MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

MAY 12, 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 the regularly scheduled quarterly meeting of the Advisory Committee on Immunization Practices (ACIP) on May 12, 2021. The meeting took place remotely via Zoom and teleconference. This document provides a summary of the meeting, which focused on a variety of topics pertaining to COVID-19 vaccines, including the recent authorization of/vote on Pfizer-BioNTech COVID-19 vaccine in adolescents 12-15 years of age, thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination, safety and effectiveness updates, and an update on emerging SARS-CoV-2 variants and vaccine considerations.

WEDNESDAY: MAY 12, 2021

WELCOME AND INTRODUCTIONS

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

Dr. Amanda Cohn (ACIP Executive Secretary) welcomed everyone and noted that an agenda for the day soon would be posted to the ACIP website. She indicated that there would be an oral public comment session at approximately 2:00 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-2021-0049. Further information on the written public comment process can be found on the ACIP website.

As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but are prohibited from participating in committee votes. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to that company. ACIP members stated COIs at the beginning of the meeting. A vote was taken during this meeting on Pfizer COVID-19 Vaccine for adolescents 12-15 years of age.

ACIP is accepting applications for new membership for the term beginning July 1, 2022. Applications are being sought from all fields of public health, internal medicine, obstetrics and gynecology (OB-GYN), pediatrics, infectious diseases, and consumer representation. Applications should be submitted by July 1, 2021. Further information and the application can be found on the ACIP website at https://www.cdc.gov/vaccines/acip/apply-for-membership/index.html. Dr. Cohn then introduced Dr. Sam Posner, Acting Director of the National Center for Immunization and Respiratory Diseases (NCIRD), to say a few words to members of the committee and to the public.

Dr. Sam Posner (NCIRD Acting Director) welcomed attendees to this emergency meeting, thanked them for their time and commitment to the ACIP, and took a few minutes to provide an update on some leadership transitions within the NCIRD. As many may already be aware, Dr. Messonnier has resigned from her position as Director of NCIRD effective Friday, May 14, 2021. Dr. Posner will continue to serve as the Acting Director for NCIRD until a permanent placement has been hired. As seen over the past year, the ACIP plays an essential role in the collective efforts to protect people from vaccine-preventable diseases. He thanked the members for their commitment to the scientific rigor and ethical and equitable health outcomes. Service on this committee has been extremely demanding during the COVID-19 pandemic, and CDC appreciates the members' stewardship of this historic and influential group. He then took a few minutes to recognize Dr. Messonnier and her amazing contributions to public health.

Many in the formal and informal ACIP community have worked with Dr. Messonnier for many years and are familiar with the outstanding contributions to public health she has made during her CDC career. Many members and their organizations have worked with her on some of these accomplishments. Dr. Messonnier began her career at CDC over 25 years ago as an Epidemic Intelligence Service (EIS) Officer and became involved with emergency response early on as one of the staff involved in the 2001 intentional Anthrax release. She has built extensive experience in prevention and control of bacterial meningitis and played a pivotal role in the successful public-private partnership to develop and implement a low-cost vaccine to prevent epidemic meningococcal meningitis in Africa. As Director of NCIRD, Dr. Messonnier oversaw strategies to counterthreats like seasonal and pandemic influenza and has led the center through the recent measles resurgence and the emergence and cyclical outbreaks of acute flaccid myelitis (AFM). Since the beginning of the pandemic, in collaboration with the ACIP and CDC's partners across public health and the state, tribal, and local, and territorial governments, Dr. Messonnier has led teams to achieve incredible things, including deploying multiple vaccines in under one year and building the information infrastructure to provide real-time data for vaccination coverage and vaccine safety data.

Dr. Messonnier is going to continue her work in public health as the Executive Director of Pandemics and Health Systems for the Skoll Foundation. She has valued the singular purpose and role of the ACIP and the varied perspectives that all of the members and the public bring to the CDC and its national immunization program. On behalf of the entire center leadership team, Dr. Posner thanked the entire ACIP for their continued service, with special thanks to Dr. Cohn and Dr. Romero for giving him a few minutes to provide this update.

Dr. Romero (ACIP Chair) said that on his behalf and on behalf of all the members of the ACIP, Dr. Messonnier would be greatly missed. She has been a role model for them and they appreciate all of her hard work during her tenure at the CDC. He then conducted the roll call during which one conflict of interest (COI) was declared by voting member Dr. Sharon Frey, who is the Site Principal Investigator (PI) at St. Louis University for the Moderna and Janssen SARS-CoV-2 vaccine trials in adults. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Overview

Dr. Doran Fink (FDA/DVRPA/CBER) explained that the purpose of this ACIP meeting was to consider the data that supported FDA authorization of the Pfizer-BioNTech COVID-19 vaccine for use in adolescents 12 through 15 years of age. These data were generated from a placebo-controlled study involving over 2200 participants, over 1100 of whom received the Pfizer-BioNTech COVID-19 vaccine and approximately 660 of whom had at least 2 months of follow-up after completion of the vaccination series. The evidence for vaccine effectiveness (VE) in this age group came from two sources of data, first an immunobridging analyses showing that neutralizing antibody responses elicited by the vaccine in adolescents 12 through 15 years of age were not inferior to those elicited by the vaccine in adults 18 through 25 years of age. Additionally, the study evaluated protection against COVID-19 of any severity for the vaccine versus the placebo control. There were zero cases of COVID-19 in vaccine recipients starting from 7 days after completion of the vaccination series. The safety of the vaccine was evaluated in all of the study participants and compared to the placebo control. It also was compared to the safety profile of the vaccine in study participants 18 through 25 years of age in the population that supported the original Emergency Use Authorization (EUA) of the vaccine in December 2020. Additionally, FDA evaluated longer-term safety data from all adult participants in the clinical trial who were 18 through 55 years of age and included in the EUA safety population. The safety evaluation did not raise any safety concerns for use of the vaccine in individuals 12 through 15 years of age beyond reactogenicity events that had been described previously with older age groups.

Introduction

Dr. Keipp Talbot (ACIP, WG Member) introduced the COVID-19 Vaccines WG session, reporting that the WG continues to meet weekly. Recent topics covered have included the clinical trial data for the Pfizer-BioNTech COVID-19 vaccine for adolescents, GRADE (Grading of Recommendations, Assessment, Development and Evaluations) and EtR (Evidence to Recommendations) Framework for the Pfizer-BioNTech COVID-19 vaccine for adolescents, clinical considerations for the use of COVID-19 vaccines in this age group, and safety updates. The major update is that the FDA an EUA on May 10, 2021 for use of the Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 Disease for individuals 12-15 years of age. She indicated that this emergency ACIP meeting was convened to hear presentations on the related safety, immunogenicity, and efficacy of BNT162b2 in persons 12-15 years of age; GRADE of the Pfizer-BioNTech COVID-19 vaccine; the EtR Framework on the Pfizer-BioNTech COVID-19 vaccine in adolescents; clinical considerations; and public comments and for ACIP to vote on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12-15 years of age. Following the vote, additional presentations would include an update from TTS following the Janssen COVID-19 vaccine, an update from the Vaccine Safety Technical (VaST) WG, an update on the COVID-19 VE studies, and an update on emerging SARS-CoV-2 variants and the implication for vaccines.

Dr. Talbot also took a moment to talk about the children in the US who have been part of this pandemic whether they have experienced infection, lost loved ones, lost parents, been out of school, and not been able to engage in their extracurricular activities. For many children, being out of school has resulted in lack of a safe place and/or food. Given all of that, she was happy that they were finally beginning to talk about the children and returning their lives to normal.

Safety, Immunogenicity, and Efficacy of BNT162b2 in Persons Aged 12-15 Years

Dr. John Perez (Pfizer) presented the safety, immunogenicity, and efficacy of Pfizer's COVID-19 vaccines in subjects 12-15 years of age. Pivotal study C4591001 was initially an adult study. Once acceptable tolerance in adults was established within the original study, Pfizer amended the protocol to allow inclusion of subjects 16-17 years of age and subsequently 12-15 years of age. The same dose and schedule were used as had been used for adults, without further dose-finding, in order to generate data to understand whether people 12-15 years of age could be included in pandemic COVID-19 immunization programs. The data presented during this session were from Dose 1 to 1 month post-Dose 2 in persons 12-15 and 16-25 years of age, and from Dose 1 to the data cut-off point of 13 March 2001 in persons 12-15 years of age. Data from subjects 16-25 years of age were used for the safety comparisons and immunobridging purposes.

The Phase 2/3 safety study began on July 27, 2020. Two doses of vaccine were given 21 days apart and then active surveillance COVID-19 was undertaken. Anyone who had potential COVID-19 symptoms triggered a telehealth or in-person visit and a nasal swab was performed. Reactogenicity was measured 7 days after each dose of vaccine using an electronic diary. This was done in a subset of individuals for 16 and above and for all participants 12-15 years of age. Non-serious adverse events (SAEs) were measured through 1 month post-Dose 2, SAEs for 6 months post-Dose 2, and deaths throughout the study for all participants. Overall, there were 2260 persons 12-15 years of age and 1097 persons 16-25 years of age. Subjects with a history of symptomatic COVID-19 or multisystem inflammatory syndrome in children (MIS-C) were excluded.

Looking at the demography, the vaccine and placebo groups were well-balanced with the demographic variables of sex, race, ethnicity, and country. Roughly half the group was female, about 86% were white, 5% were Black or African American, 6% were Asian, and about 12% were Latino. All of the subjects in the 12-15 year old cohort were from the US. In the 16 to 25 year old group, about 71% were from the US and the rest were from a smattering of other countries included in the trial.

Regarding reactogenicity in the 12-15 year old and 16-25 year old groups, local reactions by maximum severity within 7 days after each dose in the two age cohorts for Dose 1 and Dose 2 are reported for redness, swelling, and pain at the injection site. Severity is measured from Mild to Grade 4. Within each reactogenicity, vaccine is compared to placebo for each of the two age cohorts. Pain at the injection site was the most frequent. Local reaction reported in the study was 86.2% in the 12-15 year-old group with the first dose and decreased to 78.9% with the second dose. Most of the reactions were reported to be mild to moderate in severity. There is about 5% to 7% reporting of redness and swelling for Dose 1 and for Dose 2.

Turning to systemic events by maximum severity within 7 days after Dose 1, 10.1% of the 12-15 year old age group reported a fever compared to 7.3% in the 16-25 year old group. Fatigue, headache, and chills also were frequently reported in this age cohort. Vomiting and diarrhea were reported at similar frequencies to placebo. Muscle pain and joint pain were reported as well, but the frequency was slightly higher in the 16-25 year old group compared to the 12-15 year old group. For Dose 2, the frequency of fever increased from 10% with the first dose to 19.6% with the second dose. Similarly, fatigue, headache, and chills also increased with the second dose. For vomiting and diarrhea, there was really no increase. Muscle and joint pain also increased with the second dose, but were higher in the 16-25 year old group compared to the 12-15 year old. This is precisely the same pattern seen in individuals 16 years of age and above in the entire study.

To summarize local and systemic events in Phase 3 within 7 days of each dose in the 12-15 year old group (N=2254), pain at the injection site was the predominant local reaction and it was more prominent with the first dose. From a severity perspective, local reactions were mostly mild to moderate. Systemic events were predominantly fatigue, headache, chills, muscle pain, fever, and joint pain. These were more prominent after the second dose, but also were mostly mild to moderate in severity.

