccine booster doses.

THURSDAY: AUGUST 30, 2021

WELCOME AND INTRODUCTIONS

Dr. Amanda Cohn (ACIP Executive Secretary) called the meeting to order and welcomed those present. She introduced two of three new ACIP members, Drs. Sybil Cineas and Oliver Brooks, noting that they would be introduced more formally during a regular ACIP meeting. Dr. Cineas is an Associate Professor of Medicine, Pediatrics, and Medical Science in the Residency Program at Brown University in Providence, Rhode Island and Dr. Brooks a Pediatrician with Watts HealthCare Corporation in Los Angeles, California. Both of these new members have extensive experience in immunization and in healthcare.

Dr. Cohn noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 11:15 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-2021-0089. 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 state any COIs at the beginning of each meeting.

Dr. Grace Lee (ACIP Chair) conducted a roll call, during which no COIs were declared and quorum was established. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

She then highlighted that the primary focus of this meeting would be on updating the recommendations for use of the Pfizer-BioNTech COVID-19 vaccine now that it had received full licensure from the Food and Drug Administration (FDA), hearing an update from the COVID-19 Vaccines Work Group (WG) on the topic of booster doses, and ongoing discussion that began on August 13, 2021 of the PICO (Problem/Population, Intervention, Comparison, Outcome) question and key domains in ACIP's EtR Framework. Given the state of the pandemic and the importance of vaccines as a tool to address this pandemic, she reminded their colleagues and the public that the ACIP would continue to follow its usual processes regarding booster doses as is done for every other ACIP recommendation. After the FDA has the opportunity to carefully review the data submitted by the companies on booster doses, ACIP will incorporate any updated data into its deliberations and will vote on recommendations for future use of boosters in the US civilian population. It is anticipated that another ACIP meeting will be convened on this topic in the very near future.

Dr. Lee also took the opportunity to thank the ACIP Voting Members, *Ex Officio* Members, and Liaison Representatives for their continued dedication and service to this committee. She extended special gratitude to Dr. Rochelle Walensky, Dr. Amanda Cohn, the entire ACIP Secretariat Team, and all of the CDC staff and colleagues for working around the clock to ensure that ACIP has the data needed to support a robust decision-making process.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) introduced the COVID-19 Vaccines WG session, reporting that the number of individuals hospitalized with COVID-19 in the US exceeded 100,000 the previous week. This is the highest level since the peak incidence in January 2021.[1] To set the stage for the day, he reminded everyone that when considering recommending a licensed vaccine for use, never before has the ACIP made such recommendations with such a breadth and depth of information that they would consider throughout the day. There were at least 680,000 vaccinated individuals who contributed to the observational studies to be reviewed during this meeting. That is in addition to the more than 40,000 enrolled of whom more than 22,000 were vaccinated in the Phase 3 clinical trials. The number of total cases during the pandemic in the US has been more than 38 million cases reported. Since June 2021, cases in the US have risen quite sharply. Over 600,000 individuals in the US have died from COVID-19 and more than 1,000 individuals are dying each day from COVID-19 in the US. With safe and effective vaccines readily available in the US at this point in the pandemic, death from COVID-19 is largely vaccine-preventable. This observation is supported by the data to be presented during this meeting. Data from COVID-NET for the time period January 24-July 17, 2021 show that the unvaccinated rate is 16 times greater than the vaccinated rate. Preliminary data from July show that this is a strong indication that the current epidemiologic curve is really a reflection of failure to vaccinate, not vaccine failure.[2]

[1] https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases
[2] Havers et al. https://medrxiv.org/cgi/content/short/2021.08.27.21262356v1. COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years COVID-NET, 13 states, January 1 – July 24, 2021

To update the full ACIP on the COVID-19 Vaccine WG's activities in August of 2021 since the last ACIP meeting, the WG heard a number of safety updates from the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). In addition, the WG has been reviewing in detail considerations around the use of Pfizer-BioNTech COVID-19 vaccine under full FDA licensure. This included reviewing detailed and updated efficacy data from the clinical trial, and a detailed review of the risk-benefit assessment with a particular focus on the issue of myocarditis. The WG also evaluated all of the strength of evidence through the GRADE process, and reviewed the EtR Framework. In addition, the WG discussed in detail considerations for booster doses of COVID-19 vaccines. This included reviewing real-world vaccine effectiveness (VE) studies from the US and abroad, and a particular focus on what is known about hospitalized cases post-vaccination (e.g., breakthrough infections).

BNT-162b2 COVID-19 Vaccine BLA Safety and Efficacy Data

Dr. John Perez (Pfizer-BioNTech) presented COVID-19 safety and efficacy data through the data cutoff of March 13, 2021. Due to time constraints, he focused the discussion on a high-level overview of long-term safety analyses for individuals 16 years of age and older, adverse events of special interest (AESI), efficacy update, sequence data on all COVID-19 breakthrough cases, and pregnancy data through the cutoff date. Though not covered during this presentation, information also is available on human immunodeficiency virus (HIV)+ participants, participants who were SARS-CoV-2 +/- at baseline, more than 1 episode COVID-19 cases in the placebo group, placebo participants who developed COVID-19 then received BNT162b2, and booster data.

Beginning on July 27, 2020, the BNT162b2 Phase 2/3 study involved 2 doses given 21 days apart in approximately 46,000 participants. Reactogenicity data were obtained via e-diary for 7 days after each dose. Non-serious adverse events (AEs) were collected 1 month post-dose 2, serious AEs (SAEs) were collected through 6 months post-dose 2, and deaths were recorded throughout the study. The vaccine became available while the study was ongoing and subjects were unblinded so placebo subjects could get vaccinated. For individual subjects, there is a blinded placebo control follow-up period and an open-label follow up period. While the data will refresh from Dose 1 to 1 month post-Dose 2 in the BLA, all conclusions (especially about reactogenicity and lymphadenopathy) remain the same. The reactogenicity profile of participants with HIV were similar to what was observed in the non-HIV population.

During this presentation, Dr. Perez focused on safety with longer-term follow-up time, especially for those with at least 6 months of follow-up. Notably, some of the follow-up time is placebo-controlled and some is open-label. For the open-label period, Pfizer reports all of the safety data for people originally randomized to vaccine and those originally randomized for placebo. It is important to note that placebo subjects were vaccinated, the same reactogenicity lymphadenopathy safety profile was seen as in those originally randomized to vaccine. In terms of follow-up time after Dose 2 in individuals 16 years of age and older, in the originally blinded placebo control follow-up period, about 51.1% had between 4 and 6 months of follow-up and an additional 8.1% had greater than 6 months of blinded follow-up time. Looking at total exposure from Dose 2 to cutoff date, 54.5% or over 12,000 individuals had greater than 6 months of follow-up time. The demographics were very similar to what has been presented previously. Roughly there were equal numbers of males and females, the predominant race was White, approximately 1/3 were Hispanic or Latino, and about 70% to 80% were from the US.

Focusing now on safety and AEs to the unblinding date, the pattern was essentially the same as seen with the EUA. The vaccine group had a higher proportion of AEs reported compared to the placebo group. That also included a higher proportion of related AEs than the placebo group. However, when comparing SAEs, related AEs, withdrawals due to AEs, and deaths, the rates were very similar between both groups. Breaking these data down by system organ class from Dose 1 to the unblinding date, a similar pattern was seen as observed in the EUA. The top 4 categories that accounted for the major differences in AEs between the vaccine and placebo groups included general disorders and administration site concerns, musculoskeletal and connective tissue disorders, nervous system disorders, and gastrointestinal (GI) disorders. Examining the AEs individually in each of these system or organ classes, the imbalance is due to reactogenicity events being reported in those who did not have the benefit of an e-diary. For example, in the general disorders and administrative site conditions mostly reflect local reactions at the injection site and systemic reactions of fever and fatigue. Whereas, in the musculoskeletal and connective tissues disorders, it came from arthralgia and myalgia. In the nervous system, it was primarily headache. Within the GI disorders, it was nausea and diarrhea.

However, other AEs were reported at a higher frequency in the vaccine group compared to the placebo including pain in the extremity, malaise, decreased appetite, lethargy, asthenia, night sweats, and hyperhidrosis (e.g., excessive sweating). Focusing on pain in the extremity, 185 individuals in the vaccine group reported pain in the extremity compared to 44 in the placebo group. When these were assessed in the analysis in terms of when these AEs were occurring, they were clustering within 7 days after the first or second dose. With pain in the extremity, there were 88 in the 7 days after the first dose and 84 in the 7 days after the second dose. Pfizer's interpretation of these data is that since these AEs were clustering within a 7-day period after each dose, they are considered to be attributed to the experience of reactogenicity and plausibly associated with a local reactions and systemic events.

Turning to SAEs with an incidence rate of ≥0.1 events per 100 patient years by system organ class, for any SAE there were 268 reported in the vaccine group, which calculated out to an event rate of 3.2 per 100 patient years. There were 268 in the placebo group, which calculated out to an event rate of 3.3 per 100 patient years. The event rate for the vaccine or the placebo group are very similar. There were 4 SAEs attributed to the vaccine group and 1 to the placebo group. All 4 of these had been previously discussed at the time of the EUA. No additional SAEs were captured from Dose 1 to the unblinding date in this dataset. There was 1 related psoriatic arthropathy that occurred in the placebo group. In terms of deaths from Dose 1 to the unblinding date, there were 15 deaths reported in the vaccine group and 14 deaths reported in the placebo group. The incidence rate was 0.2 for both the vaccine and the placebo group. The individual events were essentially one-offs in each of the categories.

Turning to AEs through the data cutoff date for Dose 1 to 6 months after Dose 2 in vaccine recipients, previously about 32% reported any AE and now that compares to 28.8% reporting any AE in those with 6 months of follow-up. Related AEs were reported in 18.7%, which compared favorably with the 24% shown earlier. The rates remained low in the additional follow-up time in terms of any SAE at 1.6% and no related SAEs, withdrawals due to AEs, or deaths. By system organ class from Dose 1 to 6 months after Dose 2, most of the AEs were concentrated into the general disorders and administrative site conditions, musculoskeletal, nervous system, and GI disorders as seen previously. Evaluating the individual AEs, the same sort of local and systemic reactogenicity in these categories were reported by individuals who did not have an electronic diary. Looking at SAEs of ≥0.1% by system organ class from Dose 1 to 6 months after Dose 2, there were 190 events or 1.6% of the subjects who reported SAEs in over 12,000 individuals. The rate and proportion of SAEs is low in all of the categories.

In terms of AESI and other important terms evaluated during the placebo-controlled portion of the clinical trial, hypersensitivity/anaphylaxis were evaluated during the blinded control period. There were three SAE's in that category. One was due to a bee sting, one to an antibiotic, and one to an ant bite. However, in the open-label follow-up period, one subject reported an anaphylactoid reaction assessed as related to vaccine. This was in a teenager with a history of multiple allergies who developed the event 2 days after Dose 3 in the study, which was the first dose of vaccine. She had hives, self-administered epinephrine, the event resolved 10 to 30 minutes later, and this was not medically attended. Importantly, the participant received a second dose of vaccine outside the study 40 days after the first and no allergic reaction was recorded.

Bell's Palsy also was evaluated. In the placebo-controlled portion of the trial, 4 cases of Bell's Palsy were reported in the vaccine group compared to 2 cases in the placebo group. When placebo patients were able to receive vaccine and crossed over to vaccine, there were 3 additional cases reported after the crossover. Then 1 additional case was reported that originally was randomized to vaccine and reported as Bell's Palsy with additional follow-up. There was roughly equal distribution of men and women, with an age distribution from 19 to about 73 years of age. In terms of days from the last dose, there was bimodal distribution where some of the cases were occurring close to vaccination while others were occurring more distant to vaccination. All of the cases that occurred proximal to vaccination were labeled related by the investigator in this analysis. Also, 3 of the subjects had risk factors for Bell's Palsy. One subject had diabetes, one subject had a history of Bell's Palsy and a transient ischemic attack, and another subject had 3 episodes of Bell's Palsy at the same distribution she had it when it was reported in the trial. A higher rate of lymphadenopathy was reported in the vaccine group compared to the placebo at 0.4% compared to 0.03%. Appendicitis also was evaluated, with 15 cases (0.7%) found in the vaccine group compared to 12 cases (0.6%) found in the placebo. None of these were related to study intervention by the investigator.

Angioedema and hypersensitivity also were evaluated. Overall, there were 30 (0.14%) in the vaccine group versus 29 (0.13%) in the placebo group. Hypersensitivity events were mostly characterized by rashes that were maculo-papular or popular, and there were similar rates between the vaccine and placebo groups. In terms of demyelination, there were 2 cases of optic neuritis in the vaccine group compared to none in the placebo group. In both cases, there was convincing evidence that they had optic neuritis and were treated with appropriate doses of steroids, but please it is important to note that one case of optic neuritis occurred 80 days after the last dose and in the second it occurred 103 days after their last dose. There was one Guillain-Barre Syndrome (GBS) case reported in the placebo group. A large number of terms were evaluated in the study for which there were no reports as of the time of the cutoff. Most of these were neurological events and some were hematologic events and pulmonary events. There were 2 cases of bacterial meningitis reported in the study, but bacteria were identified in those cases.

Additional terms beyond those designated by the CDC as AESIs were evaluated to assess potential imbalances between the BNT162b2 and placebo groups during the blinded placebo-controlled follow-up period. In terms of myocardial infarction, 11 events were reported in the vaccine group and 17 events were reported in the placebo group. Most of these events had onset greater than 30 days following receipt of vaccine or placebo. None of these events were assessed by the investigators as being related to the study intervention. The outcome was fatal in 2 participants in the placebo group and resolved or are resolving in the other cases. There were 2 cases of encephalopathy reported in the vaccine group and none in the placebo group. In the first case, it was a toxic encephalopathy due to infection. In the second case, it was

uraemic encephalopathy. There was one multisystem inflammatory syndrome (MIS) reported in an unfortunate subject who developed multi organ dysfunction secondary to COVID-19 in the placebo group. There was 1 case of myocarditis in the placebo group. There was an additional myocarditis case reported in the vaccine group after Pfizer submitted these data. This case has been well-discussed. The only follow-up Dr. Perez had at the time of this presentation was that the case completely resolved. There was 1 event of pericarditis in the vaccine group in an elderly man that occurred 29 days after Dose 2. This was thought to be not related to study intervention. For pulmonary embolism, there were equal cases in the vaccine and placebo groups at 8 apiece. For hemorrhagic strokes, there were 4 cases in the vaccine group and 3 in the placebo group. For ischemic stroke, there were 8 cases a piece in the vaccine and placebo groups. For thrombocytopenia, there were 2 cases apiece in the vaccine and placebo groups. For both cases in the vaccine group, there was a reasonable medical event that was causally related to the low platelet count. In the first case, there was alcoholic cirrhosis. In the second case, it was secondary to sepsis. For venous thromboembolism, there were 9 cases in the vaccine group and 9 cases in the placebo group. None of these events were associated with thrombocytopenia.

In terms of pregnancy, participants had to have a negative pregnancy test to get vaccinated. Therefore, most of the pregnancies occurred well after vaccination. Overall, 42 women got pregnant in the vaccine group compared to 47 in the placebo group. A total of 5 apiece withdrew from vaccination due to pregnancy. The majority of the subjects completed 2 doses of vaccine. Most were more than 30 days out from their second dose when they got pregnant. There were 3 spontaneous abortions (SABs) in the vaccine group and 7 in the placebo group. There were 3 miscarriages in the vaccine group and 5 in the placebo group. There was 1 elective abortion in the placebo group and there was no report of fetal demise or major birth defects as of the cutoff date. In an extensive analysis that was done post-marketing, including clinical trial cases and pharmacovigilance analyses from across the globe, to date there has not been any evidence that the vaccine impacts fertility or has major birth defect outcomes.

Moving to efficacy data, the primary endpoint occurred 7 days after the second dose. Looking at the analysis in subjects without evidence of infection prior to 7 days after Dose 2, there were 77 cases in the vaccine group compared to 833 in the placebo group. This calculates to a VE of 91.1%. Looking at the individuals with and without evidence of infection prior to 7 days after the second dose, there were 81 in the vaccine group and 854 in the placebo group. This is a VE of 90.9%. Broken down by various demographic groups (e.g., age, sex, race, ethnicity, and country), overall VE was 90.9%. No matter how the data are cut and sliced through the various demographic groups, Pfizer is reporting high values of efficacy across all these demographics. In the vast majority of the cases, there are tight confidence intervals well above zero. Additionally, they did an analysis with and without evidence of infection prior to 7 days after the second dose and looked at people who were at risk of COVID-19 due to a comorbidity. A comorbidity was defined as at least one Charlson Comorbidity Index (CCI) or obesity. This was further divided by whether the subject was at risk, at risk within various age cutoffs, obesity, and whether subjects were obese in various age cutoffs. Overall VE was 90.9%. No matter how this was assessed, high estimates of VE were found across all risk factor groups with tight 95% confidence intervals.