In terms of adverse events (AEs) reported in the Phase 3 study of 12-15 year olds from Dose 1 to one month post-Dose 2, 6% in the vaccine group reported AEs compared to 5.9% in the placebo group. In the 16-25 year old group, 10.8% recorded AEs compared to 8% in the placebo group. In both age groups, there were slightly more related AEs reported in the vaccine as compared to the placebo group. There were similar rates in both age groups for any SAE, related SAEs, and withdrawal due to AEs. There is a similar range of rates between the vaccine and placebo, with low rates for all of these events. In terms of withdrawal due to AEs, there was one subject in the vaccine group in the 12-15 year old cohort who had no past medical history and developed a fever the day after vaccination of 104.7. The fever abated and resolved the next day after vaccination without sequala. The patient remains in the study and is being followed for safety. No deaths have been reported in the study.

Continuing with the 12-15 year old subjects from Dose 1 to the cut-off date of 13 March 2021, the pattern is the same as seen through one month post-Dose 2. In the vaccine group, 6.4% reported AEs compared to 6.3% in the placebo group. There were slightly more related AEs in the vaccine group compared to the placebo group. There continued to be low rates of any SAEs, no related SAEs, no additional withdrawals, and no deaths. Digging a little deeper, reporting AEs by ≥1% by system organ class (SOC) in 12-15 year olds one month post-Dose 2, there 6% overall in the vaccine group compared to 5.9% in the placebo group. The difference between vaccine and placebo is driven by 3 SOC classifications, including general disorders, gastrointestinal disorders, and nervous system disorders. These are the SOC classifications where reactogenicity AEs would be recorded. For example, the general disorders SOC is where injection-site reactions and system reactions of fever and fatigue would be reported. That is exactly what was observed in that SOC. The gastrointestinal disorders is nausea and diarrhea would be reported. Nervous system disorders is where headache is being reported.

The same pattern is observed looking at AEs ≥1% by SOC in the comparison group of 16-25 year olds, with 10.8% reporting an AE in the vaccine group compared to 8% in the placebo group. That difference is being driven by similar organ class reactogenicity events being reported as AEs. The new SOC with this age cohort is the musculoskeletal and connective tissue disorders SOC, which is where myalgias or arthralgias would be reported, with the same pattern between 12-15 and 16-25 year olds. Continuing to follow individuals to the cutoff date of

the 13 March 2021, not much more is picked up than seen one month after the second dose. Again, most of the AEs being recorded are in the general disorders, gastrointestinal, and nervous system disorders. The differences are being driven by injection-site reactions and some systemic reactions. No additional types of AEs were picked up with further follow-up.

One AE that was associated with the vaccine was lymphadenopathy in the 12-15 year olds. Overall, there were 9 at 0.8% in the vaccine group and 2 cases in the placebo group at 0.2%. Just focusing on those that were related to vaccination by the investigator, there were 7 cases or 0.6% compared to the placebo group of 0.1%. These were predominantly left axillary or left cervical lymphadenopathy. As a reminder, vaccination was given in the non-dominant arm, which in most individuals would be the left arm. Onset was within 2 and 10 days after vaccination. The duration was 1 to 10 days, where it was reported. To compare adults 16-55 years of age, 52 participants (0.4%) in the vaccine group compared to 2 participants in the placebo group had lymphadenopathy events reported up to the unblinding data and assessed by the investigators as related to study intervention. The majority of these events occurred in the arm or the neck region. They were reported with 2 to 4 days after vaccination, typically after Dose 2 and typically resolving within 1 week of starting.

Turning to SAEs by SOC and preferred term from Dose 1 to the data cutoff date of the 13 March, overall there was a low rate of SAEs reported. In the vaccine group, there were 5 events reported giving a rate of 0.4%. In the placebo group, there were 2 events reported giving a rate of 0.1%. One thing to notice about these data is that many of the AEs were reported by a single individual. For example, abdominal pain, constipation, and neuralgia was reported by 1 individual. This individual presented with abdominal pain and had multiple physical examinations and laboratory evaluations for these complaints. Ultimately, a diagnosis of functional abdominal pain was made. In the psychiatric disorders, there were reports of depression, anxiety, and suicidal ideation. All of these individuals have a history of depression and/or anxiety that was after the time of vaccination. The individuals in the depression and suicidal ideation case had been on a selective serotonin reuptake inhibitor (SSRI) 1 to 2 months before vaccination. The subject with depression and anxiety had a history of depression, was being treated with SSRIs, and had an extensive history of multiple anxiety disorders. As a reminder, there were no deaths reported in the study.

Regarding efficacy and immunogenicity, in the follow-up time after Dose 2 in the 12-15 year olds, total exposure from Dose 2 to the cut-off date was divided into <1 month, 1 to 2 months, 2 to 3 months, and >3 months. Of the vaccine group, 54.1% had between 2 and 3 months of follow-up at the time of the analysis, with an additional 4.2% having greater than three months after the second dose at the time of this analysis. Overall, 98.3% of the subjects had at least 1 month of follow-up time in the study.

In terms of the immune response and the geometric mean titers (GMTs) of the SARS-CoV-2 neutralization assay (NT50) and subjects from the two age cohorts, in this particular assay, values of 20 and above would be measurable and valid assay results. Before vaccination and in the placebo group, there was essentially no measurable neutralization results. However, 1 month after the second dose, in the 12-15 year olds, GMT increased to 1283, and in the 16-25 year olds, the GMT increased to 730.8. Therefore, the vaccine was able to generate potent neutralization responses in both groups.

Non-inferiority between 12-15 and 16-25 years of age was met. This was the primary endpoint to evaluate immunobridging between the two age cohorts. The neutralization titer in the 12-15 year-olds one month after the second dose was 1239.5. This analysis only included people who had no signs of infection prior to or during the study, so in that group, 1239.5 was the GMT. That compared to a GMT of 705.1 in the 16-25 year olds. Divide 1239 by 705, the geometric ratio is 1.76 with a confidence interval of 1.47 to 2.10. Non-inferiority is declared at the lower bound at the 95% confidence interval at >0.67; 0.67 is the natural log of 1.5, which is the non-inferiority margin used for this analysis. That 1.47 is much greater than 0.67, and hence the pre-defined non-inferiority margin in this study was met. Because the lower limit of the 95% confidence interval to GMR is >1, that indicates a statistically greater response in the 12-15 year old group compared to the 16-25 year old group.

Efficacy was assessed from a descriptive perspective looking at subjects without evidence of infection prior to 7 days after the second dose. In the vaccine group, there were no cases of COVID-19 in individuals vaccinated with BNT162b2. In the placebo group, 16 individuals developed COVID-19. That calculates out to a vaccine efficacy of 100%, with a 95% confidence interval of 75.3% to 100%. In this study, there were no severe COVID-19 cases. Looking at individuals with or without evidence of infection prior to 7 days after Dose 2, an additional 2 cases were picked up in the placebo group for a total of 18 cases in the placebo group and zero cases in the vaccine group. This calculates out to a vaccine efficacy of 100%, with a tighter 95% confidence interval. There were no severe COVID-19 cases in this analysis.

Overall, from a safety perspective, reactogenicity was found to be well-tolerated in subjects 12-15 years of age and showed a very similar pattern to what was seen in the 16-25 year olds. Pain at the injection site, fatigue, headaches, chills, joint pain, and muscle pain were the most predominant as well as fever. Increased systemic events after dose 2 was similar to that seen with 16-25 year olds. AEs overall were relatively few. The highest incidence was in the SOC of General Disorders and Administration Site Conditions, reflecting local and systemic reactogenicity events. Lymphadenopathy was identified as related to vaccination and there were no related SAEs and no deaths reported in the study.

In terms of immunogenicity and efficacy, the immune response in the Pfizer-BioNTech COVID-19 vaccine in terms of our SARS-CoV-2 50% neutralization titers in adolescents was non-inferior to and, in fact, exceeded the immune response in young adults 16-25 years of age, which provides immunobridging between adolescents in this pivotal study. In the adolescent group, efficacy analyses based on the cases reported from at least 7 days after Dose 2 through the data cutoff date, the observed VE was 100% for individuals without evidence of prior SARS-CoV-2 infection, and 100% of those with or without evidence of prior SARS-CoV-2 infection before their vaccination regimen. There were no severe cases reported in the 12-15 year old age cohort as of the data cutoff date. Overall, these immunogenicity and efficacy data strongly support the vaccine use in adolescents 12-15 years of age.

Summary of Discussion

- ACIP expressed an interest in hearing more safety and immunogenicity by race and ethnicity, which Pfizer has not performed.

- The number of children with psychiatric diagnoses raised concerns for ACIP members. CDC called upon Dr. Fink, FDA, to speak further to these. He indicated that FDA noted the numerical imbalance in SAEs related to worsening of depression that was ongoing at the time of study enrollment and evaluated the narratives of these cases provided by the

vaccine manufacturer. FDA also noted the proportion of the study population that entered the study with active psychiatric diagnoses, including most commonly attention-deficit/hyperactivity disorder (ADHD), but also a fair number of subjects (~4%) had a history of ongoing depression. FDA also noted that in 3 of the SAEs that were reported in vaccine recipients, an SSRI medication had been initiated approximately 1 to 2 months prior to study enrollment, which Dr. Perez mentioned in the Pfizer presentation just given. These SSRIs do carry a boxed warning in the FDA package inserts that they may worsen depression and cause suicidal ideation in adolescents specifically, so FDA recognizes these exposures to SSRIs and potentially contributing factors that offer the reasonable explanation for the events. The other SAEs that occurred in a subject who was not taking an SSRI, according to careful review of the narrative, revealed other psychosocial factors that were described by the participant that FDA felt constituted a reasonable explanation for the event. Taken together, although there was a small numerical imbalance with zero cases in the placebo group, the FDA did not see evidence to support a causative role of the vaccine in these events.

- ACIP expressed an interest in whether Pfizer would be assessing co-administration with other vaccines in this age group. Pfizer indicated that they have no plans to do so currently, but plans frequently change with their COVID-19 program.

GRADE: Pfizer-BioNTech COVID-19 Vaccine

Dr. Megan Wallace (CDC/NCIRD) presented GRADE for the Pfizer-BioNTech COVID-19 vaccine. The policy question under consideration for this analysis was, “Should vaccination with Pfizer-BioNTech COVID-19 vaccine be recommended for persons 12-15 years of age under an Emergency Use Authorization?” In terms of the components of the PICO question, the population under consideration is persons 12-15 years of age. The intervention is 2 doses of the Pfizer-BioNTech COVID-19 vaccine 21 days apart. The comparison is no vaccine. The WG identified 7 outcomes as the most important for the policy question: Symptomatic lab-confirmed COVID-19, hospitalization due to COVID-19, MIS-C, SARS-CoV-2 seroconversion to a non-spike protein, asymptomatic SARS-CoV-2 infection, SAEs, and reactogenicity.

The WG felt that the outcomes that needed to be considered for policy should be modified when considering COVID-19 vaccines for adolescent and pediatric populations. Symptomatic laboratory-confirmed COVID-19 remains a critical benefit. Given that the size of pediatric trials is smaller, direct efficacy data may not be robust. These studies were designed to assess immunobridging, which can be considered in support of efficacy. Hospitalization due to COVID-19, which is less common in children, remains an outcome but is important instead of critical. Death, which is rare in children, has been replaced with MIS-C, but deaths will still be monitored as part SAEs. For harms, SAEs remain a critical outcome and reactogenicity remains an important outcome.

Of note, in the case of vaccine trials, hospitalization due to COVID-19 and MIS-C are less common. The Phase 3 trials may not be designed or powered to evaluate differences between treatment groups. The WG does not necessarily expect to have direct evidence for these outcomes at this point, and to some degree, can infer that decreases in symptomatic COVID-19 would also translate into decreases in hospitalizations and MIS-C. There were no COVID-19 hospitalizations or cases of MIS-C among vaccinated or placebo participants in the available body of evidence, so these outcomes were not included in the evidence profile Dr. Wallace presented. Additionally for the outcomes of seroconversion and asymptomatic infection, no data are currently available, so these outcomes also were not included in the evidence profile.

A systematic review was conducted to identify evidence related to the policy question. Published articles were identified published using a variety of databases and search terms to identify data on vaccination with a specific vaccine formulation under consideration that involved human subjects, reported primary data, included persons at risk for SARS-CoV-2 infection, included data relevant to the efficacy and safety outcomes being measured, and included data on the dose and timing under consideration. Additional sources were sought, including obtaining unpublished data from vaccine manufacturers. Over 5300 records were identified through database searching, and one record was obtained directly from the sponsor of the Phase 2/3 trial. Ultimately, one resource was included in the evidence synthesis.

GRADE evidence type assesses the certainty of estimates from the available data. The highest level of certainty is Type 1 (high certainty), which means the WG is very confident the true effect lies close to that of the estimate. Type 2 (moderate certainty) 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 (low certainty) means that the WG's confidence in the effect estimate is limited. Type 4 (very low certainty), means that the WG has little confidence in the effect estimate. The evidence type is not measuring the quality of individual studies, but rather how much certainty the WG had in the quantitative estimates of effect across each outcome.

Initial evidence type is determined by the study design. A body of evidence from randomized control trials (RCTs) starts with an initial evidence Type of 1, indicating high certainty. A body of evidence from observational studies starts with an evidence Type of 3, indicating low certainty. The evidence type could be downgraded due to risk of bias, inconsistency, indirectness, or imprecision. Other considerations could downgrade or upgrade the evidence type.

To review the evidence of benefits, for the critical outcome of symptomatic COVID-19, one study provided data. This was the Pfizer-BioNTech Phase 2/3 RCT trial, and the data were attained directly from the sponsor. The data cutoff date was March 13, 2021. Primary analyses were performed for an evaluable efficacy population defined as all eligible randomized participants who received all vaccinations as randomized within the predefined window and have no other important protocol deviations as determined by the investigator, and who do not have evidence of prior SARS-CoV-2 infection. For these analyses, there were over 1900 persons, about 1000 per arm, who contributed 300 person years of observation, about 150 per arm. Secondary analyses included persons with prior infection. Analyses also were done for an all-available efficacy population, which includes all randomized participants who received at least 1 dose with outcomes counting any time after that. It may be helpful to think of the evaluable efficacy as similar to protocol analysis and all-available efficacy as similar to an intention-to-treat (ITT) analysis.

Using the evaluable efficacy population for all persons aged 12-15 years, there were zero cases among 1001 persons in the vaccine arm and 16 cases among 972 persons in the placebo arm, which resulted in a VE estimate of 100%. This is the outcome used for GRADE. Varying timing of outcome assessments and with inclusion of persons who had evidence of prior infection had little influence on the efficacy estimates. The Phase 2/3 trial was designed and powered to use immunobridging to evaluate efficacy. Immunobridging studies compare immunogenicity in a group of interest, for example, those age 12-15 years, with a comparison group in which efficacy has been demonstrated in clinical trials. For example, those aged 16-25 years. For the immunogenicity analyses, 209 participants aged 12-15 years and 186 participants aged 16-25 years were randomly selected from the vaccine and placebo arms of the trial for comparison. The immune response to vaccine was evaluated using the geometric mean ratio of neutralizing antibody titers comparing adolescents to young adults. Non-inferiority criteria are met when the

lower bound of the 95% confidence interval for the geometric mean ratio is not less than a preset value, which for this study was 0.67. The immune response to vaccine in adolescents aged 12-15 years was non-inferior to that observed in young adults aged 16-25 years, with a geometric mean ratio of 1.76 based on SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants without prior evidence of SARS-CoV-2 infection. In fact, antibody levels were significantly higher among adolescents aged 12-15 years than young adults aged 16-25 years.

For the sake of transparency, the WG also wanted to mention additional analyses from the study that compared seroresponse in adolescents and young adults. These analyses are considered exploratory because there is not yet an established immunological correlate of protection. Among participants without prior evidence of SARS-CoV-2 infection, 97.9% had at least a 4-fold rise in SARS-CoV-2 neutralizing titers from the vaccination to 1 month after Dose 2. There was a difference in proportions of participants who had at least a 4-fold rise because adolescents and young adults was 2.1%, but the difference was not significant.

Looking at the GRADE evidence table for the outcome symptomatic COVID-19, because the data were from an RCT, the evidence type started at 1. Regarding risk of bias, there was some concern related to blinding. Participants and study staff were blinded to assignments, but they may have inferred receipt of vaccine or placebo assignment based on reactogenicity. This was deemed unlikely to overestimate the efficacy results. Therefore, the WG considered the risk of bias to be not serious. Because there was only one study, there were no serious concerns of inconsistency. Some concern for indirectness was noted due to the short duration of observation and the available body of evidence. The VE efficacy observed at a median 2-month follow-up may be different from the efficacy observed with ongoing follow-up. However, in consideration with the strength of association, it is unlikely that the efficacy estimate for symptomatic COIVD-19, which changed substantially enough to fall below the FDA-defined efficacy threshold for licensure under an EUA to less than 50% efficacy. The WG also noted that longer-term efficacy from the adult RCT suggests that short-term efficacy will translate to longer-term efficacy. Further, the immunobridging data indicates that the immune response in adolescents is at least as strong as that observed in adults. This resulted in a final certainty of Type 1.

Regarding the data on GRADE for harm, the Phase 2/3 trial was the only study to provide data on SAEs. In terms of the raw data on a critical outcome of SAEs, in the Phase 2/3 trial, there were 5 events among the vaccine group and 2 among the placebo group. None of the events were considered to be associated with vaccination. Looking at the GRADE evidence table SAEs, the relative risk of SAEs between vaccinated and placebo was 2.5 a 95% confidence interval of 0.49 to 12.84. The certainty assessment was reduced one point due to serious concern of indirectness because the body of evidence does not provide certainty that rare SAEs were captured due to the short follow-up and sample size. There was also very serious concern for imprecision due to the confidence interval crossing the line with no effect and the width of the confidence interval containing estimates for which different policy decisions may be considered. This left the WG with a final certainty of Type 4.

Reactogenicity was evaluated using the same Phase 2/3 study. 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 worsening muscle pain, and new or worsening joint pain. In the Phase 2/3 study, Grade 3 local reactions or systemic events were reported in 10.7% of persons in the vaccine arm and 1.9% of persons in the placebo arm. Most of these events were Grade 3, with one Grade 4 event of pyrexia reported in a vaccine recipient. The relative risk for any Grade 3 or 4 event was 5.49 with a 95%

confidence interval from 3.51 to 8.58. There was no serious concern for risk of bias, inconsistency, indirectness, or imprecision. The final certainty was Type 1.

To summarize the WG's GRADE assessment for the Pfizer-BioNTech COVID-19 vaccine in adolescents, in terms of benefits, the available data indicate that the vaccine is effective for preventing symptomatic COVID-19 with direct efficacy data and supplemental immunobridging data with an evidence Type of 1. No data were available to assess the other potential benefits. In terms of harms, a total of 5 SAEs were observed in the vaccine arm and 2 in the placebo arm. There was concern for indirectness, and the wide confidence interval included both benefits and harms, so the evidence type was 4, indicating very low certainty. No SAEs were judged to be related to vaccination. Regarding reactogenicity, severe reactions were more common in vaccinated persons and 10.7% of vaccine recipients versus 1.9% of placebo recipients reported Grade 3 or 4 reactions. The evidence type for reactogenicity was Type 1.

In conclusion, the Phase 2/3 RCT of the Pfizer COVID-19 vaccine was conducted among persons aged 12-15 years in the US. The VE estimate for the Pfizer-BioNTech COVID-19 vaccine in adolescents was 100% for symptomatic laboratory-confirmed COVID-19. SAEs were more common among vaccine than placebo participants, but there was very low certainty in the estimates. No SAEs were judged to be related to vaccination. Grades 3 or 4 local or systemic reactions were more common among vaccine than placebo recipients and were reported by about 11% of vaccinated subjects. The certainty and estimates for critical benefits was Type 1, high. The certainty in the estimates for critical harms was Type 4, very low.

EtR Framework: Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12-15 Years

Dr. Sara Oliver (CDC/NCIRD) presented the EtR Framework findings for Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12-15 years. As a reminder, the EtR Framework allows the WG to describe the evidence to inform ACIP recommendations in a transparent manner. The policy question under consideration was, "Should vaccination with Pfizer-BioNTech COVID-19 vaccine (2-doses, IM) be recommended for persons 12-15 years of age under an Emergency Use Authorization?" As was just shown in GRADE, the PICO questions were updated with outcomes for adolescents. As a reminder, the EtR domains as questions about each of 7 domains: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. The intervention was updated with the Pfizer-BioNTech COVID vaccine given to adolescents aged 12-15 years and the problem as COVID-19 among adolescents aged 12 to 15 years.

For the public health problem question regarding whether COVID-19 among adolescents aged 12-15 years is of public health importance, the WG reviewed evidence on COVID incidence and burden estimates, COVID-associated hospitalization rates, COVID-associated mortality, MIS-C, and transmission. Based on the overall epi curve of the pandemic, there have been over 32 million cases of COVID reported to CDC, with the most recent 7-day moving average of 38,000 cases per day. Cases declined in recent weeks after a slight uptick in late March and early April.[1] In terms of trends among the adolescent population, much of the surveillance data in the US uses a 12-17 year age group, so much of the epi data will be presented with this age cutoff. Through the end of April, there have been over 1.5 million cases among adolescents 12-17 years of age.[2]

[1] https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases
[2] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime

In terms of the proportion of total COVID cases by age group throughout the pandemic, early in the pandemic, the older adults represented a larger proportion of cases. However, that proportion decreased in recent weeks. As more adults are vaccinated, adolescents aged 12-17 years make up a greater proportion of total cases. In April, 9% of cases were aged 12-17 years, which represents a larger proportion of total cases than adults 65 years of age and over.[3] However, it is known that diagnosed and reported cases are an underestimate. To better reflect the burden of COVID-19 the full impact of disease, CDC provides estimates of COVID-19 infections, symptomatic illness, and hospitalizations using a statistical model to adjust for cases that national surveillance networks are unable to capture for a number of reasons. For children and adolescents 5-17 years of age, there have been estimated 22 million SARS-CoV-2 infections, making up around 19% of all estimated SARS-CoV-2 infections.[4]

Looking at estimated rates of SARS-CoV-2 infections, symptomatic illness, and hospitalization rates per 100,000 population by age group, children and adolescents 5-17 years of age have the highest rates of infection and symptomatic illness. However, the proportion of symptomatic patients who are hospitalized are lower among children.[5] Moving to cumulative rates of COVID-associated hospitalizes for children and young adults from March 2020 through the end of March 2021 from COVID-NET, COVID-NET is a population-based surveillance system that collects data on laboratory-confirmed COVID-associated hospitalizations among children and adults through a network of over 250 acute care hospitals in 14 states. The rate for persons aged 12-17 years was 51 per 100,000 population. Rates for this age group have consistently been higher than those in persons aged 5-11 for most of the pandemic.[6]

To highlight recent hospitalization rates in this pediatric and adolescent population looking at the 3-week moving average rate of hospitalizations among children and adolescents, over the past 2 months, there has been a gradual increase in the hospitalization rate among adolescents 12-17 years of age. To provide some additional context to these hospitalization rates, cumulative COVID-19-associated hospitalization rates among adolescents 12-17 years by *MMWR* week were compared to the cumulative influenza-associated hospitalization rates during the H1N1 pandemic year from 2009 to 2010 from historic FluSurv-NET. Cumulative hospitalization rates for adolescents aged 12-17 years is 51.3 per 100,000 population and 23.9 per 100,000 population for H1N1 influenza. Then the last several influenza-associated hospitalization rates were added in for three of the most recent influenza seasons (2017-2018, 2018-2019, 2019-2020), ranging from 12 to 15 per 100,000. Of note, the influenza season starts at *MMWR* Week 40, so these accumulate over a shorter period of time.