An analysis of first COVID-19 occurrence after Dose 1 included anyone who received a diagnosis of COVID-19 that could occur immediately after Dose 1 until the end of the analysis. When these cases are included, VE is estimated to be 87.8%. However, when the analysis is stratified starting at ≥11 days after Dose 1 to before Dose 2, VE increases to 91.7%. After Dose 2 to 7 days after Dose 2, it is 91.4%. As time from second dose is increased from 7 days to 2 months, from 2 to 4 months, and then greater than 4 months, VE remains high. The latest value is 81.3%. In terms of severe COVID-19 in subjects without evidence of infection prior to 7 days after the second dose, there was 1 case in the vaccine group and 21 cases in the placebo group. This calculates out to a VE of 95.5%. When the analysis was repeated using the CDC definition, VE was 100%.

An analysis of the breakthrough cases that occurred in the study looked for whether there were imbalances in variants of concern (VOCs) that were overly-represented in the vaccine group compared to the placebo group. This analysis showed that the vast majority (86.1%) of the sequences that were identified were categorized as "other," meaning that they were neither variants of interest (VOIs) or VOCs. Looking at VOIs and VOCs that were actually recorded the proportions between the vaccine and placebo groups were relatively similar. This is why Pfizer concluded that there was no apparent SARS-CoV-2 lineage pattern among vaccine breakthrough cases that would suggest meaningful reduced VE against any variant through the March 13, 2021. It is important to note that at the time of the analysis, there was no Delta variant identified.

Now moving to overall conclusions. In the Phase 2/3 study, the updated efficacy analysis continued to show that the BNT162b2 vaccine at 30 µg provided a high level of protection against COVID-19. This was shown in participants across various demographic subgroups. Severe cases were observed primarily in the placebo group. The tolerability and safety profile of the vaccine in participants ≥16 years of age at up to 6 months after Dose 2 was acceptable throughout the follow-up period to the data cutoff date and consistent with results previously reported.

Summary of Discussion (Perez)

- Responding to a request for further information on the ventricular arrhythmia reported in the trial, Dr. Perez indicated that this occurred in an elderly individual who had a history of arrhythmias in the past, a pacemaker, and other cardiac issues who developed the ventricular arrhythmia a few days after receiving the vaccine. Overall, it was felt that these events that occurred in the subject were due to her ongoing cardiac issues and Pfizer believes that is a reasonable explanation for what happened.

- ACIP requested additional information about the following if/when available:

    - Additional data on spike protein antibody levels among those who were infected with COVID and whether it was mild or severe disease, particularly among those who required hospitalization or died
    - Correlates of immunity
    - Level of immunogenicity and effectiveness against the Delta variant as soon as possible, including the potential advantage of a booster
    - Rising hospitalization rate among children

Public Comments

The floor was opened for public comment during the August 30, 2021 ACIP meeting at 11:17 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–2021–0089. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Ms. Erica Pettinaro
President
Informed Choice Michigan

Hello, thank you for allowing me to speak today. My name is Erica Pettinaro. I am the President of a 501(c)(4) non-profit organization called Informed Choice Michigan. It seems we have been at a crossroads between public health and personal choice for some years, but especially now in these unprecedented times where nearly everywhere we go, if you're not wearing a face mask, you're considered a health threat. Employers and schools are forcing strict testing, contact tracing, and mask requirements all while violating the Americans with Disability Act (ADA) for not accommodating those who cannot medically tolerate face coverings. All of this, along with the fact that several states have lost their medical freedoms in recent years. Specifically when it comes to vaccinations, parents and families have hit the streets in an effort to protect their rights. People from all across the world have been standing up for their freedoms and rights to not be forced to undergo a medical procedure that is not a one-size-fits-all shot. I'm not going to sit here and talk about all of the risks of these vaccines, because you already know them. But I am here to tell you we know too and we will not forget what you do here today. We will not be going away and you cannot ignore us. History loves to repeat itself and just like during the Nuremberg trials, everyone involved will be held accountable for their actions. For those listening, I would like to say this. What this committee decides on today will be the recommendations for your children. These recommendations have huge impacts on how schools proceed with mandates. Many may think, "Mandatory vaccination laws don't affect me." But if you don't want a flu shot, this affects you. If you don't want your child getting the HPV (human papillomavirus) vaccine, this affects you. If you don't want a COVID-19 vaccine, this affects you. It is your right to choose what is medically done to your body and your children's bodies, and that is at risk of being taken away from you. Even if you do choose to vaccinate, you have that choice. Vaccine mandates mean you won't ever get that choice. Vaccine mandates also pave the way for other medical care mandates. We are not a communist/socialist country, and medical mandates do not belong here. We the people will continue to fight for our rights and the rights of all Americans. I will end my comments by saying this to the committee, you know all of the risks of these vaccines. You know kids are at minimal risk of this disease. So, what would you do if it was your child? Thank you.

Dr. Linda Wastila, RPH, MSPH, PhD
University of Maryland School of Pharmacy
Representing Her Own Views

Good morning. I am Dr. Linda Wastila, Professor at the University of Maryland School of Pharmacy. I trained as a pharmacist. I have a Master's in Public Health and a Doctorate in Health Policy. For 30 years, I've conducted federally-funded research on outcomes associated with unintended consequences of pharmaceutical policy. My views today are my own. I'm speaking today about the booster authorization and why I object to such authorization now. They fall into four domains: safety, effectiveness, availability, and necessity. For safety and effectiveness, please review the written comments submitted to the committee by my colleagues, Steve Kirsch and David Weissman, for excellent detailed documentation of their concerns. One, safety. As of August 20th, there have been 13,627 deaths and nearly 56,000 hospitalizations associated with these products reported to the VAERS. Is there any evidence that FDA and CDC have staffed up to deal with this explosion of reports? Who is following up with patients and providers to fill in the necessary details? Many reported serious adverse effects were never captured in clinical trials. Has the ACIP ever recommended a vaccine known to cause myocarditis, appendicitis, and shingles? Three serious side effects which didn't show up in the Phase 3 trials. Effectiveness. Waning immunity is the "elephant in the room." Boosters are being justified on antibody data from the manufacturers. It is becoming obvious that antibody data isn't predictive of actual clinical outcomes. Do current vaccines even deliver 50% efficacy over a season? Pfizer's 6 month RCT preprints shows waning efficacy as early as March—well before Delta emerged. We didn't learn about waning immunity until real-world evidence this summer from Israel, Provincetown, and the UK, which showed that the vaccinated make up growing proportions of cases, hospitalizations, and deaths. Indeed, as of August 15th, 514 Israelis were hospitalized for severe critical COVID-19. Of these, 59% were fully vaccinated. Please stop lying that this is a pandemic of the unvaccinated. It's a pandemic of everyone. The core list of protections remains complex and unknown. Availability. On Monday, the FDA released 2 letters, a BLA full approval and a 2-year extension on the EUA. Boosters fall under the EUA extension, not the fully approved version, of which we actually have no supply in the United States. If authorized, individuals receiving boosters will not receive approved vaccine. Indeed, no one will even though the vast majority of Americans believe they're receiving an FDA approved product. Necessity. There is overwhelming evidence that natural immunity is robust and longer lasting than vaccine-induced immunity. CDC estimates that 32% to 43% of Americans have already been infected. How can we ignore this very basic scientific precept that natural immunity trumps all when considering boosters? To not do so orders on public health malpractice. Given the rising numbers of deaths and serious side effects, lack of long-term safety data, and significant waning effectiveness of these products, how can we in good conscience recommend a third dose to healthy people?

Elizabeth Faber
State Director
Iowa Immunizes

Good morning. Thank you for the opportunity to speak. My name is Elizabeth Faber and I'm the Director of Iowa Immunizes, the statewide immunization coalition of individuals and organizations committed to protecting the health of Iowans through vaccination of children and adults. In recent years, Iowa has been directly impacted by the politicization of vaccines and it has affected our work greatly. We have seen an increase of bills introduced in our state legislature that are designed to weaken Iowa's immunization laws. In fact, in recent years, this has more than tripled from under 5 bills introduced in 3 years to over 20 this past session.

Immunization advocates and public health officials are spending valuable time and resources responding to false misinformation and educating policymakers on the importance of immunizations. Discredit of the health care and public health professionals throughout this pandemic has impacted our workforce leaving our communities vulnerable not only to this virus, but also to other public health issues. Data shows that mental health issues are at higher rates in public health professionals. Not only are they living and working the pandemic, but they are trying to change it as well. This reduces the time they are able to encourage the uptake of other important recommended immunizations. Also, if we are seeing adults in our country hesitant to get vaccinated against COVID-19, this reduces our confidence that they will be rushing to vaccinate their children when it becomes approved. Not only am I a public health professional, but I'm a mother to 4 children, 2 that have been vaccinated against COVID-19 and 2 that are not yet eligible. Here in Iowa, we are starting our second week of school and our children's hospitals are at capacity. We stand with the ACIP and the urgency of approving a vaccine for age 5 and above. However, not only am I concerned for my own children's health, but I'm also worried that their friends will not be vaccinated due to their parents' hesitancy. This hesitancy in the COVID-19 vaccine may lead to reduced trust in science for all recommended immunizations. We need to build that trust back up. On the federal level, policymakers also need to realize that they are increasing distrust in vaccines by getting ahead of the science. We must let FDA, ACIP, and CDC do their work without political influence. Thanks again to all of you for your service and dedication to keeping all Americans healthy. You are appreciated.

Ms. Patricia Neuenschwander, MSN
Nurse

Good morning and thank you very much. Thank you for allowing me the opportunity to make a public comment. My name is Patricia Neuenschwander and I've been a nurse for over 26 years. I and other medical providers count on the CDC for guidance and wisdom. We don't have time to review all the studies and information. The FDA has let us down. After promising transparency in August of 2020, they approved the vaccine without any input from the public or the VRBPAC Committee (Vaccines and Related Biological Products Advisory Committee (VRBPAC). ACIP and the CDC now is the only thing that stands in the way of this vaccine being unleashed on the public as an approved vaccine. It is very disappointing to me that we are expected to make a public comment before we even see the science other than the data presented by Dr. Perez from Pfizer. The public comment session is being held before you present the safety data, such as the information from the Vaccine Safety Datalink and the VAERS data that reviews the post-authorization vaccine safety data, which are not publicly available. The benefit-risks discussion and the GRADE and the Evidence to Recommendations Framework are also being discussed after public comment. The only gold standard randomized placebo-controlled trials and science that we have is from a preprint not yet peer-reviewed with a study data cut off of March 13, 2021—over 5 months ago and does not include any data on the Delta variant. No randomized control trials evaluated asymptomatic SARS COVID infection. Weekly testing of both groups to evaluate the true infection rate of the virus and therefore the ability to transmit to others have not taken place. In the preprint study, during the blinded period, only 51% of the participants had data for 4 to 6 months post-second dose, and only 8% of the vaccine recipients and 6% of the placebo had greater than 6 months of post follow-up after Dose 2. The article shows waning immunity down to 83.7% at 4 months. They didn't even give us the percentage of the numbers at 6 months. With the current Delta variants, the CDC's only numbers are suggesting the efficacy rates are down to 50% per the *MMWR* (*Morbidity and Mortality Weekly Report*) articles in the last 2 to 3 weeks. With the Delta variant outbreaks, having 74% of the cases in fully vaccinated people, there were only 2 studies that evaluated the serious adverse events with an unvaccinated comparator, both by Pfizer, both from unpublished

data. Your decision will be used to support mandates throughout this country. You should make it clear that this vaccine at best lessens the symptoms of COVID and does not stop the transmission of the virus. You should make it clear that it's a personal choice to take this vaccine and not a matter of public health. This committee needs to make it clear that natural immunity is far superior to any vaccine immunity. Thank you.

Ms. Katherine Falk
Parent & Vaccine Advocate

My name is Katherine Faulk and I'm a parent and vaccine advocate in Oakland, California. I really appreciate the committee's hard work during what seems like ever-more challenging times. Last time I was given the opportunity to make a comment here, I said I encourage the committee to address the problem with misinformation as much as possible, particularly as it impacts populations that have historical trauma. Many of these conversations are going to have to take place within communities rather than outsiders lecturing. Leaders in most communities can be empowered with resources that would be very helpful. I also hope that the guidance on how to allocate vaccines can include a conscious deliberate effort to avoid reinforcing systemic racism and existing inequity. As the committee moves ahead on the COVID vaccine for those 16 and up and starts discussing booster doses, the problems I mentioned are unfortunately still very much still with us. In Alameda County where I live, communities of color continue to be hit extremely hard with the disease. Most of the COVID patients are Hispanic, a medical professional acquaintance who works with local hospitals tells me. Our local TV stations had a heartbreaking story this week of the family sickened with the Delta variant, which killed the head of the household at age 53 the day after his wedding anniversary and left his widow needing ongoing mechanical assistance to breathe. One of his daughters had tried to convince him to get the vaccine earlier before it was too late, but misinformation got to him first. I checked Facebook last night and saw that a friend in West Berkeley had posted about the deaths of three of her neighbors—all unvaccinated, all in the same family. One of them had earlier expressed fear of the vaccine to her. I ask the committee to do what you can to mitigate the pandemic of misinformation that is literally killing people and encourage the allocation of resources to help with outreach. While boosting the immunity of those who already got the vaccine is important, we also really need to boost access and trust. Thank you very much.

Dr. Stanley Plotkin, MD
University of Pennsylvania

After hearing some of the prior comments, I am moved to remind you that there is no vaccine against stupidity. But the point of what I wanted to say was that I would not call the third dose a "booster." In fact, if you look at other inactivated vaccines, you will recognize that at least 4 to 6 months are necessary for optimal priming. In other words, for converting B-cells to plasma cells so that you have permanent production of antibody. I would recommend that with that, in effect, to stop using the term "booster" because the third dose of the vaccine against COVID-19 really will give a much longer persistence of antibodies, immunity, and these antibodies are clearly the correlative protection against COVID-19. So, the third doses really should have been part of the plans for the use of an activated vaccine. So, I hope you will when you come to consider the third doses that you will approve them as being part and parcel of the use of these vaccines to give prolonged and broadened immunity other strains besides the original SARS-CoV-2. That is the message I wish to convey to the committee. Thank you very much.

Mr. Edward Nirenberg
Concerned Individual

Good morning, everyone. Firstly, I do want to thank the members of the committee for their tireless service in extremely trying times, especially given some of the recent public comments that were just absolutely detached from reality. And I really do second everything that Dr. Plotkin has just said. I come to you today with several concerns. Personally, I do want to say publicly that it is not appropriate for the White House to issue booster recommendations before ACIP does. We have expert committees for a reason and I expect the White House to respect the process and listen. On the matter of boosters, there is presently clinical data. We are relying very substantially on surrogate markers of protection like antibody titers, and we seem to be offering considerable deference to PCR (polymerase chain reaction) positivity as a metric for vaccine effectiveness, which is neither meaningful nor reasonable in isolation. Effectiveness of the vaccines against severe disease remains extremely well-preserved. We really need to clarify what the goals of our campaign against COVID-19 are, because as things stand now, it essentially looks as though we are trying to stamp out any COVID-19 case and that goal is not reasonable or realistic. And furthermore, in pursuing it, we are flouting our obligation of vaccine equity for the entire world. It's immensely concerning to me that throughout much of the world, there isn't a healthcare infrastructure that can handle the burdens of COVID-19. There aren't adequate means to enforce non-pharmaceutical interventions. Approximately 1% of people have maybe had one dose of vaccine and here we are considering offering third doses to the general public. Now, of course, there are a certain number in society for whom third doses absolutely are appropriate and make sense. But ultimately, the great danger here is unmitigated spread of SARS-CoV-2 throughout the world that drives the evolution of variants that are more transmissible and potentially more virulent. And that isn't merely humanitarian issue, because it's a matter of our own safety as well. Furthermore, one group that has been particularly left behind received J&J vaccine. Data to inform recommendations for heterologous series I understand is minimal. At the same time though, we do have data showing that heterologous series of the Oxford-AstraZeneca vaccine and the Pfizer vaccine appear to be both safe and effective. Given the extraordinary spread of SARS-CoV-2 presently and the results of the Oxford study, I'm once again requesting that guidance be issued for additional doses for these individuals, many of whom are high risk and select the 1-dose options because of constraints on access. Finally, I do wish to once again note that the situation with children is still of concern and the inability to vaccinate those under 12 is a major problem in attempting to ensure a safe return to school. The recent Marin County outbreak by the Delta variant showed astonishingly high transmission. We need conversations about how we can keep schools safe for children and for the community at large. While we can vaccinate everyone over the age of 12 and reduce COVID-19, we can't be so naïve to think that this compensates for keeping a group of 20 or 40 kids clustered together in a poorly ventilated and humidified space for hours where masking is not permitted. I'm once again asking the committee to do all within its means to encourage FDA to start review of these vaccines for children under age 12.

Ms. Leah Russin, JD
Director
Vaccinate California

Hi. Thank you so much. This is Leah Russin. Thank you for your public health work. I'm a mother of a baby who was born 3 days after shelter-in-place started and 2 school-aged children. I'm also the Director of an advocacy group called Vaccinate California. I encourage you to support efforts to communicate clearly and accurately about science-based public health policy. Your work here has to be understood by the public. We've seen that today in comments.