To continue with COVID-NET, results from an investigation of 722 hospitalized adolescents, over half of whom were Hispanic or non-Hispanic Black, 31% had severe disease defined as requiring intensive care unit (ICU) admission or invasive mechanical ventilation during hospitalization. In addition, 61% of children had at least one underlying condition. The most common underlying conditions were obesity, asthma, developmental delay, and diabetes.

[3] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime
[4] Sources: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html; US Census Bureau, Population Division, 2020 Demographic Analysis (December 2020 release)
[5] https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html
[6] https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html

Moving COVID-related deaths, there have been nearly 580,000 deaths in the US, with the most recent 7-day moving average of 604 deaths per day. Between January 1, 2020 and April 30, 2021, there were 127 COVID-19 deaths among adolescents 12-17 years of age, which accounted for 1.3% of all deaths among adolescents during the same time period. While this sounds low, it is worth noting that this would still be in the top 10 causes of death among children in 2019, which is the last year that there are top 10 causes of death for comparison.[7]

Moving MIS-C, this is a severe hyperinflammatory syndrome occurring 2 to 6 weeks after acute SARS-CoV-2 infection and resulting in a wide range of manifestations and complications. Approximately 60% to 70% of patients with MIS-C are admitted to intensive care, and 1% to 2% die.[8],[9] There have been 3742 MIS-C cases reported to national surveillance as of early May. The median age was 9 years, with 21% of cases occurring in adolescents 12-17 years of age and 63% of cases occurred in children who were Hispanic or non-Hispanic Black. MIS-C has an estimated incidence of 1 to 8.5 MIS-C cases per million person-months.[10] While adolescents may have a slightly lower incidence of MIS-C compared with younger children, they generally present with more severe MIS-C compared with MIS-C patients aged 0-5 years. Both ICU admission and decreased cardiac function were more likely in patients 13-20 years hospitalized with MIS-C.[11]

Regarding adolescents in transmissions, some studies observed similar infection rates between children and adults, while others found lower infection rates among children compared to adults.[12],[13] Adolescents may be more likely to be infected than younger children. This is supported by data from several different methods, including contact tracing, test positivity, and population-based seroprevalence data.[14] Secondary transmission from adolescents can and does occur. While SARS-CoV-2 transmission among students is relatively rare, several studies suggest transmission is more likely within high school settings than in elementary school settings.[15],[16]

[7] https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Age-in-Years-/3apk-4u4f/data
[8] Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091
[9] Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic [published online ahead of print, 2021 Apr 6]. JAMA Pediatr. 2021;e210630. doi:10.1001/jamapediatrics.2021.0630
[10] Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. https://www.cdc.gov/mis-c/cases/index.html
[11] Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5(5):323-331. doi:10.1016/S2352-4642(21)00050-X
[12] Bi Q et al. Lancet Infect Dis. 2020;20(8):911-919
[13] CDC Science Brief: Transmission of SARS-CoV-2 in K-12 schools. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/transmission_k_12_schools.html
[14] Goldstein E et al. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. J Infect Dis. 2021 Feb 13;223(3):362-369.
[15] Larosa E et al. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020. Euro Surveill. 2020;25(49):2001911.

Multiple outbreaks and contact tracing investigations have demonstrated efficient transmission among children, adolescents, and young adults, including transmission to older more vulnerable household members.[17],[18] A recent publication in *Science* described results from a survey of over 1.5 million adults, including over 500,000 who are living with at least one child in school. The survey found that after adjusting for county-level incidence and other factors, but not necessarily school-based mitigation measures, living in a household with a child engaged in full-time in-person school was associated with a substantial increase in the odds of reporting a COVID-like illness, loss of taste or smell, or a positive SARS-CoV-2 test within the previous 14 days compared to those with children not attending in-person school. The association between COVID outcomes and reporting a child in the household was attenuated somewhat when that child was attending part-time schooling.[19]

In summary, adolescents 12-17 years of age are at risk of severe illness from COVID-19. There have been over 1.5 million reported cases and over 13,000 hospitalizations to date among adolescents 12-17 years. Overall, the hospitalization rate for COVID in this population is higher than the influenza-associated hospitalization rate for the same group during the 2009 H1N1 influenza pandemic. The clinical presentation of MIS-C is more severe in adolescents than in younger children. In addition, COVID in adolescents may also indirectly impact others' health. Adolescents contribute to transmission in households and communities, including older, vulnerable populations. Finally, adolescents represent an increasing proportion of recent COVID cases. Based on the review of these data, the WG felt that COVID disease among adolescents is of public health importance.

Moving to benefits and harms, the WG answered the questions, 1) How substantial are the desirable anticipated effects?, 2) How substantial are the anticipated undesirable effects?, and 3) Do the desirable effects outweigh the undesirable effects? To summarize the available evidence for benefits, overall efficacy of the vaccine was supported by both immunobridging data and clinical efficacy. The clinical trial for the Pfizer-BioNTech COVID-19 vaccine demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19 of 100% with a high certainty of evidence as just detailed in the GRADE presentation given by Dr. Wallace. Regarding the immunobridging data, the geometric mean ratio for antibodies in the 12-15 year olds compared to the 16-25 year olds was 1.76, which met the non-inferiority criteria. No hospitalizations due to COVID or MIS-C were reported by any trial participants.

In terms of potential harms, SAEs were reported in a higher proportion of recipients of vaccine versus placebo based on 5 SAEs in the vaccine group and 2 in the placebo group. This was graded at a very low certainty of evidence. Severe reactions were more common in the vaccine recipients, where a Grade 3 or higher reaction was reported by 10.7% of vaccinated versus 1.9% of the placebo group. This also was graded with a high certainty of evidence. No deaths were reported among any of the trial participants. Local reactions within 7 days were common, occurring in 91% of vaccine recipients, with pain at the injection site as the most common. Systemic reactions were common as well, with fatigue and headache as the most common. Most symptoms resolved within 1 to 2 days. Regarding other events of interest following the mRNA vaccines, no cases of anaphylaxis were reported in study participants 12-15 years of age. No cases of Bell's Palsy or facial paralysis were reported in adolescents. Among the study participants 12-15 years of age, 7 in the vaccine group that had lymphadenopathy compared to 1 (0.1%) participant in the placebo group. Most lymphadenopathy was local in the

[17] Lopez A et al. MMWR Morb Mortal Wkly Rep 2020;69:1319–1323
[18] Schwartz N et al. MMWR Morb Mortal Wkly Rep 2020;69:1457–1459
[19] Lessler J et al. Household COVID-19 risk and in-person schooling [published online ahead of print, 2021 Apr 29]. Science. 2021;eabh2939. doi:10.1126/science.abh2939

arm or neck region, occurred on the same side as vaccination, and was reported within 2 to 10 days after receiving the vaccine.

To summarize benefits and harms, the WG felt that the desirable anticipated effects were large, the undesirable effects were small, and that the balance favored the intervention, use of the Pfizer BioNTech COVID vaccine.

The questions assessed with regard to the values domain were: 1) Does the target population feel that the desirable effects are large relative to undesirable effects?; and 2) Is there important uncertainty about, or variability in, how much people value the main outcomes? The WG continues to review the scientific literature, news media, and reports. However, limited surveys have been conducted since authorization of the COVID vaccines. In terms of the overall proportion reporting positive vaccine intentions by month of data collection, surveys were conducted among adults asking about their intent to receive the vaccine for themselves. There has been a steady increase and intent to be vaccinated among adults. Surveys evaluating parents regarding their intent to have their children vaccinated have found that 46% to 60% of parents surveyed said they planned to get their children vaccinated.[20],[21],[22],[23] The most common reasons for not planning to vaccinate their children included not being sure it is safe, the vaccine was developed too quickly, that they do not trust information being published about the vaccines, or they do not have enough information.[2] Generally, parents reported a similar or slightly lower intent to vaccinate their children compared with the intent to vaccinate themselves.[3,4]

It was found that the intents to vaccinate children differed by parents' gender, age, and income status. Fathers were more willing to vaccinate their children than mothers. Older mothers were more willing to vaccinate their children than younger mothers. Higher-income households were more likely to report an intent to vaccinate, where lower-income households were twice as likely to say they were not sure about vaccinating their children compared to these higher-income households. When evaluating parents' intent for children to receive their vaccine, intent varied by race and ethnicity, which is similar to the overall intent to get vaccinated among adults. When adolescents were asked about their intent to get vaccinated, 51% reported that they would definitely or probably get vaccinated. Parents in this same survey, although not necessarily paired parents to the adolescents' interviewed, reported that 55% would definitely or probably get their adolescent vaccinated. Then parents were asked how concerned they were about their adolescent getting COVID-19 and asked if they were concerned about their adolescent having any side effects from the COVID-19 vaccines. Adolescents were asked these questions about themselves. In both samples, respondents reported moderate levels of concern about adolescents getting COVID and adolescents having side effects from COVID vaccination. Values for concern about the COVID vaccine side effects were slightly but significantly higher than values for concern about COVID disease in both populations.[24]

[20] Axios/Ipsos April 2-5; Axios/Ipsos April 16-19; Calarco and Anderson preprint; WebMD March 2021
[21] National Parents Union Survey January 2021
[22] Simonson M, Baum M, Lazer D, et al. The COVID States Project #45: Vaccine hesitancy and resistance among parents. OSF Preprints, 19 Mar. 2021. https://doi.org/10.31219/osf.io/e95bc
[23] Parents Together March 2021 Survey
[24] CDC/U Iowa Survey of Parents and Adolescents, April 2021

To summarize values, about half of parents say they are likely to get their adolescent vaccinated. The intent to vaccinate adolescents differed by parents' gender, race, and income. The intent to vaccinate adolescents were similar or slightly lower than parental intent to get vaccinated themselves. There was overall limited information on adolescent intent to get vaccinated themselves. However, one study did find that nearly 40% of adolescents said they would let their parents or caregivers decide if they would get the vaccine. When the WG asked if the target population felt that the desirable effects were large relative to undesirable effects, answers varied. Many felt that they were moderate to large but ultimately, most said that it varies. Not surprisingly, when asked if there was variability in how people value the outcomes, they felt that there was probably important or uncertainty or variability.

Moving to acceptability, the WG was asked, "Is the Pfizer/BioNTech COVID-19 vaccine acceptable to key stakeholders? A pulse survey was conducted of the jurisdictions in mid-April for their implementation planning for adolescents. Overall, most jurisdictions were taking a multi-pronged approach using existing provider networks, pediatric providers, and school-based clinics.[25] In addition, there was a survey late last year about physicians' willingness to administer the COVID vaccine in their practices. Overall, 97% of providers were willing to administer COVID vaccine. The largest perceived barrier to vaccination was parent or patient concern about the safety of COVID vaccines.[26] The CDC/Iowa survey of parents and adolescents mentioned earlier asked the location where parents would be the most comfortable receiving a COVID vaccine. Parents were the most comfortable being vaccinated at their regular doctor's office, with the local pharmacy as next.

To summarize acceptability, most jurisdictions are utilizing a variety of implementation strategies to vaccinate adolescents. Nearly all primary care providers surveyed are willing to provide COVID vaccines to their patients, and adolescents and their parents report their greatest comfort with receiving COVID vaccines at their primary care provider's office. The WG felt that yes, the Pfizer vaccine was acceptable to key stakeholders.

The primary question regarding feasibility was, "Is the Pfizer/BioNTech COVID-19 vaccine feasible to implement among adolescents aged 12-15 years? The objective of adolescent vaccination is to promote adolescent vaccination as quickly and equitably as possible, which will require a multi-pronged approach. Jurisdictions and providers already are vaccinating adolescents 16-17 years of age. Current implementation plans to expand this down to 12 years of age include leveraging current COVID vaccine infrastructure and adapting over time. This would include an early Summer sprint in May-June, followed by increasing access in June and July, and a back-to-school campaign later in the Summer at the start of the school year. This will require a stepwise approach to increasing vaccine access for adolescents. Phase 1 involves augmenting the existing public health infrastructure for vaccination, which includes all current COVID vaccine providers opening up to allow vaccination for children 12 years of age and over. Phase 2 involves strategically adding providers serving adolescents, including larger provider groups in children's hospitals as well as smaller providers needed to increase access, such as those in areas with high social vulnerability and rural areas. Phase 3 includes utilizing school-based vaccination programs in partnership with public health, pharmacies, and third parties, as well as through Health Resources and Services Administration (HRSA) sites.

[25] Source: Jurisdiction data call survey – 05/03/21-05/06/21. n=46
[26] Kempe A, et al. Primary Care Physicians' Willingness and Capacity to Contribute to COVID-19 Vaccine Delivery. Unpublished.

Increasing access to primary care providers serving adolescents has the benefits of utilizing trusted providers for providing information and education about COVID vaccines, as well as vaccinating against COVID and managing routine vaccinations, particularly as students return to school in the fall. Pharmacies and HRSA sites have a broad footprint across the nation and can rapidly expand to provide COVID vaccines for adolescents. School-based vaccinations have the benefit of reaching adolescents in their own communities, as well as being trusted sources of information for communities. Schools can partner with Federally Qualified Health Center (FQHCs), pharmacies, and/or public health to hold targeted programs to improve coverage, particularly as students return.

There are a few additional implementation considerations. First, current cold-chain storage requirements and package sizes may limit the availability of COVID vaccines, particularly to smaller primary care providers. There are recent updates to both cold-chain and package size requirements that could improve this, however. Second, for the short-term, Pfizer could be the only vaccine available for this population. And jurisdictions and vaccine providers may need to determine a process for allocation of this product of this age group. Third, there are no federal legal requirements for caregiver consent of COVID-19 vaccine or any other vaccine. However, COVID vaccine must be administered according to applicable state and territorial vaccination laws, including those related to a consent. Sites administering vaccines should follow the current state and jurisdictional policies and practices other routine immunizations in this age group. The WG felt that overall, the Pfizer vaccine is feasible to implement among adolescents.

The primary question related to resource use was, “Is the Pfizer/BioNTech COVID-19 vaccine, given to adolescents aged 12-15 years, a reasonable and efficient allocation of resources? The US government has purchased 600 million doses of mRNA vaccines, with 300 million doses of the Pfizer vaccines. These vaccines will be available at no cost.[27] There are no studies that evaluate the cost-effectiveness around the use of COVID vaccines among adolescents. However, vaccinating adolescents may allow for a greater confidence and a safe return to schools. Vaccination could lead to reduced work and school absenteeism related to COVID quarantine and isolation. There was one study that estimated that over time, school closures could have a total economic loss as high as $15 trillion over a lifetime.[28]

The WG concluded that cost-effectiveness may not be a primary driver for decision-making during a pandemic and for a vaccine used under EUA. However, it will need to be reassessed for future recommendations. The use of COVID vaccines in as many populations as possible, including adolescents, will be important to returning to pre-pandemic activities. This return to pre-pandemic activities is likely to have an overall positive economic impact. The WG felt that, yes, during the pandemic the use of the Pfizer vaccine among adolescents is a reasonable and efficient allocation of resources.

For the domain of health equity, the primary question posed was, “What would be the impact of the Pfizer-BioNTech COVID-19 vaccine, given to adolescents aged 12-15 years, on health equity?” 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. The WG identified groups who might be disadvantaged in relation to COVID-19 disease burden or receipt of a COVID vaccine using the PROGRESS-Plus Framework (Place of residence, race or ethnicity, gender or sex, socioeconomic

[27] https://www.hhs.gov/about/news/2021/02/11/biden-administration-purchases-additional-doses-covid-19-vaccines-from-pfizer-and-moderna.html

[28] https://www.oecd.org/education/the-impact-of-covid-19-on-education-insights-education-at-a-glance-2020.pdf; https://www.cnbc.com/2020/09/08/school-disruption-could-cost-the-us-economy-15point3-trillion-oecd.html

status, disability).[29] This process has been used previously for other EtRs. Evidence related to this group was gathered through a review of scientific and GRADE literature, as well as the CDC COVID-19 response data and resources. Groups have been identified as being disadvantaged in relation to COVID-19 disease burden or receipt of the Pfizer BioNTech COVID vaccine. Dr. Oliver shared a list (slide 81) and a grid (slide 82) demonstrating where published peer-reviewed literature is available describing either disproportionate COVID-19 morbidity and mortality among adolescents or among adults, which can be inferred may apply to adolescents. Additionally, grid includes where data are available demonstrating general barriers to healthcare in each of these populations. It is important to point out that there is diversity within each of these groups, as well as significant intersections between these groups. For example, Black and indigenous adolescents and adolescents who are LGBTQ+ (lesbian, gay, bisexual, transgender, questioning, and others) are considered overrepresented among the homeless youth populations.

As of May 4th, a lower percentage of Black and Hispanic or Latino adults were fully vaccinated compared with the percentage of these groups in the overall population. While these data are specific to adults, similar patterns may be seen in adolescents.[30] Again, there are two characteristics of the Pfizer BioNTech COVID vaccine that have the potential to impact health equity, cold-chain storage handling[31] and administration requirements and the need for a 2-dose series.[32] New data recently submitted to FDA on stability may reduce the need for ultra-cold storage, thereby increasing access, particularly in smaller providers. Additional support to efficiently utilize doses, as well as smaller tray size, also will improve access. The requirements for a 2-dose series will make follow-up challenging for some disadvantaged groups, such as those who are homeless, live in rural locations, and have limited to no access to healthcare. Among adults early in the vaccination program, only a small proportion did not receive the second dose of a 2-dose series. However, differences were seen by jurisdiction, race, ethnicity, and age. Overall, the multi-pronged approach described earlier to implementation can improve access and overall can improve equity. The WG felt that the impact of the Pfizer vaccine would probably increase health equity.

After reviewing the data, the WG provides a judgment on the balance of consequences. The WG felt that the desirable consequences clearly outweigh 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 proposed to ACIP. Based on the totality of data presented, the WG proposed to recommend the intervention to ACIP.

[29] PROGRESS-Plus is an acronym to identify factors associated with unfair differences in disease burden and the potential for interventions to reduce these differential effects. See O'Neill J, Tabish H, Welch V, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J Clin Epi. 2014;67: 56-64; Welch VA, Akl EA, Guyatt G, et al. GRADE equity guidelines 1: considering health equity in GRADE guideline development: introduction and rationale. J Clin Epidemiol. 2017;90:59-67.

[30] CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic as of May 4, 2021, and US Census Bureau National Population Estimates

[31] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-allows-more-flexible-storage-transportation-conditions-pfizer

[32] Kriss JL, Reynolds LE, Wang A, et al. COVID-19 Vaccine Second-Dose Completion and Interval Between First and Second Doses Among Vaccinated Persons — United States, December 14, 2020−February 14, 2021. MMWR Morb Mortal Wkly Rep 2021;70:389–395.

Summary of Discussion

- ACIP members expressed an interest in hearing additional information in the future about the following topic areas:

    - MIS-C and cardiac outcomes and long-term outcomes among MIS-C survivors
    - The impact on if/how the loss of a family member to COVID-19 has influenced a family's intent to get vaccinated
    - More details on the cold-chain and packaging changes as soon as possible
    - Additional information on if/how English as a primary or secondary language impacts whether parents are willing to vaccinate their children with COVID-19 vaccine

- AAP emphasized that while there are some gaps in the information that needs to be collected, this should not be considered barriers to moving forward. This is an urgent problem. Mortality rates in children are demonstrating that this is one of the top 10 causes of death in children under 18 years of age. While there have not been the same tens of thousands of deaths that have occurred among adults, children do not die at the same rates overall. Several datasets have shown that pandemic has caused deaths in children that are unprecedented. This is a critical need, and AAP supports the findings that the WG has assembled and presented.

Clinical Considerations for Pfizer-BioNTech COVID-19 Vaccination in Adolescents

Dr. Kate Woodworth (CDC/NCBDDD) noted that interim clinical considerations for COVID-19 vaccines are available on CDC's website and apply to the use of the Pfizer/BioNTech, Moderna, and Janssen/Johnson & Johnson COVID-19 vaccines under the FDA's EUA.[33] These clinical considerations are being updated for adolescents and to include recommendations regarding vaccine co-administration and vaccination after MIS-C or MIS-A. She highlighted some of the considerations during this presentation.

In terms of administration, the Pfizer-BioNTech COVID-19 vaccine is currently the only COVID vaccine authorized by FDA for use under EUA for adolescents aged 12-17 years. The dosing and administration schedule is the same as for adults. Syncope or fainting may occur in association with any injectable vaccine, especially in adolescents. Procedures should be in place to prevent falling injuries and manage syncopal reactions following COVID-19 vaccination. All people are recommended to be observed following COVID vaccination for at least 15 minutes, and patients should be seated or lying down during the observation period to decrease their risk for injury should they faint. If syncope develops, patients should be observed until their symptoms resolve.

Regarding issues related to consent, the federal government does not have specific requirements for medical consent for vaccination, including COVID-19 vaccines. However, states and jurisdictions have medical consent laws that address the circumstances requiring and the processes for obtaining consent. It is important to note that these laws vary across jurisdictions. Providers also may be subject to policy requirements for consent within their own organizations. All sites administering vaccines should follow current state or jurisdictional policies and practices for other routine immunizations in this age group.

[33] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/index.html

With respect to co-administration of vaccines, due to the novelty of the COVID-19 vaccines, the previous recommendation was to administer COVID-19 vaccines alone with a minimum interval of 14 days before or after administration of any other vaccine to better understand any AEs. However, substantial data have now been collected regarding the safety of COVID-19 vaccines currently authorized by FDA for use under EUA. Extensive experience with non-COVID-19 vaccines has demonstrated that immunogenicity and AE event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone. For these reasons, the clinical considerations regarding co-administration are being updated to state that, "COVID-19 and other vaccines **may now be administered without regard to timing**. This includes simultaneous administration of COVID-19 with other vaccines on the same day, as well as co-administration within 14 days.

To the question raised earlier about routine adolescent immunizations, it is important to note that these updated co-administration recommendations may facilitate catch-up vaccination of adolescents. Early in the pandemic, VFC provider orders of routine immunizations fell substantially. While overall VFC provider orders have rebounded from lows seen earlier in the pandemic, there is still a substantial deficit for 2020 and 2021, with overall orders other than influenza down by 1.7 million doses. The largest gaps are seen with vaccines primarily given to adolescents, including Tdap, HPV, and meningococcal conjugate vaccines. Many school-aged children missed recommended vaccines over the last year due to disruptions associated with COVID-19, and schools may not have focused on compliance with school vaccination requirements during the 2020-2021 school year. The need for catch-up vaccination and coordination with COVID-19 vaccination is urgent in planning for safe return to in-person school.