Important decisions like recommendations for school and participation in society turn on what you recommend today. It is thus imperative that our public health institutions speak candidly and clearly, understanding that many people are easily misled by disinformation. It is no longer enough just to get the science right. The communication needs the same level of attention and care and that must be part of your mandate. Additionally, please do all you can to speed approval of COVID vaccines for children. My son's elementary school has already endured multiple exposures in the first weeks of school and testing is now taking 3 days or longer. Make vaccines for this group, age 5 and up, a top priority and make it clear that children attending in-person school or other activities should be vaccinated. COVID boosters—please communicate who needs them and when clearly. This goes back to the communication effort. Encourage Johnson & Johnson to present their data on a second dose as soon as possible. I saw an elderly black man seeking a booster be turned away at Walgreens because he had previously received J&J (Johnson & Johnson). He later told me his doctor had sent him for a booster because he's immunocompromised. That is exactly the target community we need to be emphasizing our efforts on and he had made the effort to show up for his booster, but it is not yet approved because of a number of miscommunication efforts in the public health system. I hope the failures of communication from the many health entities don't undermine his faith and that he does show up again if and when a booster is approved for him. Other diseases—please don't forget about them. We've seen a surge of RSV (respiratory syncytial virus) this year. Please encourage rapid development of a vaccine for RSV and a better flu vaccine. We now know how fast companies can move when properly incentivized. Please encourage renewed vigor to develop a safe and highly effective vaccine for these as well as other diseases. Thank you, in the words of Ted Lasso, "I appreciate you."

Dr. Elias Kass
Licensed Naturopathic Physician
Treehouse Family Medicine PLLC

Hi. Thank you for giving me the opportunity to speak. My name is Dr. Elias Kass. I am a licensed Naturopathic Physician in Seattle, Washington working in pediatric primary care and vaccine hesitancy. I'm the father of two children, both of whom are in the car, one of whom is 2 days away from first grade. He spent his kindergarten year with headphones and a school issued iPad attending meetings from a daycare while I worked full time in clinic. Parents are understandably frustrated to have had their kids sit out for a year and a half of Alpha variant only to have their kids go back to schools full of Delta. Every day I get messages asking indirectly or directly about off-label use of the vaccine for their kids. In Washington, we are fortunate to be in a state with a solid commitment to public health with mask mandates and with vaccine mandates for many professions. But millions of kids are walking into schools without masks surrounded by adults who may or may not be vaccinated and without the opportunity to become vaccinated themselves. Or they're just not going to school because their families can't bear the risk of them becoming infected. I implore you to acknowledge the urgency of vaccines for kids under 12 and to convey that urgency to the FDA. Pediatric cases, hospitalizations, and deaths are on the rise, but parents are stuck trying to divine a timeline from the tea leaves of media interviews. From a statistical perspective, vaccine availability for kids under 12 would substantially lower the effective reproduction number. There are roughly 48 million unvaccinated people in this group alone—15% of the entire population. We know the trials are underway, but we also know that trials are substantially larger and longer than the trials were for expanding to adolescence. The FDA might consider issuing emergency use authorization in a rolling fashion, for example authorizing 11 year olds when the data is available without waiting for the entirety of the trial down to 5 years old. Eleven-year-olds are particularly vulnerable as many are unvaccinated 6th graders in middle schools. The FDA should commit to expedited review of the

data as it becomes available. We need to know that our kids matter as much as the adults. We kept them at home to protect them. While we're all focused on the wave of COVID-19 bearing down on us, we're already drowning in RSV and influenza is looming on the horizon. We're always eager to hear about updates in active immunization for RSV and progress in a universal influenza vaccine. Thank you.

Safety Update for COVID-19 Vaccines: VAERS

Dr. John Su (CDC/NCEZID) reported that VAERS had received a total of 2574 reports of myocarditis or myocarditis with pericarditis as of August 18th, which collectively he referred to as myopericarditis after COVID-19 vaccination. Of these, 1903 were reports of myopericarditis and 671 were reports for pericarditis alone. Looking at preliminary myopericarditis reports to VAERS following COVID-19 vaccination broken down by manufacturer and dose number, consistent with past updates, there have been more reports of myopericarditis after Dose 2 relative to Dose 1. In terms of some characteristics of preliminary reports of myopericarditis to VAERS after known mRNA COVID-19 vaccination through August 18th, the updated data reflect what has been observed in the past. The median age among persons reporting after Dose 2 has been younger relative to Dose 1. The median time to onset is somewhat shorter at 2 days after Dose 2 versus 3 days after Dose 1. In addition, there is greater preponderance among males relative to females.

Regarding the estimated expected versus observed reports during the 7 days after vaccination with mRNA vaccines after Dose 2, some of the observed cases among those 12-29 years of age were verified by provider interview or medical records review to meet the CDC definition for myocarditis. The reports for persons 30-65 years of age were identified by automated computer search looking for standardized codes assigned to these reports indicating myocarditis. Those 12-29 years of age represent somewhat of a lower bound in that the counts might have been higher than in this analysis. Conversely, those 30-65 years of age represent an upper bound in that some of these cases probably will be ruled out in comparison to the case definition such that the counts might be somewhat lower than presented in this analysis. Notably, the estimated expected counts are presented as a range because the background rate for myocarditis itself is a range of about 1-10 per 100,000 person years. That said, among males 12-49 years of age and females 12-29 years of age, more observed cases were seen than estimated to be expected for this time period.

Estimates expected versus observed reports during the 7 days after the Pfizer-BioNTech vaccine are consistent with past updates for males 12-49 years of age and females 12-24 years of age, with more observed cases than estimated to be expected during this time period. After Dose 2 of the Moderna vaccine during the same 7-day risk window, almost no reports were observed among those 12-17 years of age. This might be anticipated given that the Moderna vaccine is not authorized to these age groups. Among males ages 18-49 years of age and females 18-29 years of age, more cases were observed than estimated to be expected during this time period.

With respect to the care patients have received and their outcomes, 1339 preliminary reports of myopericarditis after COVID-19 vaccination to VAERS were identified among persons less than 29 years of age. Of these, 742 were determined to meet the CDC definition for myocarditis. Of the 742,[3] there were 701 individuals hospitalized. Among the 701 patients, the majority (N=667)

[3] https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf

were discharged and 515 (77%) of them were known to have recovered from symptoms at time of the report.

Looking at reporting rates of myopericarditis per million doses administered by manufacturer, sex, and dose number in the 7-day risk period as of August 18, 2021, regardless of age group or manufacturer, higher reports tended to be observed after Dose 2 relative to Dose 1. A reporting rate was not calculated for the Moderna vaccine for those 12-15 years of age because the numerator and denominator were so small that the resulting reporting rate was a clear outlier and would not make sense. To avoid confusion, it was not reported in this presentation.

In terms of ongoing investigations to assess the health effects of myocarditis after COVID-19 vaccination, CDC is currently engaged in enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports.[4] This involves assessment of longer-term functional status and clinical outcomes among persons less than 29 years of age reported to have developed myocarditis after mRNA COVID-19 vaccination among the reports that met CDC case definition. This surveillance includes a 2-component survey that will be administered to persons who are at least 90 days out from the onset of their symptoms of myocarditis. This 2-component survey includes a patient survey that is meant to ascertain the functional status, clinical symptoms, quality of life, and need for medication or other treatment for their myocarditis. The second component is a survey to be administered to healthcare providers (HCP) such as cardiologists to gather data on the patient's cardiac health and functional status. With regard to timeline, data collection began in August 2021 and will continue through November 2021. As of August 18th, VAERS has received 742 reports of myocarditis or myopericarditis after COVID-19 vaccination that met case definition based upon provider interview or medical record review. Of those 742 reports, there were 253 patients who met the minimum 90 days post-myocarditis diagnosis who are eligible for interview. That data collection is currently underway and updates will be provided as they occur.

To summarize, as of August 18th, VAERS has received 2574 reports of myopericarditis (N=1903) or pericarditis (N=671). The epidemiology of myopericarditis after COVID-19 vaccination remains consistent with what has been reported in previous updates, primarily being seen among younger males after Dose 2 of mRNA vaccination. Symptom onset clusters within several days of vaccination. Limited follow-up information in VAERS case reports suggests that most patients (77%) appear to be recovered from their symptoms at the time of the report or follow-up. Counts observed exceeded estimated expected accounts in males through 49 years of age and females through 29 years of age. Enhanced surveillance for myopericarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports is ongoing.

Safety Update for COVID-19 Vaccines: VSD

Dr. Nicola Klein (Kaiser Permanente Northern California) reminded everyone that the VSD was established in 1990 and is a collaborative project between CDC and 9 integrated healthcare delivery systems throughout the US that includes data on over 12 million members of these healthcare institutions. The overall aims of the Kaiser Permanente Northern California-led VSD Rapid Cycle Analysis (RCA) are to: 1) monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members; and 2) describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity. Surveillance began in December 2020, with 23 outcomes being monitored.[5]

[4] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html
[5] See slide 4 in Dr. Klein's slide set

In terms of vaccine uptake in the VSD through August 21st, more than 13.3 million doses total have been administered to VSD members. To date, 66.5% of the age-eligible VSD population is fully vaccinated. Most vaccines given in the VSD are Pfizer and Moderna mRNA vaccines, which was the focus of this presentation. Looking at the analytic strategy for the RCA analysis through August 21st, the primary analysis focused on the number of outcomes observed in the risk interval of 1-21 days after COVID-19 vaccinations were compared to the number expected. The number expected was derived from the "vaccinated concurrent comparators" who were in a comparison interval of days 22-42 after COVID-19 vaccination. On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval. Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, and calendar dates. Dr. Klein shared a graphic to illustrate.

Looking at outcome events in the 21-day risk interval for all ages combined after either dose of any mRNA vaccine compared with outcome events in vaccinated comparators on the same calendar days, none of the outcome events being monitored had signals. Focusing on the myocarditis/pericarditis chart review summaries in the younger population 12-39 years of age after mRNA as of 8/21/21, a total of 100 of 102 cases have been completed. These are cases that were identified during the 1-98 days post-vaccination. All initial chart review is followed by adjudication by the infectious disease clinician and/or cardiologist. These adjudications confirm incidents following vaccinations, confirm the incidents based on CDC definitions, and evaluate the level of certainty for myocarditis. Adjudication confirmed 78/100 (78%) post-vaccination myocarditis/pericarditis cases, with 56 confirmed cases being among persons 12-39 years of age with the onset during the 0-21 days after Dose 1 or Dose 2. Those were the cases on which Dr. Klein focused during this presentation.

In terms of the descriptive characteristics of the confirmed myocarditis/pericarditis 0-21 days after any dose by age group, approximately half were White and next largest ethnic group was noted to be Hispanic. The diagnoses for most of those 12-17 years of age were acute myocarditis or myopericarditis. This was a little more evenly divided amongst those 30-39 years of age. The symptoms of diagnostic testing for persons 12-17 years of age and 18-29 years of age were abnormal proponent troponin levels. Only about half of the persons 30-39 years of age had abnormal troponins. Just under half (43%) of persons 12-17 years of age, a third (30%) of persons 18-29 years of age, and a third of 82% of persons 30-39 years of age had abnormal findings on their echocardiograms. With regard to level of care and discharge status, the younger individuals were all treated in an emergency department(ED), hospitalized, or admitted to the Intensive Care Unit (ICU). There were no ICU cases among persons 18-39 years of age. The length of stay was somewhat longer for persons 12-17 years of age of mostly up to 2 days, somewhat shorter for persons 30-39 years of age in the 0-1 day range, and about evenly amongst persons 18-29 years of age.

Now turning to the analyses of confirmed myocarditis and pericarditis after mRNA vaccines among persons 12-39 years of age as of 8/21/21. As a reminder, the chart-confirmed cases among persons 12-39 years of age statistically significantly clustered during the first week after vaccination. Of note, this analysis covered 0-21 days and 0-7 because of this temporal cluster. For confirmed myocarditis/pericarditis in the 0-21 day risk interval among those 12-39 years of age compared to the outcome events of the vaccinated current comparators after both doses of mRNA vaccines, there was an elevated rate ratio (RR) of 5.63 (2.31-16.44). The adjusted RR for both vaccines was 3.81 (1.14-14.26) after Dose 1 and 8.31 (3.07-28.28) after Dose 2. These were statistically significant by confidence intervals. Looking by product and dose, the adjusted RR for both Pfizer doses was 3.62 (1.39-11.11) and was statistically significant. Given that there were no cases in the Moderna comparison interval, the adjusted RR could not be estimated. It is

highly statistically significant because the lower bound of the confidence interval for the both-dose analysis was 3.32% and the Dose 2 analysis was 3.79%, which are well above one. For both products combined and separately, elevated RR of myocarditis were seen in the 0-21 day window.

Moving to the 0-7 day risk interval among those 12-39 years of age, the same pattern holds though the numbers are actually larger. For both mRNA products, the adjusted RR was 15.5 (6.07-47.22) for both doses. After Dose 2, the adjusted RR was 23.84 (8.49-83.64). After Dose 2 of Pfizer, the adjusted RR was 22.9 (6.60-106.13). While there is no estimate for Moderna, the lower bound of confidence interval after both doses and Dose 2 was well above 9, so these are all highly statistically significant. Those 18-39 years of age in the 0-7 day risk interval also were analyzed because both mRNA products are used in persons 18 years of age. Looking at this smaller subgroup, there was an elevated RR over 10 for both doses and over nearly 13.8 after both doses combined. The same pattern is seen by product-specific and dose-specific analyses, with the Moderna product being highly statistically significant, with a lower bound of confidence levels being above 9. Now turning to confirmed myocarditis/pericarditis among persons 12-17 years of age for Pfizer only in the 0-7 and 0-21 day risk intervals by dose compared with outcome events in vaccinated comparators on the same calendar days. There were zero events in the comparison interval, so it was not possible to estimate the RR. However, the lower bound of confidence interval showed a very similar pattern and was highly statistically significant for both the 0-21 and 0-7 risk intervals after both doses and Dose 2.

Given that the myocarditis/pericarditis concern following an mRNA vaccine has evolved over time, the 3-month follow-up start review has been set up to follow these myopericarditis cases. As of August 27th, chart reviews having completed 29 of 34 cases that were time-eligible for 3-month review. This means that least 3 had passed since their initial event. Of these 29, 24 had at least 1 follow-up visit at least 7 days since the initial encounter. These 24 cases were reviewed to obtain information regarding symptoms and diagnostic evaluations from their most recent follow up visit, including their recovery status in terms of ongoing symptoms, medications, and exercise restrictions. Many of the 24 cases had follow-up visits well before the 3-month time period. The follow-up period was a median of 53 days (13-57 days) for persons 12-17 years of age (N=3), a median of 31 days (11-99 days) for those 18-29 years of age (N=11), and a median of 86 days (10-152 days) for those 30-39 years of age (N=10). The numbers are small, so it is difficult to draw any conclusions. Among persons 12-17 years of age, 2 had new or worsening symptoms, 8/11 persons 18-29 years of age had new or worsening symptoms, and 8/10 persons 30-39 years of age had new or worsening symptoms. Notably, all 3 persons 12-17 years of age had been in the ICU during their initial encounter. In terms of the current status at the most recent follow-up visit for the same cases, all 3 of the youngest individuals were still on exercise and physical activity restrictions, while 2 of the persons 18-29 years of age and none of the persons 30-39 years of age were still on exercise and physical activity restrictions.

Now moving to the anaphylaxis chart review summary, which was updated for 213 out of the 216 cases through July 31, 2021. Of the 213 cases, 66 (31%) were confirmed as post-vaccination anaphylaxis with a day 0-1 ED visit. The rate of confirmed cases following receipt of Pfizer vaccine was 5 per million doses. The rate following receipt of Moderna vaccine was 4.5 confirmed cases per million doses. The rate following receipt of Janssen vaccine was 7.6 confirmed cases. It is important to note that the US has not used that much Janssen vaccine and this was based on only 3 cases.

To summarize, the rate of anaphylaxis following mRNA vaccines is approximately 5 confirmed cases per million doses. That is consistent with what has been observed for several months in the VSD. There have been no signals for myocarditis/pericarditis or for any other outcome in the 21 days after both mRNA doses in the overall VSD population, including all ages ≥12 years. In the subgroup 12-39 years of age, the rate ratio for myocarditis/pericarditis was elevated after both Pfizer and Moderna during days 0-21 after vaccination, and especially during days 0-7. In subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons 12-39 years of age.

Vaccine Safety Technical (VaST) WG 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 or approval of vaccine safety data for COVID-19 vaccines; 2) serve as the central hub or technical subject matter expertise from the 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, exactly one week after the first dose of COVID-19 vaccine was administered in the US, the VaST WG has had 32 independent meetings to review vaccine safety data and 8 joint meetings with the COVID-19 Vaccines WG focused on safety. In addition, the VaST WG has shared its assessment 9 times since the start of the pandemic during ACIP meetings or through updates on the VaST WG webpage. US federal agencies have partnered closely with the VaST WG to provide updates on COVID-19 vaccine safety surveillance activities in real time, so the VaST WG wanted to recognize the incredible work by the safety teams at the CDC, FDA, Department of Defense (DoD), Veterans Administration (VA), Indian Health Services (IHS), and all of their safety investigators supporting all of the government efforts.