Moving to clinical considerations for people with a history of MIS-C or MIS-A, which are severe hyperinflammatory syndromes occurring 2 to 6 weeks after acute SARS-CoV-2 infection and result in a wide range of manifestations and complications, the mechanisms of MIS-C or MIS-A are not well understood but include a dysregulated immune response to SARS-CoV-2. Children with a history of MIS-C have high antibody titers to SARS-CoV-2. However, it is unknown if this correlates with protection against reinfection and for how long protective antibodies persist. It is unclear if people with a history of MIS-C or MIS-A are at risk for reoccurrence of the same dysregulated immune response following reinfection with SARS-CoV-2 or in response to a COVID-19 vaccine.

People with a history of MIS-C or MIS-A may choose to be vaccinated. Considerations for vaccination may include clinical recovery from MIS-C or MIS-A, including return to normal cardiac function; personal risk of severe acute COVID-19, such as age or underlying conditions; level of COVID-19 community transmission and personal risk of reinfection; lack of safety data of COVID-19 vaccines following these illnesses; and timing of any immunomodulatory therapies. Current evidence suggests that the risk of SARS-CoV-2 reinfection is low in the months after initial infection, but may increase with time due to waning immunity. Thus, people with a history of MIS-C or MIS-A should consider delaying vaccination until they have recovered from illness and for 90 days after the date of diagnosis of MIS-C or MIS-A, recognizing that the risk of reinfection and, therefore, the benefit from vaccination might increase with time following initial infection. HCP or health departments can request a consultation from the Clinical Immunization Safety Assessment (CISA) COVIDvax project if they have complex COVID-19 vaccine safety questions that are not addressed by CDC guidance.[34]

[34] https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html

Regarding contraindications and precautions, anaphylactic reactions have rarely been reported following receipt of COVID-19 vaccines. Information is available on the CDC website regarding preparing for the potential management of anaphylaxis at COVID-19 vaccine sites.[35] The following are considered to be contraindications to vaccination with COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine
- Immediate allergic reaction of any severity to a previous dose or known (diagnosed) allergy to a component of the vaccine
- Known polysorbate allergy is no longer a contraindication to mRNA vaccination but is a contraindication to Janssen COVID-19 vaccine and thus, a precaution to mRNA COVID-19 vaccination.

CDC recommends that vaccine providers observe all persons for 30 minutes after vaccination who have a history of immediate allergic reaction (any severity) to a vaccine or injectable therapy, contraindication to a different type of COVID-19 vaccine, and/or a history of anaphylaxis (due to any cause). All other persons should be observed for at least 15 minutes following vaccination.

CDC has developed some additional resources pertaining to COVID-19 vaccines that will be relevant for vaccine providers, parents, and teens. CDC has developed additional tools that providers can use at the vaccination site to help identify persons with contraindications or precautions to vaccination, including a pre-vaccination checklist. There are numerous resources available regarding COVID-19 vaccine administration, storage, reporting, patient education, and more on the CDC's website at the following links:

COVID-19 Vaccination:
https://www.cdc.gov/vaccines/covid-19/index.html

For Healthcare Professionals:
https://www.cdc.gov/vaccines/covid-19/hcp/index.html

Engaging in Effective COVID-19 Vaccine Conversations:
https://www.cdc.gov/vaccines/covid-19/hcp/engaging-patients.htm

Toolkit for Medical Centers, Clinics, and Clinicians:
https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html

In closing, Dr. Woodworth posed the following questions for ACIP's consideration and discussion:

1. Does ACIP agree with the proposed clinical considerations related to vaccination?
2. Are there any sections of the clinical considerations that ACIP would like to discuss?

[35] https://www.cdc.gov/vaccines/covid-19/downloads/IntermConsid-Anaphylaxis-covid19-vaccine-sites.pdf

Summary of Discussion

- Concern was expressed about the relaxation of timing between vaccines, decrease in immunization rates, and insufficient immunogenicity and safety data when COVID-19 vaccine is co-administered with other vaccines. ACIP members inquired as to whether there is a way to encourage sponsors to study co-administration with routinely administered adolescent vaccines and what education tools will be available related to co-administration:

    - Dr. Oliver indicated that CDC agrees that having solid data would be helpful and is pursuing multiple avenues for ways to obtain additional data. This information can be brought to ACIP during future meetings.

    - Dr. Fink responded that FDA absolutely encourages vaccine manufacturers to study concomitant administration when concomitant administration would be anticipated to occur in practice with use of the vaccine. The studies to generate data on concomitant administration in terms of both safety and immunogenicity can become very complex based on the number of vaccines and number of antigens being evaluated. The added benefit of these data do need to be balanced in some way with the primary goal of generating safety and effectiveness data to support use of the COVID vaccines in certain age groups. FDA's regulatory precedent has not been to require concomitant administration studies as a condition of authorization or licensure, though such studies are certainly encouraged.

    - Dr. Cohn pointed out that no data will be available before the summertime to consider for co-administration. There are a couple of small studies for which there is hope of having some safety data before influenza season. Given the concerns around childhood and adolescent back-to-school vaccinations, this language in the clinical guidance is being proposed in the absence of additional data that specifically looks at co-administration because of the known safety profile of COVID vaccines along with many years of experience with co-administration with inactivated vaccines. CDC is working on multiple educational tools for providers and parents regarding co-administration, timing of administration, et cetera.

    - ACIP members remained concerned about some vaccines for which co-administration might have more anticipated AEs, such as the recombinant zoster vaccine. It is known that at baseline, adults who get that vaccine have been surprised by how significant impact it has in terms of reactogenicity. Given that both vaccines have significant reactogenicity profiles, it might be worth making individuals aware that co-administration is some cases might have a greater impact than anticipated. Members felt that the clinical guidance should be better fleshed out, given that many vaccination sites adhere so strictly to the guidelines without understanding the reasoning behind them to the point that they do not change quickly to modifications in the recommendation and may be limiting the ability for people to get necessary vaccines. In addition, patients are very concerned and may not understand or appreciate why there was a change unless it is clearly explained to them that it was not for any safety concern but rather was out of an abundance of caution. There is a tremendous amount of safety data on other vaccines and co-administration, as well as expert opinion. However, perhaps adult co-administration should be separate from pediatric co-administration due to the overwhelming concern for the pediatric population.

- Dr. Maldonado, AAP Liaison Representative to ACIP, stated that the AAP put together a policy statement that was embargoed until after the end of this ACIP meeting and to be read at this point. This statement was developed in consultation with a variety of groups and has received full approval from the AAP Board, as well as the Committee on Infectious Diseases (CID). This policy statement is organizational principles to guide and define the child healthcare system and/or improve the health of all children around COVID-19 vaccines children and adolescents and reads:

  "Vaccines are safe and effective in protecting individuals and populations against infectious diseases. New vaccines are evaluated by a longstanding, rigorous, and transparent process through the US Food and Drug Administration and the Centers for Disease Control and Prevention by which safety and efficacy data are reviewed prior to authorization recommendations. The American Academy of Pediatrics recommends the following related to COVID-19 vaccine and children and adolescents: 1) The AAP recommends COVID-19 vaccination for all children and adolescents 12 years of age and older who do not have contraindications using a COVID-19 vaccine authorized for use for their age; 2) Any COVID-19 vaccine authorized through Emergency Use Authorization by the FDA recommended by the CDC and appropriate by age and health status can be used for COVID-19 vaccination in children and adolescents; and 3) Given the importance of routine vaccinations and the need for rapid update of COVID-19 vaccine, the AAP supports co-administration of routine childhood and adolescent immunizations with COVID-19 vaccines or vaccinations in the days before or after for children and adolescents who are behind on or due for immunizations based on the CDC/AAP Recommended Child and Adolescent Immunization Schedule who are at increased risk from vaccine-preventable diseases."

- Dr. Schaffner, NFID Liaison Representative to ACIP, indicated that NFID welcomes the new recommendations and clinical guidance from the CDC and the AAP regarding co-administration and emphasized especially that there will be the usual influenza vaccination campaigns that go on in the Fall and essentially all adolescents are recommended to receive influenza vaccine. NFID certainly will welcome data on the subject of co-administration as they become available. The same permissiveness for co-administration now extends to adults as well.

- Dr. Fryhofer, AMA Liaison Representative to ACIP speaking as a practicing physician, offered kudos to CDC for its proposed guidance on co-administration and said she was very reassured by the AAP statement of support. She was very excited that it was confirmed that co-administration also applies to adults. However, she shared the concerns expressed about co-administration with vaccines that have adjuvants in terms of the potential impact on reactogenic side effects. As a practicing physician, she would welcome more specific guidance about co-administration with certain vaccines. While people may get vaccinated elsewhere, she is the one they will call when they experience side effects.

- ACIP expressed an interest in hearing about any discussions concerning booster doses. Dr. Oliver indicated that CDC the WG are continuing to follow studies for this and will bring information to ACIP as soon as they have information on duration of immunity and/or booster doses.

- Dr. Howell, AIM AMA Liaison Representative to ACIP, indicated that AIM represents the 64 awardees who are implementing COVID vaccine and other vaccines around the country. From a programmatic perspective, AIM would be supportive of co-administration. Over the summer months, there would be a lot of missed opportunities with high school activity, physicals, and other back-to-school immunizations if COVID vaccine is not given at the same time as other vaccines. In the third bullet in the clinical guidelines regarding co-administration, something else to consider would be school requirements and deciding whether to co-administer with COVID vaccines, given that many states have school requirements for different adolescent vaccines.

During the break, the co-administration language was revised to address some of the concerns raised by members to read as follows:

Coadministration

- COVID-19 vaccines were previously recommended to be administered alone, with a minimum interval of 14 days before or after administration of any other vaccines. This was out of an abundance of caution and not due to any known safety or immunogenicity concerns.

- However, substantial data have now been collected regarding the safety of COVID-19 vaccines currently authorized by FDA for use under EUA. Although data are not available for COVID-19 vaccines administered simultaneously with other vaccines, extensive experience with non-COVID vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone.

- COVID-19 vaccines and other vaccines **may now be administered without regard to timing**. This includes simultaneous administration of COVID-19 vaccines and other vaccines on the same day, as well as co-administration within 14 days.

- It is unknown whether reactogenicity is increased with co-administration, including with other vaccines known to be more reactogenic, such as adjuvanted vaccines.

- When deciding whether to co-administer with COVID-19 vaccines, providers could consider whether the patient is behind or at risk of becoming behind on recommended vaccines and the reactogenicity profile of the vaccines.

Public Comment

The floor was opened for public comment during the May 12, 2021 ACIP meeting at 2:00 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–2021–0049. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Mrs. Alycia Finch
Parents Protecting Education

Good afternoon members of the Advisory Committee on Immunization. My name is Alycia Finch. I represent Parents Protecting Education (PPE). Thank you for selecting me to reiterate concerns from colleagues and parents in my community. Before I begin, I'd like to thank the Centers for Disease Control and Prevention for diligently working to resolve the pandemic's devastating consequences on our global community. Your steadfast scientific work is essential to promoting a lasting solution to the challenges the US and other governments face to building a healthy community. Today, I speak on behalf of the parents who are skeptical of resolving this challenge by mandating a vaccine. While we are aware there are large numbers of communities who desire this vaccination, there's also a large community who desires the ability to choose a sound medical decision based on each child's medical needs. The CDC's recommendation has

a great influence on our local, state, and federal government's decisions to mandate vaccinations for our nation's children. I plead for the consideration as a mother responsible for the well-being of my children. My husband and I are committed to raising our children using a mindful and educated decision-based approach to health. The benefits of this vaccine may be great for one family and not for others with medical conditions. The facts are that these vaccinations, despite their positive intent, are too new to understand the lasting effects on our communities' children at large. Clinical trials have not had the time to gauge the long-term effects on the development and the growth of our children, and for this reason alone, we ask you to recognize in your decision-making that communities with significant medical challenges need and should be able to require a choice as far as the mandating or the requirements of this vaccine goal in our communities. I thank you so much for your time and consideration today.