The VaST WG previously presented US data on the risk of anaphylaxis and myocarditis following mRNA COVID-19 vaccines and thrombosis with thrombocytopenia syndrome (TTS) and GBS following Janssen COVID-19 vaccine. In addition, the VaST WG continues to conduct prospective surveillance on a long list of pre-specified AESIs. The WG also meets with obstetrics experts to review safety data on COVID-19 vaccination of pregnant individuals, and hopes to provide an update to the entire ACIP on the topic of maternal immunization in an upcoming meeting. The safety data are then incorporated into the decision-making processes, and as would be presented by their colleagues later in the day, the benefit/risk assessments will continue to be updated with new and emerging data. The VaST WG works with its CDC colleagues and liaison representatives on clinical considerations to ensure that they support informed discussions about the benefits and risks of available vaccines, as well as clinical guidance to support early detection and appropriate management. More recently, the VaST WG has provided guidance for the use of post-approval safety data in GRADE, given the large amount of accumulated safety data observed in over 200 million individuals in the US who have received over 368 million COVID-19 vaccine doses.

The VaST WG continues to review data on myocarditis, GBS, and TTS from all of the federal agencies. The WG also has been fortunate to have the opportunity to review data previously from countries such as Israel and Canada, recognizes that those data are continuously changing and being updated, and appreciates that collaboration and transparency. The VaST WG is fortunate to have the Chair of the World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety (GACVS) on the WG as well.

Now turning to anaphylaxis following mRNA vaccines. Anaphylaxis following COVID-19 vaccines was identified first in December 2020. Safety data and a VaST WG assessment were presented during the January and March 2021 ACIP meetings. CDC and FDA recommended risk mitigation strategies at that time. These strategies continue to be in place and include screening for risk prior to vaccination, monitoring for symptoms post-vaccination, early recognition and management of anaphylaxis on-site, and provider and patient education by CDC and key partners.[6] In addition to sharing these data during open ACIP meetings, CDC's colleagues also have published these data to ensure that providers will remain updated and the public. Tools to support safe administration of COVID-19 vaccines were shared widely and continue to be used in vaccination clinics.

VAERS initially presented data on the rate of anaphylaxis early in the vaccination program. It was approximately 11.1 per million doses administered for Pfizer-BioNTech and 2.5 per million doses administered for the Moderna vaccine in the very early weeks of the vaccination program.[7] More recent data from the VSD among persons 12 years of age and older have demonstrated that the rates are similar to each other at about 5 per million following Pfizer doses administered and about 4.9 per million following Moderna doses administered. Similar to earlier findings, a majority of these cases seem to occur in females and after the first dose. The VaST WG's assessment is that there is no substantial change in the benefit/risk balance with risk mitigation strategies in place.

The VaST WG also has been monitoring myocarditis following mRNA vaccines closely. Myocarditis following COVID-19 vaccines was first identified in May 2021.[8] CDC issued clinical guidance for myocarditis/pericarditis following mRNA vaccines in May 2021. Data were presented at the VRBPAC meeting, which is the federal advisory committee to the FDA, on June 10th. Data on myocarditis and the VaST WG assessment also were presented during the ACIP meeting on June 23, 2021[9] and a *Morbidity and Mortality Weekly Report* (*MMWR*) was published. EUA fact sheets were revised with a warning added on June 25, 2021. With the FDA approval of Pfizer-BioNTech COVID-19 vaccine on August 23, 2021, additional information on myocarditis/pericarditis was included in the package insert.[10] *MMWR* publications summarizing ACIP's deliberations on myocarditis were published and clinical considerations specific to myocarditis and pericarditis also were put on the CDC website to guide clinicians and vaccinators.

Dr. Su and Dr. Klein updated ACIP earlier in the day with very granular information on rates of myocarditis, from which Dr. Lee highlighted the 0-7 day risk interval. The rates appeared fairly similar in VAERS and VSD despite different methods being used. The rates were higher following Dose 2 versus Dose 1. There was male predominance and the VAERS data demonstrated the heterogeneity seen by age, with younger individuals having higher rates.

The VaST WG has been very interested in having a better understanding of the clinical course of these individuals. VAERS has reviewed these numbers, which shift daily because this is real-time information. At the time this presentation was drafted, 845 cases had been reviewed for individuals less than 30 years of age. Of those cases, approximately 88% of the reviewed cases

[6] https://www.cdc.gov/vaccines/acip/meetings/slides-2021-1-27-21.html; https://www.cdc.gov/vaccines/acip/meetings/slides-2021-02-28-03-01.html
[7] https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm; https://www.cdc.gov/mmwr/volumes/70/wr/mm7004e1.htm
[8] https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html
[9] https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.htm
[10] https://www.fda.gov/media/151707/download

met the CDC case definition and 77% were known to have recovered from symptoms at the time of the VAERS report. VSD has chart-reviewed 98 cases among individuals 12-39 years of age and at the time the presentation was drafted, 56% of cases met chart confirmation criteria for myocarditis within 0-21 days of vaccination. Of the cases, 100% had chest pain, pressure, and discomfort. Elevated troponin, abnormal electrocardiogram (EKG) findings, and abnormal magnetic resonance imaging (MRI) were common. Although some small differences were noted per doctor/client presentation by age group, 76% were discharged within 0-2 days and 100% were discharged home.

The VaST WG has discussed all of the data available to date and agrees that the data suggest an association of myocarditis following mRNA vaccination among adolescents and young adults. Further data are being compiled to understand potential risk factors, optimal management strategies, and long-term outcomes. As noted earlier, the long-term follow-up data include a patient survey and functional status, clinical symptoms, quality of life, and ongoing need for medication or treatment and the provider survey on cardiac health and functional status.

The FDA fully licensed the Pfizer-BioNTech COVID-19 vaccine for those 16 years and older on August 23, 2021. As part of that approval, the FDA issued post-marketing requirements for the Pfizer-BioNTech COVID-19 mRNA vaccine specifically related to myocarditis, including: 1) a Non-Interventional Post-Approval Safety Study to evaluate the occurrence of myocarditis and pericarditis in the US; 2) a Post-Conditional Approval Active Surveillance Study to evaluate the occurrence of myocarditis and pericarditis in Europe, with a sub-study to describe the natural history of myocarditis and pericarditis; 3) a prospective cohort study of at least 5 years in duration for potential long-term sequelae of myocarditis after vaccination in collaboration with the Pediatric Heart Network; and 4) sub-studies of clinical trials to prospectively assess the incidence of subclinical myocarditis following second dose in a subset of participants 5-25 years of age and 16-30 years of age.[11]

A study published earlier in the week on the safety of the Pfizer-BioNTech mRNA vaccine in Israel evaluated the risk of AEs such as myocarditis in a 42-day window after vaccination and in a 42-day window after COVID-19 infection. This study found a 3.2-fold risk of myocarditis after vaccination versus an 18.3-fold risk of myocarditis after COVID-19 infection. This translates to a risk difference of 2.7 per 100,000 persons vaccinated versus 11 per 100,000 persons infected. AEs such as acute kidney injury (AKI), deep venous thrombosis (DVT), intracranial hemorrhage, arrhythmia, myocardial infarction (MI), and pulmonary embolism (PE) were substantially higher after SARS-CoV-2 infection. While certain AEs such as lymphadenopathy are more common in vaccinated individuals, vaccines also appear to have a protective effect against AKI and intracranial hemorrhage in these data—perhaps due to prevention of COVID-19 infection.[12]

In summary, the VaST WG will continue to ensure a review of near-real-time safety data in the US. This is a collaboration across US federal agencies, which has been essential for a successful vaccination program. The WG also will continue to collaborate with global vaccine safety colleagues on key issues that impact benefit/risk balance, including a focus on myocarditis and booster doses. The VaST WG is committed to providing updates to the ACIP COVID-19 Vaccines WG and the ACIP during future meetings.

[11] https://www.fda.gov/media/151710/download
[12] Barda et al., NEJM 2021

Benefit-Risk Discussion for Use of Pfizer-BioNTech COVID-19 Vaccine in Individuals ≥16 Years of Age

Dr. Hannah Rosenblum (CDC/NCIRD) presented the benefits and risks of the Pfizer-BioNTech COVID-19 vaccine in individuals 16-29 years of age, first providing a brief background. Since January 2020, there have been more than 38 million COVID-19 cases in the US. From June through August 2021, there has been a rapid rise in the number of cases throughout the country.[13] This rise has been reflected in increasing numbers of hospitalizations due to COVID-19. For persons 0-17 years of age and 18-29 years of age, the peak in January 2021 was recently exceeded and continues to increase.[14] Given that forecasts of US COVID-19 cases and hospitalizations projected ongoing increases for the upcoming 4 weeks, CDC models were used to take the increases into account for the benefit/risk analyses.[15]

Data from COVID-NET, which is a population-based surveillance system of hospitalized patients with COVID-19 in the US, were used to review severe COVID-19 outcomes for the 3 age groups for the focus of the rest of this presentation: 16-17 years of age, 18-24 years of age, and 25-29 years of age. Among patients hospitalized from March 2020-June 30, 2021, almost 25% of hospitalizations for COVID-19 among persons 16-17 years of age resulted in ICU admission, 5.6% of those hospitalized required mechanical ventilation, and 0.7% died in the hospital. Each mean length of stay was about 5 days and median length of hospital stay ranged from 2 to 3 days.

Multisystem inflammatory syndrome in children (MIS-C) and MIS in adults (MIS-A) are severe disorders that might occur following acute SARS-CoV-2 infection, particularly in younger individuals. Over 4500 patients have met the MISC case definition criteria reported to CDC. Because these tend to follow the trend of COVID-19 cases, a rise is expected in MIS-C and MIS-A reports over the next few weeks to months.[16]

Four recent studies describe the increased risk of myocarditis with SARS-CoV-2 infection. In a retrospective cohort[17] using data from more than 800 US hospitals and a recent national study from Israel,[18] patients with SARS-CoV-2 infection had a 16 to 18 times higher risk for myocarditis compared to patients without SARS-CoV-2. Risk of myocarditis among individuals post-SARS-CoV-2 infection also was 6 to 34 times higher than the risk among those who received mRNA vaccine in two other US studies.[19,20]

As ACIP has discussed previously, myocarditis following mRNA vaccination is rare, has been observed primarily in males under 30 years of age, and occurs particularly after the second dose. Both the benefit/risk assessment presented to ACIP in June for adolescents and young adults and in July for adults 18 years of age and older showed that the benefits outweighed risks of mRNA vaccination.

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[13] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime; accessed 8/27/21
[14] https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions; accessed 8/27/21
[15] https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/forecasts-cases.html, accessed 8/27/2021; https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/hospitalizations-forecasts.html, accessed 8/27/2021
[16] https://www.cdc.gov/mis-c/cases/index.html
[17] Boehmer & Kompaniyets, et al., Association between COVID-19 and myocarditis using hospital-based administrative data. Pre-publication; CDC authors.
[18] Barda et al. Safety of the BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Setting. NEJM. August 25, 2021
[19] Singer ME, et al., Risk of Myocarditis from COVID-19 Infection in People Under Age 20: A Population-Based Analysis. medRxiv. Pre-print. July 2021.
[20] Block et al., Occurrence of myocarditis, pericarditis, and anaphylaxis in children and young adults after COVID-19 vaccination compared to SARS-CoV-2 infection. Pre-publication; CDC and university-affiliated authors

Dr. Rosenblum highlighted three recent publications about the clinical course of myocarditis following mRNA vaccination. The first[21] was a case series in *Pediatrics* of 7 hospitalized males that described rapidly resolving clinical symptoms. The second[22] was a case series in the *Journal of the American Medical Association Cardiology (JAMA Cardiology)* of 15 patients hospitalized after Pfizer-BioNTech vaccination. There were no ICU admissions and overall, they had benign short-term hospital courses. The final is a multicenter study[23] across 16 hospitals that compared patients with post-vaccination myocarditis to a cohort with MIS-C. These patients also had mild hospital courses with quick clinical recovery and on follow-up, all patients had normal ventricular function.

In addition to that published information, the available data from VAERS and VSD seen earlier in the day show consistent clinical outcomes. Among the cases reported to the VAERS in persons 16-29 years of age, 93% of patients were hospitalized and 4% were admitted to an ICU. The great majority were discharged to home and additional follow-up is ongoing. In the VSD, 94% were hospitalized with a mean length of stay of 1.9 days, 4 of the 16 were admitted to an ICU, and 100% were discharged home. There have been no confirmed myocarditis deaths reported in the systems.

In summary of the background information, COVID-19 incidence and hospitalization rates are increasing rapidly. Rare myocarditis occurs after mRNA vaccination more frequently in males. Myocarditis can occur with SARS-CoV-2 infection and at higher rates compared to myocarditis following mRNA vaccine. Young adults hospitalized for COVID-19 had an average length of stay of 5 days, with roughly 5% requiring mechanical ventilation. COVID-19 deaths occurred and varied by age. Those who were hospitalized following post-vaccination myocarditis had an overall shorter length of stay and there have been no post-vaccination myocarditis deaths confirmed to date.

Moving to the quantified benefits/risk analysis of Pfizer-BioNTech COVID-19 vaccine, a similar direct estimation approach was used to explore benefits and risks per million doses of vaccine as has been described in previous presentations to ACIP. Calculations for the benefits of vaccination were based on age- and sex-specific case incidence data from CDC and hospitalization data from COVID-NET. VE was used from the Phase 3 trial and benefits were assumed for a 120-day period. The potential harms of the Pfizer-BioNTech vaccine were estimated per million doses by age and sex using VAERS data for cases received and reviewed through August 18th within a 21-day risk window since vaccination. Because cases have been increasing at rates not seen in prior analyses, a few adjustments were made to estimate the benefits. A multiplier of 1.5 was used for case incidence rates to account for increasing cases. This was estimated from the CDC forecasts shown earlier. For hospitalization rates, a 4-week average was used of weekly rates during July 10-31 for more stable estimates by age and sex. These averages were multiplied by a factor of 3 to account for projected increases in hospitalization through August. In addition to the benefits over a 120-day period, estimates were calculated for benefits at 180 and 365 days to account for future benefits that would accrue beyond 4 months. The following estimates were framed around the day's policy discussion about Pfizer-BioNTech COVID-19 vaccine for individuals 16 years of age and older. Other vaccines and age groups can be considered with future policy questions.

[21] Marshall, et al. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. Pediatrics. August 2021.
[22] Dionne, et al. Association of Myocarditis with BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children. JAMA Cardiology 2021; Aug 10; epub ahead of print.
[23] Jain, et al. COVID-19 Vaccination-Associated Myocarditis in Adolescents Pediatrics Aug 2021. prepublication ahead of print

Now to look at the number of confirmed myocarditis cases, the number of second doses of Pfizer vaccines administered, and the reporting rates for myocarditis per million doses by age and sex through August 18. The greatest reporting rates were seen in males 16-17 years of age and 18-24 years of age.[24] Looking at the estimated COVID-19 cases prevented versus myocarditis cases for every million Pfizer-BioNTech COVID-19 vaccinations over 120 days, for males 16-17 years of age, it is estimated that more than 56,000 cases and about 500 hospitalizations would be prevented per million doses and an estimated 73 myocarditis cases would be expected per million doses of vaccine. Among persons 18-24 years of age, the estimated benefits would be greater and the estimated myocarditis cases would be fewer. In the oldest age group of persons 25-29 years of age, the estimated benefits would be even greater still and the estimated myocarditis cases would be fewer. Calculating the benefits with a VE of 74.6% for COVID-19 cases and 84% for hospitalizations, which is lower VE than was found in the Phase 3 clinical trial for both cases and hospitalizations, the benefits still outweighed the potential harms.

While the analyses so far assumed a 120-day time period, the following analyses estimate benefits and harms over longer periods of time. At 120 days, 500 hospitalizations were estimated to be prevented among males 16-17 years of age and 73 myocarditis cases might be expected. Adding the benefits and harms for 180 days for both age groups (16-17 and 18-24), estimates were made assuming that the current COVID-19 epidemiology is stable. However, it is important to remember that it is unknown exactly how rates might change in the future. The number of myocarditis cases per million remained constant because the risk occurs within a 21-day window following vaccination. In this scenario, the benefits continue to outweigh the harms. The benefits and risks were then plotted at 365 days. While the area of uncertainty was slightly larger, the risk of myocarditis stayed consistent. In this scenario, the benefits were even greater and outweighed the harms for both age groups.

In summary, this direct approach benefit/risk assessment for Pfizer-BioNTech COVID-19 vaccine and myocarditis considered the individual benefits of vaccination versus individual risks and considered vaccine against no vaccine. The WG assessed that the benefits of vaccination outweigh the risks for each age and sex group evaluated. As in previous analyses, the relative balance does vary by age and sex.

Summary of Discussion (Su, Klein, Lee, Rosenblum)

- ACIP members requested additional information on the following topics:
    - Race/ethnicity breakdowns in the VAERS case reports of myopericarditis or pericarditis
    - A breakdown of race/ethnicity in all data presented
    - Potential for under-reporting in VAERS, given that it is comprised of self-reporting or provider-reporting, in terms of how it compares to what has been seen with other vaccines and in other systems
    - Myopericarditis following COVID vaccination among younger individuals who are athletes and if so, whether any specific sports appear to be involved
    - More granularity regarding myopericarditis or pericarditis in terms of additional doses and the potential to mitigate risk, ensure safety, and provide protection
    - Long-term outcomes for myocarditis

[24] https://covid.cdc.gov/covid-data-tracker/#vaccinations

  - Anaphylaxis in terms of a breakdown by dose, a breakdown by race/ethnicity, and consideration of whether emerging data suggest that the 20-minute observation period can be relaxed
  - Similar risk-benefit data among persons 12-15 years of age

- It was observed by several ACIP members that the myocarditis cases being observed are very different from typical cases seen clinically in the hospital.