Mrs. Savannah Starkey White
Representing Son, Baby Remy

My name is Savannah Starky. I am representing my son, Baby Remy. I'm an individual. Thank you for the opportunity to speak today. In February of 2020, I stood in front of you and I spoke on behalf of my son, Baby Remy. I'd like to honor my son today by speaking about the topic at hand. Baby Remy passed away approximately 12 hours after his CDC recommended schedule at his 2-month appointment. His autopsy came back anaphylactic adverse reaction to the multiple vaccinations received the day prior. The current schedule had been approved for decades and we still have thousands of infants, children, and adults dying and suffering as a result of them. I can't emphasize enough how important it is to truly know all of the adverse effects of a vaccine no matter how small you might consider it. To you, my son was just one baby, but to my children, my husband, and myself—he was our world and it is forever shattered. Pfizer is filing for the full FDA approval of their COVID vaccine this month. It's no secret that the vaccine comes with significant immediate reactions. The list of adverse reactions is growing and the number of complaints are tripling daily. We do not know enough about the long-term effects of this vaccine to approve it for full FDA approval. Based on the limited study that you all conducted yourselves, 77.4% reported at least 1 systematic reaction. Lymphadenopathy, Bell's palsy, appendicitis, acute myocardial infarction, cerebral vascular accidents were all reported and considered adverse reactions just from your studies alone. There have been thousands of additional reports to VAERS for serious adverse reactions, blood clots, nerve pain, rashes, hives, multiple deaths, and dozens of others are trickling in. Concerns of infertility are rippling through social media and flooding doctors with concerned patients. We do not know the long-term effects of this vaccine. We will not know this for 5, 10, or even 20 years. This information is critical and it must be known before the FDA approves it, especially for our children. Our children are our future. We have to protect them by not jumping the gun. America is looking up to you to do the right thing. I challenge you to advise the FDA to deny the full approval of the Pfizer vaccine as it stands right now. Thank you.

Janelle Sullivan
Heartline Foundation

Hi. I'm Janelle Sullivan from Heartline Foundation. I have a son who is recovered from severe autism. I spoke in front of this panel in the past about how I've recovered him. "Autism, Beyond Despair" was a book that was very helpful. It actually has a chapter as a rebuttal to Paul Offit's book, "Autism's False Prophets." I recovered him doing what Paul Offit says not to do. This panel likes to pretend the anti-vaccine families are child abusers to autistic kids. Your CDC schedule caused my son to bang his head on cement and to have absence seizures. It is guilty of the worst child abuse on this planet and I seriously fear what your recommendations are

going to cause. You have the power today to say “no.” You have the power. It is so much easier for you to do this now than it will be later. You will not be able to take this decision back. It’s going to affect so many lives. These children are not affected from COVID. They are affected from your lockdown measures. They are affected from masking, from social distancing, and from not receiving the contact and the love and the hugs and the high-fives that were meant to be given and received. Our hearts are not meant to be kept separate. They are meant to come together and do great things, and they're also meant to heal, and they don’t need you putting all of these poisons in our body. We need to have the ability to say “no.” Your recommendations, your schooling, has encouraged doctors to say things like, “You can’t breathe around the unvaccinated.” My father-in-law was told that and he stayed away from me for three and a half years. My child had a seizure following his last vaccines and people request that he not be invited to parties. People that my husband was in their wedding parties of keep their children away from us. You guys are doing to us just what the Germans did to the Jews. They said that they were guilty of spreading diseases. I see you. I see what you’re doing and I’m telling you because of what you’re doing, more people are listening to me than ever before. More people are coming to our side. Please stop this now. Thank you.

Susie Olsen Corgan
Concerned Individual

Hello. My name is Susie Olsen Corden. Thank you for the opportunity to speak once again today. I realize we have a limited timeframe, so I’m just going to highlight a few points really quickly. One of three of my main issues with this COVID-19 vaccine is the fact that implications of fertility impairment have not been studied, so how can we recommend a vaccine to 12 to 15-year-olds that could potentially cause impairment in their fertility? Why weren’t these studies done prior to recommending these vaccines? These studies need to be done now and parents need to be given informed consent. Prior to administration of these vaccines they need to be told that these studies were not done. Combining vaccines. One of the primary questions today was in regard to safety data and co-administration of the mRNA vaccine simultaneously with routinely recommended adolescent vaccines. After listening to the ACIP meeting today, it is clear that these studies have not been done. Yet I keep hearing that in the absence of data, you will still recommend administration of the mRNA COVID-19 vaccines along with routinely recommended vaccines. Adolescents are going through things that adults are not. Hormonal changes during puberty and brain development should be closely looked at in studies prior to any administration of these vaccines. In the absence of data, ACIP should not be recommending this vaccine. Today I heard about deaths. We heard that 127 deaths were attributed to COVID-19 disease 12 to 17-year-olds; however, since we are discussing the interim recommendation of COVID-19 vaccination for 12 to 15-year-olds, I’m highlighting just that data which is needed to make this decision today. Thus by age, according to CDC, it says that we have had a total of 17 deaths in 12-year-olds, 13 in 13-year-olds, 15 in 14-year-olds, and 24 in 15-year-olds. That is a total of 69 deaths that have been attributed to COVID-19 in 12 to 15-year-olds. While the loss of any life is tragic, especially in children, we have to look at this and declare there is no emergency for children in this age range. How can you, the members of ACIP, who are entrusted with making these decisions, recommend this vaccine based off this data?

Lindsay Maher, BS, MS
Informed Choice Iowa

My name is Lindsay Mayer with Informed Choice Iowa. I'm here today also from a virology perspective. My background is in virology and I studied at the University of Iowa. It has been well-documented and demonstrated that kids are at extremely low risk of serious illness from COVID-19. In comparison, around 600 children died in the influenza season of 2017 and 18, which you reflected earlier in your hospitalizations, in comparison to 282 deaths in children related to COVID. This despite already having a widespread influenza vaccination campaign in America. Quite frankly, it does not matter how efficacious this vaccine is in stopping illness in children, considering healthy children are never actually seriously impacted and considering a primary concern that risk transmission was not even evaluated in this trial. So, why are we not practicing these base medicines? Will we be doing more harm than good considering that children have a 99.99% survival rate from COVID and have demonstrated that they are not a primary source of transmission in this pandemic. The Pfizer vaccine has already been associated with 1719 deaths according to the passive reporting system, VAERS, which we know grossly underestimates the true numbers, given that both the FDA and Department of Health and Human Services have published studies on this. Yet here we are today discussing data that hasn't been seen or analyzed by the public, hasn't looked at asymptomatic transmissions, lacks data in those with underlying health conditions, or data on co-administration of this vaccine with others on the schedule. And still, this body plans to vote on emergency approval for which there isn't even an emergency in children. Finally, Pfizer has again failed to test this product in a cohort that truly represents the US population of children. A 2011 study found 54% of our nation's children have a diagnosed chronic illness. In the adult trial, only 10% of the total 46,000 participants who received the vaccine had a chronic illness, with no autoimmune conditions represented in that group at all, and the rest fall under the definition of small numbers as does this trial. It failed to enroll representative numbers of those with underlying conditions, yet this group plans to roll it out so all 12-15 year olds regardless of what their health is like. How can you confidently say that it isn't going to significantly harm them more so than benefit them? How can you say this is safe when you do not know what the chances are for them developing a new onset chronic disease, cancer, fertility issues, hospitalizations, disability, or death as a result of taking this experimental vaccine that was only tested in 2620 participants. It's clear that children's well-being is not the priority in approving this authorization. Irrational recommendations will do no good, will certainly cause harm, and will further discredit our federal health agencies. You do not gain public trust through quickly approving experimental vaccines that will eventually be forced on millions of American children in order to attend schools. You will only increase those who distrust the entire public health industry, as well as the entire recommended schedule. So, go ahead, vote "yes" if you want to increase vaccine hesitancy for an unnecessary product for a situation that isn't a true emergency. Or vote "no" and get your questions actually answered. Thank you.

Ms. Allison Winnike, JD
President and CEO
The Immunization Partnership

Good Afternoon Chairman Romero and members of the committee. My name is Allison Winnike and I am President and CEO of The Immunization Partnership. Our non-profit mission is to eradicate vaccine-preventable diseases by educating in the community, advocating for evidence-based public policy, and supporting immunization best practices. Thank you to the committee and to the COVID-19 Vaccine Work Group for your tremendous work during this pandemic reviewing scientific data and developing vaccine recommendations to keep all Americans safe and healthy. Your scientific recommendations are an important tool that states use to carry out their constitutional duty to protect the public's health. As we move into vaccinating adolescent populations against COVID-19, we are observing that hesitancy among parents has been amplified even as compared with those parents' own comfort in receiving their adult COVID-19 vaccine. And it's understandable that parents may have additional questions or fears regarding COVID-19 vaccines for their children. We have observed many questions and concerns regarding these vaccines' impact on hormonal changes, reproductive issues, allergies, and potential long-term effects when administered to adolescents. And so it is critical that trusted messengers proactively share medically accurate and culturally appropriate information with these parents to address these issues before they fall victim to misinformation and disinformation spread online. We can build trust and comfort through dialogue, listening to concerns, explaining this peer-reviewed data, and meeting them where they are whether physically or emotionally. As presented today, a recent survey indicated that 74% of parents would feel comfortable with their child receiving a COVID-19 vaccine in their regular provider's office as opposed to other venues such as pharmacies or vaccine clinics. So, we should take heed of these parental preferences and states should rapidly enroll pediatricians and other adolescent healthcare providers as accessible COVID-19 vaccine providers. At the same time, we need to promote health equity and continue to offer accessible vaccine administration sites for those who lack a regular medical home and those who continue to experience barriers to access. It is imperative that we increase our lackluster immunization rates by increasing demand for these life-saving vaccines. As we expand our COVID-19 vaccination experts into the adolescent population, I recommend a multi-prong approach proactively addressing parental questions, incorporating parental feedback and best practices to increase confidence, and continuing to expand access to trusted vaccination locations. Thank you so much for your important work and the opportunity to share our comments.

Mr. Richard Robbins
Parent of 13- and 15-Year-Old Daughters

Hi. Thank you very much to the committee. My name is Richard Robbins. I'm speaking today as a parent of 13- and 15-year-old daughters and thus have a vested interest in your decision. After the FDA gave its authorization for 12-15 year olds on Monday, I went to the ACIP website to see how quickly my daughters would be able to get vaccinated and saw that there was an opportunity for public comments prior to today's vote. I thank you for this opportunity on behalf of my daughters who are eagerly awaiting the opportunity to get their vaccines and return to some approximation of normal life. I strongly recommend that you vote in favor approving the vaccine for 12-15 year olds today. I recognize that there is irony in my recommending that you listen only to scientists, as I am not a scientist, but the overall recommendation of doctors and scientists that the vaccine is safe and effective. Pfizer's trial results are nothing short of miraculous. As you know, the Phase 3 trial demonstrated 100% efficacy and robust antibody responses among the half of the 2260 adolescents who received the vaccine versus 18 cases in

the placebo group. Further, the trial found that the vaccine was well tolerated with limited side effects. On the other hand, even if the risk of COVID is lower for adolescents than for the elderly, it is still a serious and risky disease. A recent article by Dr. Kristin Moffitt, Pediatric Infectious Diseases Doctor and Researcher at the Boston Children's Hospital and Assistant Professor Pediatrics at Harvard Medical School, reported that over 400 children have died from the COVID infection. More than the number of childhood deaths during the deadliest flu season in the past two decades. Further, in the NewScientist's Helen Thompson wrote of the first study of long COVID in children. It's found that nearly half of children with both symptomatic and asymptomatic COVID-19 are experiencing long-term effects many months after the initial infection. More than half of children aged between 6- and 16-years-old who contracted the virus have at least one symptom lasting more than 120 days, with 42.6% impaired by these symptoms during daily activities. As my daughters can attest, young people have endured many hardships this past year. This meeting is a good example of how Zoom is an imperfect replacement for live in-person interactions, especially for school children. It is important that children are able to safely resume going to school, seeing friends, and having some approximation of normal life as soon as possible. It is even more important that in doing so, they do not risk transmitting the virus to older family members who are even more at risk. We need to do everything we can to get as many Americans vaccinated as soon as possible. This is an important step. Thank you for all the work you are doing. I look forward to your vote and assuming you approve, look forward to taking my daughters to get vaccinated tomorrow, but nowhere near as much as my daughters look forward to getting their shots.

Mrs. Mya Olson
Representing Herself/Other Parents

Good afternoon and thank you for your time. My name is Mya Olsen and I'm from South Dakota. I'm commenting today for myself along with the millions of parents who are protected by the Nuremberg Code which states, "The experiment should be such as to yield fruitful results for the good of society unprocurable by other methods or means of study and not random and unnecessary in nature." Right now, we know that there are other methods of treatment for COVID-19 that are successful without death as an adverse event. The Nuremberg also states, "No experiment should be conducted where there is a priori reason where death or disabling injury will occur," which we also know is tragically not the case as your very own reporting system has reported 11 deaths associated with the COVID-19 vaccine since granting emergency use authorization for 16- to 18-year-olds a little over a month ago. Your own Paul Offitt stated in an interview that it would be a mistake to put out to the American public a vaccine that was only tested in a few thousand people, which is what we're doing right now. Your trial for this age group had very small enrollment population and a very short timeframe, and there were severe injuries within the trial. Just this past week, a 15-year-old in Colorado died after receiving the vaccine. You are currently charged with approving the vaccine for the children with no long-term studies, with over 1700 deaths associated with this vaccine as per your own reporting system. Allowing this vaccine to stay on the market is unprecedented, as the FDA pulled the rotavirus after far fewer deaths. Not only that but Pfizer has pled guilty to a felony violation of the FDA for misbranding with the intent to defraud or mislead. What is to say that isn't happening again? The children aren't at risk for this disease. Per the CDC, there were 69 deaths for this age group. Why is it that you are asking them to carry the burden of a society on their shoulders? I ask that you do not approve this vaccine without further long-term studies. I mentioned the quote from Paul Offitt earlier. I will now quote from the governor of my life, Luke 17:2, "It were better for him that a milk stone were hung around his neck and he cast into the sea than he should offend one of these little ones." Please don't vote to pass this.

Vote: Pfizer COVID-19 Vaccine for 12-15 Year Olds

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

> *Pfizer-BioNTech COVID-19 vaccine (2-doses, IM) is recommended for persons 12-15 years of age in the US population under the FDA's under an Emergency Use Authorization.*

Motion/Vote: Pfizer COVID-19 Vaccine for 12-15 Year Olds

Dr. Poehling made a motion and Ms. Bahta seconded to approve the recommended language for Pfizer COVID-19 Vaccine for 12-15 Year Olds as presented. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention due to a conflict of interest (COI). The disposition of the vote was as follows:

15 Favored:	Ault, Bahta, Bell, Bernstein, Chen, Daley, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
1 Abstained:	Frey

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

Dr. Talbot: I just want to say how excited I am. This will mean that the rest of my family can be vaccinated. That's a little selfish because I know we have less than 12 years of age to go, but just to set an example, my husband and I are vaccinated, my 16-year old is vaccinated, and now my 12- and 15-year olds will be in line, and I'm ever so thankful.

Dr. Kotton: Similarly, I'm very excited to have this vaccine approved for this age group. This is a really important issue for the summer. It's also a very good way to provide better community immunity, especially for immunocompromised patients who have these teenagers in their families, and this is another way to get closer to ending this horrible pandemic.

Dr. Lee: I just wanted to make a comment because I think sometimes we lose the importance of children and adolescents in the midst of a pandemic. There's been such a focus on older adults in particular. I think that the childhood experience that our kids have gone through will have long-lasting consequences that may extend across generations to be honest. We don't really fully yet understand the total mental health, physical health, and educational impact of the pandemic on our kids. We know that there are already disparities in hospitalizations and disparities in MIS-C. I anticipate that with disparities in infection as well, the consequences could be far more severe than we anticipate. I strongly advocate for taking a life-course approach to thinking about COVID and the impact of COVID for our generation and for generations to come.

Dr. Daley: Yes, thanks so much. Two brief comments. One is the US focus and the other is global. In terms of the US focus, I think one thing we haven't talked about a ton, a little bit but not a ton, is that there really have been 130 million doses of Pfizer vaccine given and to date, the safety profile of that vaccine in use has been really positive. So, I think I want to remind everyone that the intensive safety scrutiny of this vaccine will continue after the authorization.

We're just going to get more data about the 12-15 year olds. The global comment is that I think if we look at what's happening elsewhere in the world, that's evidence of what happens if you don't have adequate supplies of safe and effective vaccines. That is what happens and so we're in this very privileged position where we can see declining deaths and declining case rates because of these vaccines, and so this is just another group that will be vaccinated and it will continue those downward trends.

Dr. Bernstein: I just wanted to reiterate what everyone else is saying that benefits far outweigh the risks. I think this will provide protection for 12-15 year olds. It will decrease transmission within their families, it will contribute to community immunity, and it will allow kids to more safely go back to camps this summer and back to in-person school. So I'm excited for the idea that 12-15 year olds are eligible for vaccine.

Dr. Poehling: I want to reiterate the importance of this vaccine for the teenage children themselves. COVID-19 hospitalizations are increasing in children, with over 13,000 hospitalizations. April 2021, children comprised 9% of all cases and that's even higher than those 65 years of age and older. Children can have severe disease from COVID-19 infection themselves, as well as from MIS-C. Long-term implications of COVID-19 can be very significant. For example, we had a teenager who presented with a heart attack with their COVID-19 ailments and fortunately did survive, but that will have long-lasting impact. While deaths are uncommon in children, COVID-19 deaths are one of the top 10 causes of death for children. Many children have underlying conditions putting them at increased risk. COVID-19 vaccine is both safe and effective. Many parents and adolescents want to be protected by being vaccinated, and I'm so glad we have the vote to enable them to do that today.

Dr. Romero: Let me just say that this is one more step closer to gaining immunity and bringing the pandemic closer to the end. We still have the younger age group to deal with, and we are dealing with that, and we still need to vaccinate the rest of the world. But, we have made significant steps and are on the road. As usual, I want to think all of you (voting members, liaisons, and *ex officios*) for all of the time and work that you spent and dedicated to this effort. This is now our 15th meeting this year. That translates to roughly 5 years of work in a single year. So again, thank you. It does not go unnoticed and unappreciated. So thank you very, very much and good work to all of you.

Thrombosis with Thrombocytopenia Syndrome (TTS) Following COVID-19 Vaccination

Dr. Tom Shimabukuro (CDC/NCEZID) recapped the background of the TTS situation, described updated data for TTS following COVID-19 vaccination, and summarized the most recent data. He explained that thrombosis occurs when blood clots block blood vessels. Thromboses can be venous our arterial and complications can include heart attack, stroke, and other infarctions. Causes and risk factors include trauma, immobility, inherited disorders, autoimmune diseases, obesity, hormone therapy or birth control pills, pregnancy, smoking, cancer, and older age and sometimes may include pain and swelling in extremities, chest pain, numbness or weakness on one side of the body, and a sudden change in mental status. They are diagnosed primarily through imaging studies and blood tests. Platelets, also called thrombocytes, are colorless blood cells that help blood clot. A normal platelet count is 150,000-450,000 per microliter. That is usually shorthanded to 150-450. Platelets stop bleeding by clumping and forming plugs in blood vessel injuries. Thrombocytopenia is a condition in which one has a low platelet count of below 150. Dangerous internal bleeding can occur when platelet counts fall below 10,000 per microliter. Though rare, severe thrombocytopenia can cause bleeding into the brain, which can be fatal.

A Health Alert Network (HAN) notification went out on April 13, 2021 summarizing cases of cerebral venous sinus thrombosis with thrombocytopenia (CVST) after the Janssen vaccine and announcing that CDC and FDA had initiated a pause and would convene an emergency meeting to review the data. The emergency meeting was convened on April 14, 2021. About 10 days later, there was a follow-up meeting on April 23rd during which updated results were presented. Following that, meeting the CDC issued an *MMWR* recommending resuming vaccine. The reason CDC was following this condition closely in its post-authorization surveillance was due to reports of CVST or unusual clotting in the presence of thrombocytopenia following the AstraZeneca (AZ) vaccine in Europe. Updated recommendations of ACIP which were issued April 27, 2021 after the April 23rd meeting.[36] At that time, ACIP concluded that the benefits of resuming vaccination with Janssen outweighed the risks and reaffirmed the interim recommendations under FDA' EUA, which included the new warning.

Most of the data on TTS comes from the Vaccine Adverse Event Reporting System (VAERS), which is the nation's early warning system for vaccine safety. It is a spontaneous reporting system or passive surveillance system that is co-managed by CDC and FDA. This systems relies on individuals to report events into VAERS. As a passive surveillance system, it has the limitations of passive surveillance in general. It is not designed to assess causality. However, it has a large population under surveillance and is, therefore, able to detect rare AEs and unexpected patterns for these rare events, which it did with TTS. CDC's Clinical Immunization Safety Assessment (CISA) Project was instrumental in conducted a detailed clinical review of these cases in consultation with its consultants and hematologists, neurology experts, and other vaccinology experts at CISA sites.

Case finding for TTS following COVID-19 vaccines occurs in a variety of ways. One way is that HCP contact CDC directly about potential TTS cases by phone or by email by astute HCP who recognize a TTS case or potential TTS case, often to inform CDC that they have simultaneously reported to VAERS. CDC may initiate an investigation along with the HCP and facilitate the report into VAERS. Also, FDA physicians screen incoming VAERS reports daily to identify potential TTS cases. In addition, CDC searches the VAERS database of process reports daily for possible TTS cases. Medical records are requested for all potential TTS case reports to confirm thrombosis with laboratory evidence of thrombocytopenia using a working case definition. CDC and FDA medical officers review TTS case reports and available medical records. CISA experts, including hematologists, are consulted as necessary. There is an interim Brighton collaboration case definition for TTS. Some of the criteria are new onset of thrombocytopenia, no known recent exposure to heparin, and the presence of venous or arterial thrombosis. In addition to rare thromboses (e.g., CVST), it currently includes more common thromboses like deep vein thrombosis (DVT), pulmonary thromboembolism (PE), ischemic stroke, and myocardial infarction. CDC has adopted a modified version of this interim Brighton collaboration case definition, which is divided into two tiers to organize searches and clinical reviews. In consultation with specialists at CISA, CDC has reviewed its criteria for identifying cases and decided that for specificity and to avoid including a lot of non-cases into the Tier 2 category and then into the overall TTS case count, requiring a positive heparin PF4 ELISA HIT antibody test adds specificity and is appropriate.

[36] https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7017e4-H.pdf

Taking a high-level look at US COVID-19 vaccine