- Messaging is critically important with regard to natural immunity versus vaccine immunity in that it does not require being sick to become immune. ACIP members emphasized that given how serious COVID disease is, the side effects being observed are not as significant as the disease itself. This messaging must be well-conveyed, especially to the vaccine-hesitant.

- The risk of myocarditis following vaccination is generally within 7 days, while the benefits last far longer than 7 days. With that in mind, ACIP members stressed that it is important to continue to look ahead, particularly as schools have re-opened with a significant proportion of children in attendance who have not had the opportunity to be vaccinated because they are not yet eligible for vaccination.

- It was suggested by some ACIP members that the term “myopericarditis” be used instead of myocarditis because clinicians are very specific about the use of language. If the term “myocarditis” is used, cardiologists may impose typical myocarditis protocols to a point that patients with a short-term event following vaccine do not need.

- AAP encouraged ACIP to consider posting simplified graphics to depict the short- and long-term risks and benefits of COVID-19 vaccine related to myocarditis, particularly given that there is quite a debate brewing about whether children should be vaccinated and the risk/benefits. This will become increasingly important as additional EUAs are expanded to younger age groups.

GRADE: Pfizer/BioNTech COVID-19 Vaccine

Dr. Julia Gargano (CDC/NCIRD) presented the GRADE assessment for the policy question under consideration, “Should vaccination with Pfizer-BioNTech COVID-19 vaccine (2-doses, IM) be recommended for persons 16 years of age and older?” In terms of the PICO question, the population under consideration is persons ages 16 years and older. The intervention is 2 doses of the Pfizer-BioNTech COVID-19 vaccine 21 days apart. The comparison is no vaccine. The WG identified the following 6 outcomes as the most important for the policy question: Symptomatic Laboratory-Confirmed COVID-19, Hospitalization Due to COVID-19, Death Due to COVID-19, Asymptomatic SARS-CoV-2 Infection, SAEs, and Reactogenicity. For benefits, 2 “critical” outcomes were selected, prevention of symptomatic laboratory-confirmed COVID-19 and prevention of hospitalization due to COVID-19. There were 2 “important” benefits selected, prevention of death due to COVID-19 and prevention of asymptomatic infection. The “critical” harm identified was SAEs overall. Additionally, specific harms that have been identified during real-world use were evaluated. An additional “important” harm, reactogenicity, also was evaluated.

For all outcomes, data from randomized controlled trials (RCTs) were evaluated when available. No RCT data on asymptomatic infection were available. For benefits, observational studies of VE were evaluated. For SAEs, safety surveillance data were reviewed for specific outcomes. To identify relevant RCTs, the WG relied on clinicaltrials.gov as the definitive source. Relevant Phase 1, 2, or 3 trials of Pfizer-BioNTech COVID-19 vaccine were included using the following inclusion criteria: 1) involved human subjects; 2) reported primary data; 3) included adults (age ≥16 years) at risk for SARS-CoV-2 infection; 4) included data relevant to the efficacy and safety outcomes being measured; and 5) included data for the dosage and timing being recommended (30 µg, 2 doses at 0 and 21 days). Additional resources also were sought, including obtaining unpublished data from vaccine manufacturers.

To identify relevant VE studies, an ongoing publicly available systematic review conducted by the International Vaccine Access Center's (IVAC's) and the WHO using studies identified through August 20, 2021 was used.[25] This effort compiles information on published and pre-print studies using the following criteria:

- ❑ Published or preprint study with adequate scientific details
- ❑ Includes group with and without infection or disease outcome
- ❑ Laboratory-confirmed outcome
- ❑ Vaccination status confirmed in ≥90%
- ❑ Studies assessing one vaccine or pooled mRNA vaccines
- ❑ Includes participants who did or did not receive a COVID-19 vaccine
- ❑ VE calculated comparing vaccinated to unvaccinated and including confidence intervals if possible

From this database, the WG included studies that provided VE estimates for at least one of the benefits defined in the PICO question. Of note, studies that report on VE against any infection were not included. Studies were included that specifically evaluated VE against symptomatic or asymptomatic infection. Studies were only included that had estimates of VE specifically for the Pfizer-BioNTech COVID-19 vaccine and not estimates for mRNA vaccines as a group. The WG reviewed studies of general population and specific populations as long as they included persons aged at least 16 years. For observational data on vaccine safety, in consultation with VaST, data were included from safety surveillance systems that had been presented to ACIP.

To summarize the evidence retrieval for all records included in the evidence synthesis, 79 records were identified from the IVAC systematic review and 7 were identified through other sources. Forty-one full-text articles or other resources were assessed for eligibility and 32 were included in the evidence synthesis. A total of 28 records of observational studies were identified that met the inclusion criteria and addressed one or more of the PICO outcomes. A risk of bias assessment was conducted using the Newcastle-Ottawa Scale (NOS), which assigns up to 9 points based on specific criteria related to selection, comparability, and assessment of outcome or ascertainment of exposure. Studies with NOS scores less than 7 were considered to have serious study limitations.

For each outcome, the body of evidence was assessed for suitability for pooling. Given that the WG was working with a fluid evidence base that included pre-prints that had not been peer-reviewed and wanted to produce the most reliable pooled estimates possible, estimates with serious limitations were excluded from the pooled estimates used for GRADE. Although sensitivity analyses, including these studies, were conducted. If multiple studies were conducted

[25] https://view-hub.org/resources

in the same population, the most representative study was selected. Meta-analyses were conducted using the remaining studies. Initial estimates were evaluated for heterogeneity using I^2 statistic. Sensitivity analyses were conducted to assess influence of study characteristics (e.g., special population vs. full population, preprint vs. peer-reviewed, standard/extended dosing interval, study design, circulating variants). The pooled estimates were developed to summarize the estimates across several studies distinctly for GRADE and describe the best available real-world data available for this policy question at this time. However, the WG acknowledges that the included studies represent different populations and times and that the science in this area is developing quickly. For this GRADE analysis, the WG did not aim to parse out effects of time since vaccination and circulating variants.

As a reminder, GRADE evidence type assesses the certainty of estimates from the available data. The highest level of certainty is Type 1, which means the WG is very confident the true effect lies close to that of the estimate. Type 2 means that the WG is moderately confident in the effect estimate, but there is a possibility the true effect could be substantially different. Type 3, or low certainty, indicates that the WG's confidence in the effect estimate is limited. Type 4 indicates very low certainty, meaning the WG has little confidence in the effect estimate. The evidence type is not measuring the quality of individual studies, but how much certainty there is in the quantitative estimates of effect across each outcome. The initial evidence type is determined by study design. A body of evidence from RCTs starts with initial evidence of Type 1, indicating high certainty. A body of evidence from observational studies starts with initial evidence of Type 3, indicating low certainty. The evidence type can be downgraded due to risk of bias, inconsistency, indirectness, or imprecision. Other considerations could downgrade or upgrade the evidence type.

Now moving to a review of the evidence of benefits. For Outcome 1, Symptomatic Laboratory-confirmed COVID-19 Randomized Studies with an Unvaccinated Comparator, there was 1 study. This was the Pfizer-BioNTech Phase 2/3 RCT among persons ≥16 years of age that was conducted in several countries and enrolled over 40,000 participants.[26] The data were published and available through pre-prints and additional data were obtained directly from the sponsor. The analysis included the data through the unblinding date with a data cutoff date of March 13, 2021. Using the available efficacy population for all persons aged at least 16 years of age, there were 77 cases among 19,711 persons in the vaccine arm and 833 cases among 19,741 persons in the placebo arm. This resulted in a VE estimate of 91.1% and a 95 percent confidence interval of 88.8%-93.1%. This was the primary outcome of the study and the outcome used for GRADE. VE also was over 90% in a number of key subgroups, including those aged 65 and older, those aged 75 and older, those at risk due to presence of a comorbidity or obesity, and those aged at least 65 years and at risk. In terms of VE by timing, efficacy increased to 90% in the interval from 11 days after Dose 1 until Dose 2. Efficacy was 96% from 7 days after Dose 2 to 2 months, 90% from 2-4 months, and 84% from 4 months through unblinding.

Now, moving on to the observational studies for symptomatic laboratory-confirmed COVID-19. There were 17 VE studies reviewed that evaluated this outcome.[27] The pre-print studies captured a more recent time period than the peer-reviewed studies. Of the 10 peer-reviewed studies, 5 were not included in the pooled estimates because they provided data on the same population or a subgroup from a larger study. The most common study design was test-negative design, followed by retrospective and prospective cohort studies. Study locations were

[26] Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors; and Thomas et al., preprint; additional unpublished data obtained from authors

[27] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf Slides 20-22

predominantly in European and Middle Eastern countries. There were 7 available pre-print articles with data on symptomatic laboratory-confirmed COVID-19. Of these, 4 were not included in the pooled estimate because they provided data for the same population or had study limitations. The VE estimate for the 8 observational studies that were pooled was 92.4%. Sensitivity analyses using different choices of studies resulted in pooled estimates ranging from 90.4% to 93.5%.

Looking at the GRADE Evidence Table for the outcome of symptomatic laboratory-confirmed COVID-19, the RCT body of evidence, the evidence started at Type 1. There was no serious risk of bias identified and no concerns for inconsistency, indirectness, or imprecision. The RR of 0.09 and tight 95% confidence interval strongly favored vaccination. The evidence type was Type 1, or high, for this critical outcome. The evidence type for the observational studies started at Type 3. No serious study limitations or risk of bias were identified in the 8 studies included. There also were no serious concerns identified for inconsistency, indirectness, or imprecision. The RR was 0.10, which strongly favored vaccination, with a 95% confidence interval of 0.05 to 0.16. Because this was a strong association, the evidence type could be graded up. For observational studies, the final certainty was Type 2, or moderate.

The second outcome for consideration was hospitalization for COVID-19. For this outcome, there was the one Pfizer/BioNTech phase 2/3 RCT. The protocol included a definition of severe COVID-19 as a COVID-19 case with at least 1 of following: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death. This did not necessarily require hospitalization. The WG obtained data on hospitalization due to COVID-19 from the sponsor. For the secondary endpoint of severe COVID-19, VE was 95.3%. Efficacy against severe COVID-19 requiring hospitalization, which was the PICO outcome and the outcome used for GRADE, was 100%. The WG also learned that there were additional hospitalizations among persons who were diagnosed with COVID-19, but for whom specimens were not confirmed using a protocol-approved assay. The WG requested and obtained additional data from the sponsor on these. Efficacy was 96.6% against severe COVID-19 based on the CDC definition after Dose 1 and including all hospitalizations for COVID-19, even cases for which SARS-CoV-2 was not detected in a study-approved assay.

There were 13 observational studies that examined effectiveness against hospitalization for COVID-19 that met the WG's inclusion criteria.[28] Of these, 6 studies were peer-reviewed and 7 were pre-prints. The most common study design was retrospective cohort. Study locations were prominently in Middle Eastern, European, and North American countries. Of the 6 peer-reviewed studies, 2 were not pooled due to including population subgroups of a larger study or having an overlapping population with another study. Of the 7 available pre-print articles, 3 were not included in the pooled estimate because they were population subgroups of a larger published study. For the 8 observational studies included in the meta-analysis, the pooled VE estimate was 94.3%. Sensitivity analyses resulted in pooled estimates of 89.4% to 95.7%.

Looking at the GRADE Evidence Table for the outcome of hospitalization for COVID-19, the initial evidence type for the RCT was Type 1. This was downgraded 1 point due to concern over imprecision. The availability of only 1 randomized study with a total of 31 cases introduced fragility in the estimate, even though the 95% confidence interval did not include 1. The final certainty estimate for hospitalization for COVID-19 based on RCT data was Type 2. The initial type for the observational studies was Type 3. The certainty in the estimate based on this body

[28] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf Slides 27-29

of evidence was not downgraded for risk of bias, inconsistency, indirectness, or imprecision. Certainty was upgraded 1 point for a strong association. The final certainly estimate based on the observational data also was Type 2.

Outcome 3, death due to COVID-19, was not an efficacy endpoint in the RCT protocol. For this outcome, the WG included any COVID-19 death in eligible randomized trial participants irrespective of the confirmation of the COVID-19 diagnosis by a trial protocol-approved assay. There were a total of 7 deaths due to COVID-19 among trial participants, including 1 among vaccinated persons and 7 among placebo recipients. The available data indicates a VE of 83% with a wide 95% confidence interval due to small numbers. Of the 7 deaths among persons with COVID-19, 3 had cases of COVID-19 confirmed using one of the three protocol-approved assays. There were 6 observational studies that examined VE against death due to COVID-19 that met the WG's inclusion criteria, of which 2 were peer-reviewed and 4 were pre-prints.[29] All were cohort studies. Of the 6 studies, 2 were not included in the pooled estimate as they included subgroups of a larger study. For the 4 observational studies included in the meta-analysis, the pooled VE estimate was of 96.1%. Sensitivity analyses using different choices of studies to pool resulted in pooled estimates of 95.6% to 96.8%.

Looking at the GRADE Evidence Table for the outcome of death due to COVID-19, the initial evidence type for the RCT was Type 1. No serious risk of bias or serious concerns for inconsistency were identified. There was serious concern of imprecision. The RR of 0.17 favored vaccination, but the very wide 95% confidence interval did not rule out harm. The final certainty was Type 2. The body of evidence from observational studies started with an evidence type of Type 3. No serious study limitations or risk of bias were identified that reduced certainly and there were no serious concerns for inconsistency, indirectness, or imprecision. In light of this strong association, the certainty was raised 1 level to Type 2.

For Outcome 4, asymptomatic SARS-CoV-2 infection, the RCT did not provide any data. There were 5 observational studies that examined VE against asymptomatic SARS-CoV-2 infection and met the WG's inclusion criteria.[30] There were 3 peer-reviewed studies and 2 pre-prints. Most of the studies were cohort studies and 4 of the 5 studies were conducted in Middle Eastern countries. Only 2 of the 5 studies were included in the pooled VE estimates as 1 of the 5 had study limitations and the other 2 included population subgroups from a larger study. The VE estimates from the 2 included studies had 95% confidence intervals that did not overlap. The pooled VE based on the meta-analysis from these 2 studies was 89.3%. Including a third study that did not meet inclusion criteria, the pool VE was 81.1%, so this would not have changed the assessment meaningfully.

Looking at the GRADE Evidence Table for asymptomatic infection, the included observational studies began at evidence Type 3. The included studies were not downgraded for risk of bias. There was serious concern of inconsistency, but no serious concerns for indirectness or imprecision. The relative risk of 0.11 favored vaccination. The final evidence certainty was Type 4 or very low.

Now turning to GRADE on harms. For Outcome 5, SAEs, there were 2 RCTs. These included a large Phase 2/3 trial as well as a published Phase 1 trial. The Phase 1 study included data on adults aged 18 to 55 years and 65 to 85 years, including 12 who were vaccinated with the relevant dose and 3 who received placebo who were randomized with the relevant dose in each

[29] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf Slides 34-35
[30] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf Slides 39-40

age group. The WG evaluated the safety data from the study, including local and systemic reactions and SAEs. From the Phase 1 trial, 1 SAE was identified in the vaccinated group unrelated to vaccination and 0 were identified in the placebo group. In the Phase 3 trial data, 1.2% in each arm had any SAE. The FDA classified 2 SAEs as related to vaccination, which were shoulder injury and lymphadenopathy.

Specific SAEs also were evaluated that were identified in safety surveillance during the period of the EUA that were previously described to ACIP, myocarditis and anaphylaxis. An RCA from the VSD evaluated chart-reviewed cases of myocarditis among persons aged 18-39 years following Dose 2. Based on events occurring in a 7-day risk interval after vaccination versus a comparison interval in vaccinated individuals, the adjusted rate ratio was 9.1% with a 95% confidence interval of 2.1% to 48.6%. The rates of myocarditis were 368 per 1 million person-years based on 9 cases in the 0-7 day risk interval and 48 per 1 million person-years based on 3 cases in vaccinated comparators. Data from VAERS showed an elevated ratio of observed to expected myocarditis cases in the 7-day interval following vaccination among females in the age group 16-24 years and among males in the age group 16-49 years, with higher observed to expected ratios in males than females. Although VAERS data are subject to the limitations of a passive surveillance system, the elevated risk of myocarditis following Pfizer-BioNTech vaccination is consistent with that observed in the VSD. Regarding anaphylaxis, an RCA of data from the VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged 12 years and older. Based on events occurring in a 0-1 day risk interval after vaccination, the estimated incidence of confirmed anaphylaxis was 5 per million doses administered. The absolute reporting rate to VAERS was similar, with 4.7 per million dose administered.

Looking at the GRADE Evidence Table for SAEs based on RCT data, the RR indicated a relative balance of SAEs between the vaccinated and placebo groups overall, with a RR risk of 1.00 and a 95% confidence interval of 0.85 to 1.18. The certainty assessment was reduced 1 point due to serious concern of imprecision because the confidence intervals indicate that both reduced and increased risk of SAEs are possible. The final certainty for the RCT data was Type 2. The GRADE evidence profile for the specific SAEs of myocarditis and anaphylaxis, which includes a narrative description of the quantitative data, started with Type 3 data from observational surveillance systems and did not decrease or increase the certainty. The final certainty was Type 3.

Reactogenicity was evaluated using the Phase 1 and Phase 2/3 RCTs.[31],[32] The Phase 2/3 trial did not solicit data on everyone, but on a subset of over 8000 participants. Both randomized studies used the same events and grading scale. The local reaction solicited for the 7 days following vaccination were injection site pain, redness, and swelling. The systemic events solicited were fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and or new or worsened joint pain. In the Phase 1 study, Grade 3 local reactions or systemic events were reported in 8.3% of persons in the vaccine arm and none of the persons in the placebo arm. In the Phase 2/3 study, Grade 3 events were reported by 10.6% of persons in the vaccine arm and 2.3% of persons in the placebo arm. Pooling the data from the 2 trials, estimated RR for any Grade 3 or higher event was 4.69 with a 95% confidence interval from 3.83 to 5.73. There was no serious concern for risk of bias, inconsistency, indirectness, or imprecision. The final certainty was Type 1.

[31] Walsh et al., New England Journal of Medicine; additional unpublished data obtained from authors
[32] Walsh et al., New England Journal of Medicine; additional unpublished data obtained from authors
Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors; and Thomas et al., preprint; additional unpublished data obtained from authors

Looking at the overall GRADE assessment for the Pfizer-BioNTech COVID-19 vaccine, in terms of benefits, the available data indicate that the vaccine is effective for preventing symptomatic COVID-19 with an evidence type of Type 1. For hospitalization and death, the available evidence favors the intervention and certainty was Type 2. Observational data were available to assess prevention of asymptomatic infection, and the certainty was Type 4. In terms of harm, in the RCT, SAEs were balanced between the vaccine and placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare but more common following vaccination. SAEs had a certainty of Type 2. In terms of reactogenicity, severe reactions were more common in vaccinated persons and about 10.7% of vaccine recipients versus 2.3% of placebo recipients reported Grade 3 or 4 reactions. The evidence type for reactogenicity was Type 1.

In conclusion, this GRADE evaluation focused on recommendations following licensure of the Pfizer-BioNTech COVID-19 vaccine that were in use for several months under an EUA. Evidence for benefits are supported by a body of evidence comprising one large Phase 2/3 RCT and numerous observational studies conducted worldwide. The RCT demonstrated efficacy against the two critical outcomes of symptomatic disease and hospitalization. Direct evidence of efficacy for hospitalization and prevention of deaths was limited from the RCT, but was additionally supported by a body of evidence from VE studies. Few data were available to assess prevention of asymptomatic infections. Regarding harms, Grade 3 reactions were more common in vaccine than placebo recipients. Overall, RCT evidence showed that SAEs occurred at a similar frequency in vaccine and placebo groups overall. However, two specific and rare but serious AEs have been associated with vaccination as identified through safety surveillance systems.

Dr. Lee called upon Drs. Shimabukuro and Oster to clarify some of the issues pertaining to myocarditis. Dr. Shimabukuro took a moment to go over how myocarditis and myopericarditis cases are identified. The *MMWR*[33] mentioned earlier documents the CDC case definition in Table 1 for acute myocarditis, both probable and confirmed, and acute pericarditis. There is a note at the bottom of the table stating that myopericarditis is a "term that may be used for patients who meet the criteria for both myocarditis and pericarditis." The CDC case definition was developed in consultation with CDC's own cardiologist consultants and the Clinical Immunization Safety Assessment (CISA) Project team and their cardiologists and infectious disease consultants. It is the case definition that CDC's clinical abstractors use when reviewing VAERS reports and medical records and requesting additional information or contacting the providers to determine whether a case meets case definition. CDC has substantial information on the VAERS cases and the clinical course of these cases. As Dr. Su mentioned earlier, CDC is in the process of conducting an enhanced surveillance project to assess long-term outcomes. CDC also uses a standard a extraction form for the VSD cases, which also is based on the CDC case definition. Dr. Matt Oster is one of CDC's cardiologist consultants who has been leading CDC's surveillance reviews of the VAERS cases and the analysis, which is currently under review for publication.

Dr. Oster added that it sometimes can be challenging clinically to evaluate and diagnose these children. That is why these case definitions were defined. Some children will overlap in these findings. For instance, a child with chest pain and EKG findings would meet criteria for the definitions of both myocarditis and pericarditis and will be considered a case of myopericarditis. As mentioned before, there has been a lot of concern about these children due to the chest pain and elevated troponin. However, vaccine-associated myocarditis is thought to be very different

[33] https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf

from traditional myocarditis. A lot has been published to date on the imaging findings in these children. While a lot of times there is some sub-endocardial inflammation in association with the other criteria, there are well-defined criteria for diagnosing myocarditis. There are the Lake Louise Criteria, which the children with vaccine-associated myocarditis are meeting. The big concern in the cardiology community is that while it is great that the children improve quickly and need little treatment, findings are very troubling. This is not typically seen in pericarditis. Some of the MRIs also show more mild myocarditis that would not necessarily be seen in just pericarditis. That is why CDC is following up. There have been some publications from people who did some early MRIs 1 to 2 months after these cases that showed some improvement in some of the MRI findings, but still some persistence of inflammation. Therefore, it is still too early to tell how they will do. The great news is they do tend to get better from a symptom standpoint without a lot of treatment. It is important to follow them to make sure that they make a full recovery in the long-term.

EtR Framework: Pfizer-BioNTech COVID-19 Vaccine

Dr. Kathleen Dooling (CDC/NCIRD) presented the EtR Framework for Pfizer-BioNTech COVID-19 vaccine, also called Comirnaty®. Endorsed by the ACIP, the EtR Framework provides a structure to describe the evidence to inform ACIP recommendations in a transparent manner. The policy question for this EtR assessment was, “Should vaccination with Pfizer-BioNTech COVID-19 vaccine be recommended for people 16 years of age and older?” In December 2020, ACIP made an interim recommendation for the use of Pfizer vaccine under the FDA’s EUA. Now that FDA has issued full approval of the BLA, the question before ACIP regarded whether ACIP should update the interim recommendation to a standard ACIP recommendation.

As a reminder, the population under consideration is people 16 years of age and older in the US. The intervention is the Pfizer-BioNTech COVID-19 vaccine standard dosage of 30µg as a 2-dose primary series given 21 days apart. The outcomes include: symptomatic COVID-19 (PCR-confirmed); hospitalization due to COVID-19; death due to COVID-19; asymptomatic SAR-CoV-2 infection (assessed using PCR); SAEs (including death, myocarditis/pericarditis and anaphylaxis); and reactogenicity (≥Grade 3 or worse reactions). The EtR domains include: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. These domains each have central questions. Moving through each of the domains, the public health problem refers to COVID-19 and the intervention refers to Pfizer-BioNTech COVID-19 vaccine.

First, a description of the public health problem. The question here regards whether COVID-19 is still a problem of public health importance. COVID-19 cases have been increasing since early July. As of August 27th, over 38 million COVID cases have been reported to CDC. The most recent 7-day moving average was over 145,000 cases per day. Deaths also have been increasing. The current 7-day moving average is almost 1000 deaths per day from COVID-19 in the US. Hospitalization rates also have been increasing since early July. For persons 18-49years of age, hospitalization rates are approaching that seen during the peak of the epidemic last winter. Looking at hospitalization rates in COVID-NET from January to mid-July, rates of hospitalization in unvaccinated persons are many-fold higher than those for fully vaccinated people from 24 times higher among adults under 50 years of age to 13 times higher in unvaccinated older adults. The high hospitalization rates among adults have been putting an enormous burden on the healthcare system, with 23 states reporting that they have exceeded 80% of ICU capacity and at least 1 state reporting having exceeded over 100 percent capacity. One of the drivers of the current surge in infections is the Delta variant. Delta is the dominating

circulating variant and is estimated to be more than twice as contagious as the Alpha variant, the previously circulating dominating variant.[34]

Switching gears now to vaccination. The number of doses administered per day in the US peaked in April, but has been slowly increasing again since July. However, it is important to note that approximately 38% of the population 16 and older are not yet fully vaccinated. Vaccine coverage varies by age.[35] In terms of the percent of people receiving 1 or more doses of COVID-19 vaccine, people 50 years of age and older have achieved high coverage of 80% or higher. People 18-49 years of age have achieved coverage between 59% and 72%. The two youngest age cohorts, some of whom only became eligible for vaccination in April or May, so far have coverage of 49% (12-15 years of age) and 57% (16-17 years of age). It should be noted that coverage is still increasing steeply among these groups. That continued strong uptake among young people is seen very clearly in people who are fully vaccinated with Pfizer vaccine. Since mid-April most, people achieving full vaccination with Pfizer vaccine are younger than 50 years old. COVID-19 vaccination coverage also varies by geography. Only 6 states or territories have achieved coverage of 70% or more in the population 12 years of age and older.

To summarize the public health problem domain, COVID-19 cases, hospitalizations, and deaths have been increasing. The Delta variant is the dominant circulating variant of SARS-CoV-2 in the US and is estimated to be more than 2 times as transmissible as previous variants. Over 173 million people are fully vaccinated in this country. However, vaccination coverage varies by age and geography. Increasing cases are taxing the healthcare resources, with many states facing ICU bed shortages. The WG group determined that COVID-19 continues to be an important public health problem.

The benefits and harms domain sought to answer questions regarding how substantial the desirable anticipated effects and undesirable anticipated effects are, and whether the desirable effects outweigh the undesirable effects. As a reminder, Dr. Gargano presented the GRADE assessment of the benefits and harms earlier. The level of certainty for the benefits of Pfizer-BioNTech COVID-19 vaccination among people 16 years and older was Type 1 or high certainty for the prevention of symptomatic COVID. The clinical trial and observational study evidence demonstrated that the Pfizer vaccine prevented both hospitalization and death due to COVID. Both outcomes were rated as Type 2 or moderate certainty. Two observational studies showed a benefit of vaccination for the prevention of asymptomatic SARS-CoV-2 infection. However, the evidence was Type 4 or very low certainty.

Regarding potential harms after vaccination, SAEs in the clinical trial were balanced between the vaccine and the placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare, but more common following vaccination. This body of evidence was rated as moderate certainty. Moreover, as presented by Dr. Rosenblum, in the highest risk population of males 16-29 years of age following the second dose, the WG group felt that the benefits of vaccination with Pfizer-BioNTech COVID-vaccine outweighed the risks of myocarditis/myopericarditis. With respect to the final outcome of reactogenicity, severe reactions within 7 days were more common among vaccinated people. In fact, any Grade 3 reaction was reported by 10.7% of the vaccinated group versus 2.3% of the placebo group. This was deemed to be Type 1 or high level of certainty.

[34] https://covid.cdc.gov/covid-data-tracker/#variant-proportions; https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html August 28, 2021
[35] https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic

It is worth noting here that since the interim ACIP recommendations were made for Pfizer-BioNTech vaccine in December 2020, there are now sufficient data to report out on all of the outcomes of interest with additional follow-up time and large observational studies. The level of certainty for the vaccine's prevention of hospitalization and death due to COVID-19 has increased. In addition to more than 22,000 people randomized to receive the Pfizer vaccine in the clinical trial, more than 680,000 vaccinated people contributed person time to the real-world VE studies. Millions of vaccinated people contributed to the post-authorization safety monitoring. The WG felt that the desirable anticipated effects were large, the undesirable anticipated effects were small, and the balance favored the intervention of the use of Pfizer vaccine in people 16 years of age and older.

The values domain aimed to address questions pertained to how the target population feels about the balance of desirable to undesirable effects, and whether there is important uncertainty about how the target population values these outcomes. To assess this domain, the WG reviewed the scientific literature, news media, and gray literature reports. The surveys were limited to those conducted since authorization of COVID-19 vaccines, but survey questions generally included all COVID vaccine types. In terms of positive vaccine intent in surveys completed between December 2020 and August 2021, there was overall positive vaccine intent. The people who reported that they were already vaccinated or probably or somewhat likely to get vaccinated increased from December to May and has remained at about 70% since then. The most common reasons reported for not getting vaccinated included concerns about side effects, belief that the vaccines are too new, and belief that vaccination is not necessary.[36] Of those not vaccinated in a Kaiser Family Foundation (KFF) Survey, 20% said they would only get vaccinated if required and 36% said they would definitely not get vaccinated.[37]

In that same survey, while 68% of people indicated a positive vaccination intent, 10% said that they would wait-and-see, 14 percent% said they would definitely not get vaccinated, and 6% said they would get vaccinated only if required. The unvaccinated people were then asked whether they would be more likely to get vaccinated if one of the vaccines currently authorized for emergency use received full approval from the FDA. Of the respondents, 49% of the wait-and-see and 8% of the definitely-not group reported they would, in fact, be more likely to get vaccinated under those circumstances. Overall, 31% of unvaccinated respondents said they would be more likely to get vaccinated after a COVID-19 vaccine received full FDA approval. The WG felt that the target population probably feels that the desirable effects are large, but that there was important uncertainty or variability in how much people value the main outcomes.

The acceptability domain sought to answer the question regarding whether Pfizer-BioNTech COVID-19 vaccine is acceptable to key stakeholders. COVID-19 vaccination has been implemented in a large variety of settings, including state and local health departments, healthcare sites, hospitals, mass vaccination clinics, long-term care facilities (LTCF), retail pharmacies, and HCP offices. As of August 29, 2021, all of the aforementioned stakeholders had contributed to more than 207 million doses of Pfizer-BioNTech COVID-19 vaccine being administered.[38] Vaccination with Pfizer-BioNTech COVID-19 was already highly acceptable to stakeholders under the FDA EUA and ACIP interim recommendation. Vaccination may be more acceptable to stakeholders under full FDA approval and a standard ACIP recommendation. The WG felt that the Pfizer-BioNTech COVID-19 vaccine is acceptable to key stakeholders.

[36] KFF COVID-19 Vaccine Monitor: June 2021. June 30, 2021. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-june-2021/; Quinnipiac Poll. August, 2021. https://poll.qu.edu/poll-release?releaseid=3815

[37] KFF COVID-19 Vaccine Monitor: May 2021. May 28, 2021. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-may-2021

[38] https://covid.cdc.gov/covid-data-tracker/#vaccinations

The question related to the feasibility domain pertained to whether the Pfizer-BioNTech COVID-19 vaccine is feasible to implement. Barriers to implementation may include complexity of recommendations, vaccine storage and handling requirements, financial barriers, and supply barriers. The WG looked at each of these in more detail. With regard to complexity of recommendations, the Pfizer-BioNTech COVID-19 vaccine is currently the only COVID-19 vaccine for which FDA has approved a full BLA. The BLA has only been issued for some indications, which may add complexity to current recommendations. In other words, the approval for ages 16 years of age and older exists under the BLA whereas vaccination of adolescents 12-15 years of age and an additional dose in immunocompromised people proceeds under the EUA.

Vaccine storage and handling requirements[39] for Pfizer COVID vaccine have become more feasible since ACIP made its interim recommendations in December 2020. However, the ultra-cold storage requirements of -90ºC to -60ºC impacts where vaccine can be stored. The ultra-cold storage maximum time has been extended from 6 to 9 months. Subsequently, freezer storage is permissible at regular vaccine freezer temperatures e (-25ºC to -15ºC) for up to 2 weeks. Vaccine may be kept at refrigerator temperatures (2ºC to 8ºC) for up to 1 month (31 days). The minimum size of orders is currently 450 doses, which may present feasibility problems for low throughput sites without ultra-cold storage.

With respect to possible financial barriers, all COVID-19 vaccines are provided to the US population free of charge. However, health systems or health departments incur costs for vaccine implementation, clinics, and outreach and education. Financial hardships may arise if vaccine recipients need to take time off to receive the vaccine or experience post-vaccination reactogenicity that prevents them from working. Vaccine supply in the US is sufficient for implementation of the intervention. As of August 29th, more than 209 million doses of Pfizer-BioNTech have been administered in the US, demonstrating that the vaccine is feasible to implement. The WG felt that the Pfizer-BioNTech COVID-19 vaccine is feasible to implement.

The resource domain aimed to address whether the Pfizer-BioNTech COVID-19 vaccine is a reasonable and efficient allocation of resources. For unvaccinated people, the estimated costs associated with hospitalization due to COVID was $1.5 billion in July.[40] Vaccine doses purchased with US taxpayer funds will be given to people living in the US at no cost.[41] Several public published modeling studies[42] have found that COVID-19 vaccination is likely to be of reasonable economic value and also may be cost-saving under many circumstances. The WG concluded that cost-effectiveness may not be the primary driver for decision-making during a pandemic. This will need to be reassessed for future recommendations. The WG felt that Pfizer-BioNTech COVID-19 vaccination for people 16 years of age and older is a reasonable and efficient allocation of resources.

The equity domain sought to answer what the impact on health equity would be of a standard ACIP recommendation for Pfizer-BioNTech COVID-19 vaccine for people 16 years of age and older. As a reminder, health equity is when everyone has the opportunity to be as healthy as possible, and no one is disadvantaged from achieving this potential because of social position or other socially determined circumstances. In addition to identifying groups that may be

[39] Pfizer-BioNTech COVID-19 Vaccine Storage and Handling Summary (cdc.gov); Pfizer-BioNTech COVID-19 Vaccine EUA Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) (fda.gov)
[40] Peterson-KFF Health System Tracker
[41] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/no-cost.html
[42] Padula et al. 2021. J Med Econ; Bartsch et al. 2021 J Inf Dis; Gupta et al. 2021 Health Aff; Kohli et al 2021 Vaccine

disadvantaged with respect to COVID-19 disease and COVID vaccination, the WG reviewed the scientific and gray literature as well as the CDC response data and resources. The WG agreed that these groups could experience barriers with respect to vaccine access; low vaccine confidence; certain places of residence (e.g., rural or frontier locations, various congregate living settings); racial and ethnic minority populations; disadvantaged socioeconomic status; and personal characteristics associated with discrimination.

The COVID-19 pandemic has had unequal impacts across the US population. In terms of the cumulative COVID-19 associated hospitalizations since the pandemic began through mid-August 2021, compared to white adults, Hispanic adults experienced twice the cumulative hospitalization rates, Black adults almost 2.5 times, and American Indian/Alaska Native (AI/AN) populations have experienced 3 times as much hospitalization. This analysis included data on all adults and did not take into account the age structure of different populations.[43] In terms of the estimates of excess deaths in 2020, focusing on those 25-64 years of age, compared to prior years, all the race and ethnic groups shown experienced excess deaths in 2020. However, compared to white and Asian young adults, Hispanic, Native Hawaiian/Pacific Islander, Black and AI/AN young adults had 2 to 4 times the excess deaths.[44] Important strides have been made toward equitable vaccine administration over the course of the COVID-19 vaccine rollout. AI/AN populations have the highest coverage, with more than 50% percent of the population receiving at least 1 dose. Other race and ethnic groups had similar coverage by August. However, coverage among Black populations was lower at 31%. Although improvements had been made in equity coverage, there is still work to be done to ensure that everyone has the necessary access and information to be vaccinated.[45]

As for the reasons why some adults have not received vaccine, unvaccinated Hispanic and Black adults were more likely than whites to cite worries about missing work and having to pay for the vaccine as major reasons for not being vaccinated. In addition, unvaccinated Hispanic adults are more likely than unvaccinated white adults to say they are too busy, would have difficulty traveling to a vaccination site, or are not sure where to get the vaccine.[46] COVID-19 vaccination coverage also varies by geography. Even within a state, coverage can vary greatly by county. Only 5% of counties in the US have achieved 70% or higher vaccination coverage among people 12 years of age and older.[47]

In summary, the WG concluded that COVID-19 has resulted in disproportionate hospitalization and mortality in minority populations. Equitable uptake of COVID-19 vaccine has improved over time, but work is still needed to continue to improve vaccine confidence and vaccine access for all. The WG had varying opinions on the impact of a standard ACIP recommendation for Pfizer-BioNTech COVID-19 vaccine would have on equity. It is likely that the impact would vary by community. Overall, many work group members felt that they did not have enough information to predict the impact of a standard ACIP recommendation on health equity and that it may vary by population.

[43] https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network as of August 22, 2021
[44] Rossen LM, Ahmad FB, Anderson RN, et al. Disparities in Excess Mortality Associated with COVID-19 — United States, 2020. MMWR Morb Mortal Wkly Rep 2021;70:1114–1119. DOI: http://dx.doi.org/10.15585/mmwr.mm7033a2
[45] https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends as of August 24, 2021, and US Census Bureau National Population Estimates
[46] https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-june-2021/ June 8-21, 2021
[47] https://covid.cdc.gov/covid-data-tracker/#vaccinations-county-view August 29, 2021

In summary, the WG concluded that COVID-19 is still an important public health problem. The anticipated desirable effects from vaccination with Pfizer-BioNTech COVID-19 vaccine are large and the undesirable effects are small, favoring the intervention. The certainty of the evidence for critical outcomes was graded to be high or moderate. The WG felt that the target population probably valued the intervention, but that there also was important uncertainty in how the population values the outcomes. The intervention was acceptable to stakeholders, feasible to implement, and a reasonable use of resources. The WG group had varying opinions on the impact of a standard ACIP recommendation for Pfizer-BioNTech COVID vaccine would have on equity. It is likely that the impact would vary by community. Overall, most WG members felt that the desirable consequences clearly outweighed undesirable consequences in most settings. In addition, after reviewing the totality of information presented in the EtR Framework, the WG discussed the type of recommendation to propose to ACIP. The options were: 1) we do not recommend the intervention; 2) we recommend the intervention for individuals based on shared clinical decision-making; or 3) we recommend the intervention. The WG members supported recommending the intervention.

Summary of Discussion (Gargano & Dooling)

- Some sentiment was expressed that perhaps equity should be addressed in every domain as opposed to standing alone, given that it is such an important consideration for all vaccines.

- It was observed that in addition to the Delta variant being twice as transmissible and now dominating and that the unvaccinated are experiencing higher rates of illness compared to people who are fully vaccinated, human factors of contact are also problematic. The epidemiology of this current wave started to take off in July, possibly when people were having closer contacts, more contacts, and contacts where distance was not maintained and less masking was used.

- A question was raised regarding whether the Pfizer vaccine would still be covered under the Countermeasures Injury Compensation Program (CICP) and if the EUA Fact Sheets would be replaced by the standard Vaccine Information Sheet (VIS) if ACIP voted to recommend full approval:

    - Dr. Dooling responded that this raised an important discrepancy from business as usual in that vaccines receiving full approval from FDA and recommended by ACIP have a VIS that is handed out any time a person receives a vaccination. With the vaccines authorized under emergency use by FDA and given interim recommendations by ACIP, the vaccine Fact Sheet performed many of the same functions as the VIS. This is a very rare circumstance of having a vaccine recommended that both has full BLA as well as EUA. To minimize the complexity, providers will be expected to continue to give out the Fact Sheet that has been bolstered with many of the items that typically would be included in the VIS.

    - Dr. Cohn indicated that the CICP would continue to cover any potential injuries related to a Pfizer vaccine given under a BLA because these vaccines are still US government-purchased and distributed and the public health emergency continues.

    - Dr. Rubin (HRSA *Ex Officio*) added that the COVID-19 vaccines currently authorized through the FDA EUA or approved by the FDA are COVID countermeasures under the Public Readiness and Emergency Preparedness Act (PREP Act). Individuals who think they might have an injury as a result of COVID-19 vaccines are eligible to

apply for benefits under the CICP. Full FDA approval of the Pfizer COVID-19 vaccine does not remove its coverage from the CICP or provide coverage under the VICP. Three things must occur in order to add a new vaccine to the VICP: 1) the vaccine must be recommended by the CDC for routine administration to children and/or pregnant women; 2) Congress must enact an access tax on the vaccine; and 3) the HHS must add the vaccine to the VICP through publication of a notice of coverage in the *Federal Register*. That has not yet been done for COVID-19 vaccines to date.

- ACIP members indicated that they would like additional information/discussion on the following:

  - Performance of the Pfizer vaccine and Delta variant
  - Myocarditis/pericarditis
  - Equity and the fundamental disproportionate impact of the COVID-19 pandemic on communities of color, and considerations for how to remedy this
  - Messaging

Vote: Pfizer-BioNTech COVID-19 Vaccine For People ≥16 Years of Age

Dr. Kathleen Dooling (CDC/NCIRD) presented the following proposed recommendation for an ACIP vote:

> *The Pfizer-BioNTech COVID-19 vaccine is recommended for people ≥16 years of age under FDA's BLA approval.*

Summary of Discussion

- It is important to note that this recommendation would be in addition to the current interim recommendations under FDA's EUA for us of his vaccine in people 12 years of age and older and for a third dose of vaccine among immunocompromised persons.

Motion/Vote: Pfizer-BioNTech COVID-19 Vaccine For People ≥16 Years of Age

Dr. Poehling made a motion and Ms. Bahta seconded to approve the recommended language for Pfizer-BioNTech COVID-19 vaccine for people ≥16 years of age. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Following the vote, ACIP members were invited to make a statement on the rationale for their vote or provide additional comments:

- Dr. Kotton: I would just like to say that I am very appreciative for the incredible amount of work that was presented today and the really amazing, amazing amount of data that has been shown. It is wonderful that we are at this time where we can reach a decision as far as whether we wanted to proceed with this recommendation. Thanks to everyone who worked so hard to get us to this point.

- Dr. Talbot: I would like to reiterate how hard our FDA and CDC colleagues have worked through this pandemic. They have been working extra hours, not just for a few months, but now for 18 months, and they have done this. I want to remind the American public that our public health infrastructure was stretched prior to the pandemic. I would like everyone who made public comment in regard to how much more the CDC can do to remember to reach out to their representatives, and Congressmen, and Senators, that the CDC needs to be funded fully on a yearly basis with a stable budget to cover not only our routine healthcare so that kids are vaccinated for everything, but also to handle epidemics and pandemics. I think our colleagues have been very overworked, and I want people to know they are working just as tirelessly as they were in the beginning. But we need everyone else's help, too, to spread the news that this vaccine is safe. If you've been vaccinated, raise your arm and tell everyone about it. Be loud and proud. I think the second thing I really want to bring home is that our kids need to be in school, and everyone wants to do it with going back to completely normal. And I don't think that's possible. I think our kids are going to be scarred if we don't get them back in school. They need to be masked and everyone who has anything to do with a child who is not old enough to be vaccinated yet should be vaccinated for the benefit of those children, and for other loved ones who might be immunocompromised. So once again, tell everyone you've been vaccinated. Encourage everyone to be vaccinated. I'm saying this not just as an infectious disease doctor, not just as an epidemiologist, not just as an ACIP voting member—but as a mom of two children. Please go get vaccinated so our kids can go to school. Thank you.

- Dr. Chen: I want to echo what Dr. Keipp Talbot just said, that I really appreciate what the CDC and FDA have been doing behind the scenes. They're really unsung heroes continuing to work, you know, for 18 months tirelessly. It's just been tremendous. Through today's presentations, which were really amazing, I've been highly encouraged by the clear demonstration of the safety and effectiveness of the Pfizer-BioNTech vaccine that we saw. I also just wanted to emphasize that we don't have the expectation that the Pfizer vaccine or any of the other COVID vaccines confer immortality nor invulnerability against predictable life events, for example, the occurrence of cancer, motor vehicle accidents, or other things that can cause someone to get hospitalized or die and just because of timing, it's not related. I also wanted to just mention an imminent, predictable event that is coming up, which is non-COVID respiratory viruses. As we return back to in-person classes for our children, as we enter into the fall and winter season, we should not be surprised by the eventuality of seeing a rise in infections from seasonal respiratory viruses like influenza, RSV, rhinovirus, and others, which we are already seeing right now with that signal. You know, these COVID vaccines will not prevent runny nose, sore throat, fever, cough, nor the hospitalizations or possible deaths due to those non-COVID respiratory viruses. I have many pediatric medical colleagues that have voiced their concerns about the expectation of an overwhelming number of hospitalizations in children in the coming months. Medical systems are already preparing to surge upwards to 200 or more percent of their normal capacity to handle these pediatric hospitalizations. Clearly, the Pfizer vaccine and all these

other COVID vaccines have demonstrated a very strong track record for safety and effectiveness, especially in the prevention of hospitalization and death due to COVID. Again, this is just a warning for the upcoming season, because we're going to see other respiratory viruses mixed in with this present pandemic. While we have an FDA-approved COVID vaccine for adults and EUA authorization for children 12 years of age and older, in the coming months, I look forward to reviewing the data that we will have, hopefully soon, for safety and efficacy for younger children. I'm looking toward having this vaccine be available to protect this vulnerable and precious part of our population. I'll end my comments there. Thank you.

- Dr. Daley: I have several broad comments I'd like to make. How will history judge this moment in time? This is a question that I was asked a few weeks ago during an interview, and I've been thinking about it ever since. I think that there are several crucial developments that will be judged very favorably over the course of time. You know, last fall, several of our national health experts stated that we'd be fortunate to have a vaccine that was 70% effective against the new respiratory virus. And yet, here we are with a vaccine demonstrating greater than 90% efficacy and 96% efficacy against death. I think history is going to judge this as a moment of incredible scientific innovation. Second, this is my opinion alone, but I've been struck by how well our existing processes and systems have functioned in the environment of this unprecedented pandemic. This will echo some of the comments that Dr. Talbot made, but I'd like to highlight the processes at work at the FDA. The Food and Drug Administration is responsible for protecting public health by ensuring the safety, efficacy, and security of drugs, biologics, and medical devices. Even with the urgency of the pandemic, the FDA has followed their established processes on maintaining an appropriately high bar for licensure. Some in the press and in the public have urged the FDA to speed up their reviews, and I would state the opposite. Take the time that you need to conduct the extraordinarily detailed and careful review that you'd perform with any other licensed medical product. In fact, I'm confident that that's happened. I'd also like to highlight the work of this group. As Dr. Lee, our committee Chair, has reminded us, the ACIP needs to follow all the established processes, including the rigorous GRADEing of scientific data and the integration of this GRADE into the Evidence to Recommendations Framework. This process was just demonstrated so clearly by the presentations just given by Dr. Gargano and Dr. Dooling. Finally, I want to highlight that prior to the pandemic, the United States had an extensive system for monitoring the safety of authorized and licensed vaccines. This system includes multiple components, including the VAERS and VSD that we heard from today. During the pandemic, the system has been enhanced such as by the creation of v-safe and by the addition of other federal partners that contribute data to this safety assessment. That system has allowed us to detect these rare but potentially serious adverse events following vaccination. As Dr. Lee showed in her presentation, these data then are used to reevaluate risk versus benefit. And these data can also be used to mitigate adverse events whenever possible. I think we all fully recognize that the story is not all rosy and that there are many areas of concern. We've really suffered from a plague of disinformation and misinformation, and as many as 72 million individuals in the US 16 and older are not vaccinated. And we have these new variants that have emerged with increased transmissibility. Cases, hospitalizations, and deaths are on the rise. Even in consideration of these challenges, in response to that question I was asked about how history is going to judge this moment, my personal judgment is that this is a time of incredible scientific innovation and I'm hugely grateful for that. Entering the pandemic in the United States, we were in the fortunate position of having established systems to license vaccines, to recommend vaccines, to evaluate vaccines using real-world safety data, and then these systems were enhanced for the pandemic. And they really met the challenges of

the pandemic, and by and large, performed very well. I just think that the fact that we're here today voting on recommendations of a licensed vaccine against COVID-19 is historical in and of itself, and it just further reinforces the points that I've just made. Thank you very much.

- Dr. Poehling: I wanted to also send my sincere thanks to the many people who've been working to make this day possible. I voted in favor after reviewing the large amount of safety and effectiveness data from randomized controlled trials, observational studies, and multiple safety monitoring systems. Over 209 million doses have been administered. The hospitalization rate among unvaccinated is much, much higher, over 19-fold times higher, than that of the vaccinated. The Delta variant is far more transmissible, with high replication and viral loads, and is causing over 100,000 infections and over 1000 deaths per week. Vaccines and masks work to protect us, our families, our children, and our community. I encourage all eligible to be vaccinated and use masks to protect you and all those that you love.

- Dr. Duchin (NACCHO): I just wanted to say that this is a miraculous accomplishment to have such an effective vaccine so quickly. I just want to remind people that right now when not everyone can be vaccinated, and even when not all of those who are eligible are vaccinated, that we really need to use all tools at our disposal in addition to vaccines to fight this Delta outbreak in particular. And that means using the best quality mask, the best-fitting and highest-filtering mask we can, understanding the critical importance of improving indoor air quality through ventilation and filtration, and reducing high-risk activities. Vaccines are wonderful, they're miraculous, but we need to use all tools at our disposal right now.

- Dr. Lee: I agree with the comments of many of my colleagues on the call about the importance of vaccination. The one thing I did want to emphasize is that the BLA is inclusive of pregnant women, and as we know, the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and CDC have really strengthened the recommendations around vaccination of pregnant individuals because of the severity of disease that we're seeing. I just wanted to remind our colleagues and the public how important this particular population is, both because they're suffering far worse complications from COVID infection with significant severity of disease and it's also impacting their infants. I think this is an opportunity for us, in that we know that only 10% to 15% of pregnant women are actually vaccinated, so we have a long way to go. We've talked a lot about disparities. I actually think that pregnant women should be included in that mix. We really need to think about how to strengthen our vaccination rates in the pregnant population.

Framework for COVID-19 Booster Doses

Dr. Sara Oliver (CDC/NCIRD) presented the framework for COVID-19 vaccine booster doses, reminding everyone that there are two distinct potential uses for an additional dose. During the last meeting, ACIP recommended an additional COVID-19 vaccine dose after receipt of a primary series as a way to provide protection for those who may not have mounted an appropriate immune response to the initially-recommended series. Booster doses are vaccine doses administered when the initial sufficient immune response to a primary series may have waned over time, which was the topic of this presentation. In thinking through the recommendations for booster doses of COVID vaccines, the main question to be answered regards whether booster doses are needed for those previously vaccinated with a primary series. As with other recommendations for COVID vaccines, Dr. Oliver emphasized that the

data would be reviewed in a systematic and transparent fashion. Policy on booster doses will be coordinated with FDA for regulatory allowance and ACIP for recommendations around use.

As discussed during the last meeting, recommendations for booster doses would apply only to those who had completed a primary series. To date, over 365 million vaccine doses have been administered in the US. Over 60% of those 12 years of age and over are fully vaccinated. In terms of the daily count of newly fully-vaccinated individuals, the average number of doses administered has been increasing since mid-July. As a result, there is an increase in the number of fully vaccinated individuals. Increases in recent weeks have been primarily among those 18-64 years of age.[48]

The framework for booster doses also was discussed during the last meeting, while the WG began to provide data to inform booster dose policy during this session. At the time of the EUA, the median follow-up time was about 2 months. Data were presented earlier in the day from Pfizer regarding the longer follow-up time for those in the clinical trials. Work will continue with the manufacturers to review the follow-up from clinical trials during upcoming meetings.

For this presentation, Dr. Oliver summarized recent US publications[49] evaluating waning immunity based on data through July 2021. VE estimates against hospitalization have remained high over time, while VE estimates against infection have had some decreases over time for the last 1 to 2 months. There are a variety of reasons that could explain this decline. One aspect could be waning immunity due to time since the primary series. However, there is another factor to consider as well as seen from previous presentations throughout the day around the increases of the Delta variant. In May, Delta was around 7% of sequenced isolates. By mid-July, this was up to 94% of sequenced isolates. The impact of the Delta variant leads to the next question regarding whether VE is reduced for the Delta variant.

Looking at VE estimates by outcome for the Alpha variant compared to the Delta variant, among global studies assessing infection with Alpha versus Delta,[50] there was a mild decrease in Delta VE. There may be a variety of factors that can impact these results and variation by countries, including differences in study methods, intervals between doses, and timing with vaccination and variant increases. In studies comparing pre-Delta and Delta time periods,[51] the pre-Delta VE estimates were high at 87% or higher. Since the introduction of the Delta variant, VE against infection ranged from 39% to 84%. VE against hospitalization remained high, from 75% to 95%. To summarize VE estimates since the introduction of the Delta variant by any infection, symptomatic infection, hospitalization, and severe disease and by vaccine type, regardless of the vaccine evaluated, all vaccines remain effective in preventing hospitalization and severe disease. However, they may be less effective in preventing infection or mild illness. The reasons for lower effectiveness likely include both waning over time and the Delta variant.

It also was important to evaluate how the need for booster doses may vary by sub-population. In a study looking at adults 60 years of age and over that highlights VE for symptomatic infection with the Pfizer vaccine for several of the recent VOCs,[52] VE against symptomatic infection was high. However, some decreases were noted against VOCs. It is important to note that these differences were not statistically significant, and there were small numbers and very

[48] https://covid.cdc.gov/covid-data-tracker
[49] Tenforde et al, Rosenberg et al, Nanduri et al, Fowlkes et al, Puranik et al (Slides 13-15)
[50] Tartof et al, Sheikh A, et al, Tang et al, Abu-Raddad et al, Nasreen S et al, Bernal Lopez et al, Stowe et al (Slide 17)
[51] Isreali Ministry of Health Committee, Haas et al, Pouwels et al, Puranik, Rosenberg, Tenforde (Slide 18)
[52] Nasreen et al: https://www.medrxiv.org/content/10.1101/2021.06.28.21259420v2.supplementary-material

wide confidence intervals for several of the different variants. In another study,[53] VE against hospitalization in adults 65 years of age and over has decreased slightly over time, but has remained high. Differences by time interval since vaccination were not significantly different.

Data with preliminary VE against COVID-19 associated hospitalization among fully vaccinated patients 18 years of age and over by age group and month showed that VE remains high at 94% or higher for adults 18-49, 50-64, and 65-74 years of age. Preliminary VE against hospitalizations in adults 75 years of age and over decreased in July, but still remained at over 80%.[54] Now to look at VE among HCP by days since the second dose of the primary series, variant predominance, the pre-Delta time period, the time period when the Delta variant was predominant. The VE against infection among front-line workers, including HCP, declined somewhat over time and from the pre-Delta period to the Delta period. However, the VEs were not significantly different.[55] In terms of VE against infection among LTCF residents, there was some question initially regarding how medically frail adults may respond to the vaccine. However, data from the National Healthcare Safety Network (NHSN) show that VE was 74% or higher with the mRNA vaccines. However, moving into the recent months when Delta was the primary variant, VE has fallen to just over 50%.[56]

To put the estimates for older adults, HCP, and LTCF residents into the overall context, lower VE against infection was seen for LTCF residents. VE among older age groups and HCP are comparable with other subgroups, and follow-up is needed to monitor these VE estimates over time.

Another aspect of booster dose decisions pertains to the benefits and harms and whether booster doses of COVID vaccines are safe and immunogenic. Pfizer, Moderna, and Janssen are all conducting studies to evaluate the safety and immunogenicity of booster doses. While information about the immunogenicity of these booster doses has been reported in the press, it is important for ACIP to review sufficient safety data for booster doses as well. During upcoming ACIP meetings, the manufacturers will present data on third doses. It is also important to answer the question regarding whether booster doses of COVID vaccines will reduce COVID incidence, hospitalization, and mortality. The WG is evaluating the data available to discuss the potential impact of COVID booster doses in a variety of populations and settings. While the data are limited currently, the WG will present data to ACIP as soon as it becomes available.

In terms of whether booster doses improve VE against the Delta variant and other VOCs, immunogenicity data (including sera from study participants who received a booster dose) can evaluate neutralizing antibody data for variants of concern, including Delta. No correlate of protection is available, but there is a growing understanding around the impact of neutralizing antibodies. This understanding can be used to infer the impact of booster doses from studies of neutralizing antibodies to clinical protection against Delta and other VOCs. The WG will provide presentations to ACIP on this during upcoming meetings.

[53] Tenforde et al: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm
[54] Unpublished COVID-NET data
[55] Data from HEROES-RECOVER Cohort; Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e4.
[56] Adapted from: Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70. Slide courtesy of Ian Plumb.

Feasibility also will be an important aspect for booster doses. Some aspects of implementation will be more feasible than a primary series roll-out. Supply and number of vaccination sites should not be a serious limitation. However, there will be some aspects of implementation that could be more complex. Individuals received a variety of primary series. Upcoming data will evaluate booster dose response for the same vaccine as the primary series (homologous), as well as a different vaccine as the primary series (heterologous). Booster dose policy will need to address individuals who received all primary series. Another aspect that could impact implementation includes the possibility of different doses. Some COVID vaccine booster studies have evaluated various doses for booster vaccines for the same product. The data on these studies will need to be reviewed and feasibility of implementation discussed.

Now moving on to the summary and WG considerations. It is not uncommon for a vaccine series to require several doses. Vaccines that require more than one dose does not necessarily mean that annual boosters are needed. For many vaccines, the final dose is given at least 6 months after the initial dose. This table shows a sample of vaccines that can be given to adolescents or adults that require more than one dose and with the last dose given at 6 months or further:

Sample of Adult Vaccines Requiring >1 Dose	1st Dose	2nd Dose	3rd Dose
Herpes Zoster (shingles)	Initial	2-6 Months	
Hepatitis A	Initial	6 Months	
Hepatitis B	Initial	1-2 Months	6-18 Months
Human papillomavirus (HPV) (Age ≥15 at initial vaccination)	Initial	1-2 Months	6 Months

To explain why that occurs, the initial dose of a vaccine is typically thought of as a priming dose. It induces an immune response that includes B-cells, T-cells, and antibodies. However, subsequent doses of the vaccine can produce a boosting effect that can lead to a broader response within the immune system. The time between doses can allow for more of the boosting effect within the immune system. In a pandemic setting, it can be important to achieve high protection early, with a second dose given at a shorter interval. However, it may mean that a later dose for this boosting effect is needed as well. Again, this does not necessarily mean that an annual booster dose would be needed.

The data seen during this meeting have demonstrated that COVID vaccines continue to maintain high protection against severe disease, hospitalization, and death. Protection against infection, including asymptomatic or mild infection, appears to be lower in recent months. It is very difficult to distinguish the role of time since primary series and the impact of the Delta variant on this. While the data seen during this session reported through July, data through August will be shown at future ACIP meetings. It is important to monitor trends of effectiveness by severity of disease over time. Policy around booster doses requires continued evaluation of effectiveness, monitoring the impact of both time and variants, and the ability of booster doses to improve protection.

As a reminder, ACIP made recommendations in December 2020 and early 2021 for allocation of initial doses of COVID-19 vaccines in Phases 1a (LTCF residents, HCP), 1b (Adults ≥75 years of age, Frontline Essential Workers), and 1c (Adults ≥65 years of age, All Essential Workers, Adults 16-64 years of age with high-risk medical conditions). Early in the vaccine roll-out, ACIP voted for a risk-based approach to allocation of COVID vaccines, highlighting the highest-risk individuals. However, there was substantial variation in how this was implemented across states and jurisdictions.

In terms of WG considerations, the WG continues to emphasize that the top priority should be continued vaccination of unvaccinated individuals. Planning for delivery of booster doses to vaccinated individuals should not deter outreach for delivery of primary series to unvaccinated individuals. The WG also feels that the priority for booster dose policy should be the prevention of severe disease in at-risk population, and that simplicity and flexibility will be important to support equitable and efficient delivery of booster doses. It is also important to assure global vaccine availability. Uncontrolled spread globally that could result in new variants threaten control of the pandemic everywhere. In addition to global equity, policy around booster doses should consider equity in the US population as well. Access to booster doses may vary by population and setting. Lessons learned around equitable access in the early primary series roll-out should be applied to booster dose considerations. The WG highlighted that in addition to the immunogenicity data, they need to review available safety data for booster doses. The balance of benefits and risk for booster doses may vary by age and other factors. Any policy for booster doses needs to take this benefit/risk balance into account.

The WG emphasized that it is critical to wait for additional safety data and regulatory allowance for booster doses. At this time, the work group has discussed a risk-based approach for booster dose recommendations. To prevent severe disease in the most at-risk population, primarily LTCF residents and older adults, and any age criteria can be discussed with further reviews of the data. In terms of supporting a strained healthcare infrastructure, VE against severe disease remains high for HCP, but HCP with even mild disease may not be able to work. Prevention of mild disease takes on greater importance as a public health goal in this population. Time since vaccination with the primary series is also important. For many vaccines, a minimum interval is beneficial for boosting effect. However, the ability to benefit from this boosting effect extends well beyond that minimum interval.

ACIP will continue to review additional data during upcoming ACIP meetings, including manufacturer data on safety and immunogenicity of booster doses and data on effectiveness, breakthrough infections, and epidemiological data through August. The WG and ACIP will continue to have further discussions around feasibility, implementation, and the balance of benefits and risk by age group and by population. ACIP can meet again in mid-September to review the data just mentioned, and then can have a subsequent ACIP meeting following FDA authorization for any booster doses for a possible vote around populations for use. In closing, the following questions were posed for ACIP discussion:

1. Does ACIP agree with the proposed risk-based approach for COVID booster dose recommendations that the WG discussed?
2. What other questions would be important for ACIP to address?

Prior to opening the floor for discussion, Dr. Cohn emphasized for those who were listening to this meeting that while ACIP was discussing the potential for using booster doses in the future, at this time ACIP and CDC strongly advise against giving individuals an additional dose outside of the already-recommended and authorized recommendations for immunocompromised persons. She called upon Dr. Demetre Daskalakis, CDC's Deputy Incident Manager for the Vaccine Task Force, to share information on what CDC has been telling its partners and jurisdictions around the appropriate use of vaccine. Dr. Daskalakis prefaced this by emphasizing that COVID vaccines are a lot different than other vaccines and drugs that come to the market. Specifically, they are distributed by the US government and are under provider agreements that state very clearly that providers must administer the vaccines in accordance with all program requirements and recommendations of the CDC, ACIP, and FDA. Notably, this applies to both EUA and FDA-approved COVID vaccines. Accordingly, use of the products outside of those that

have been approved and authorized by the FDA (e.g., off-label) is not recommended. It is important to remember that this vaccine is much different than other vaccines coming to the market, because it also would violate the provider agreement and could expose providers to the following risks. First, administration of the product off-label or not following FDA, CDC, and ACIP guidance may not be covered under the PREP Act declaration. Therefore, providers may not have immunity from claims. Second, individuals who receive an off-label dose may not be eligible for compensation under the CICP. As mentioned earlier, this vaccine under a BLA would still be covered under the CICP. If a patient experiences an AE with a vaccine used off-label or off-recommendation, they may not be covered under this program. Importantly, this is a condition of the agreement and off-label doses would be in violation of the CDC program provider agreement, which potentially could impact the ability of the provider to remain a provider in the CDC program. Third, administration fees may not be reimbursable by payers if the vaccine is used off-label or outside of FDA and ACIP guidance.

Summary of Discussion

- There seemed to be general agreement among ACIP members with the proposed risk-based approach for COVID booster dose recommendations that the WG discussed. However, it was noted that a risk-based approach lends itself toward complexity. This could be challenging in terms of implementation, which speaks to the need for some level of simplicity. Liaison members also emphasized the importance of simplicity.

- Other comments, questions, and issues raised as being important for ACIP to address included the following:

    - Pregnant women as a group at increased risk of COVID disease
    - Lessons learned and data regarding equity among a variety of groups (e.g., younger communities of people of color, Latinx communities, Black communities, indigenous people, incarcerated populations and other congregated settings, et cetera), especially from partners and others responsible for distribution, given that much seems to have been based on local decisions that were driven by ease rather than equity
    - The importance of continuing to encourage vaccines for all who are unvaccinated in addition to focusing on booster doses, not either/or, and emphasizing that a recommendation for booster doses does not mean failure of COVD vaccines in any way—COVID vaccines are a huge success in terms of preventing hospitalizations and deaths
    - More information on the need for booster dosing in terms of whether it is an issue of waning immunity after the second dose of mRNA or first dose of the Janssen product, or if it is because of the Delta variant such that a modification of the current vaccines may be needed
    - Concern that those who received a third dose prior to approval by the FDA due to the premature White House announcement about booster doses might not be covered by the PREP Act, which highlights the critical need for recommendations to go through normal avenues
    - Liaison members expressed great concern with people getting vaccinated with an additional dose on their own or institutions providing extra doses to employees without any recommendations, and implored CDC to make clear statements and guidelines that can be discussed with patients regarding why getting an extra dose without a recommendation is not a good idea

- The impact of the increasing opening up of society with less stringent measures other than vaccine in terms of if/how that has affected transmission of the Delta variant and what appears to be lower efficacy over time
- Continue to recognize the data gaps
- Consideration should be given to taking a global approach to boosters will all available vaccine products versus a product-specific approach, with a request to federal colleagues to take that into consideration in interpreting the information around the PREP Act and enable ACIP to have flexibility to ensure the intent of any guidance
- Moving into the Fall with the potential for a booster dose, influenza vaccine, et cetera, perhaps the WG could consider how to help clinicians think through co-administration in order not to fall behind on influenza and other routine immunizations
- Continue to emphasize the difference between a third dose and a booster, given that they are getting interchanged in the media and in public discussions, which is causing a lot of confusion about who should get what
- Present data to ACIP on a regular basis about US contributions of vaccine to other parts of the world, knowing that there if there is COVID *anywhere*, there is potentially COVID *everywhere*
- Remember that some populations do not put their elders in long-term care and instead live more in multi-generational households
- It is important to remember that when a vial of this vaccine is opened, it has a limited shelf-life and this important resource should not be wasted
- Reset expectations for what these vaccines can do in terms of being remarkably effective in keeping people out of the hospital and from dying, but not expecting that they can/will prevent all infections

- Dr. Lee emphasized that it was clear that CDC, ACIP, all of their colleagues within the federal agencies, and the White House are committed to ensuring that they are able to protect the health of the public and they all have that same goal in mind. Given the uncertainties in the data and the many potential paths forward, ACIP's goal is to try to find a way to make sure they have as deep an understanding as possible of all of the issues in order to provide the best possible recommendations for the public. New data are emerging daily and ACIP will continue to meet in sessions that are open to the public to review and consider those data.

CERTIFICATION

Upon reviewing the foregoing version of the August 30, 2021 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADA	Americans with Disability Act
AE	Adverse Event
AESI	Adverse Events of Special Interest
AGS	American Geriatric Society
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaska Native
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
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
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
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ED	Emergency Department
EHR	Electronic Health Record
EtR Framework	Evidence to Recommendations Framework
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HCP	Health Care Personnel / Provider / Professional
HCW	Health Care Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus

HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
JAMA Cardiology	*Journal of the American Medical Association Cardiology*
J&J	Johnson & Johnson
KFF	Kaiser Family Foundation
LTCF	Long-Term Care Facilities
MASO	Management Analysis and Services Office
MedDRA	Medical Dictionary for Regulatory Activities
MIS	Multisystem Inflammatory Syndrome
MIS-A	Multisystem Inflammatory Syndrome in Adults
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*
NOS	Newcastle-Ottawa Scale
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PICO	Problem/Population, Intervention, Comparison, Outcome
PIDS	Pediatric Infectious Disease Society
PREP Act	Public Readiness and Emergency Preparedness Act
PT	Preferred Terms
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
RSV	Respiratory Syncytial Virus
SAB	Spontaneous Abortions
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
SMFM	Society for Maternal-Fetal 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
VE	Vaccine Effectiveness
VIS	Vaccine Information Sheet
VOC	Variant of Concern
VOI	Variant of Interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization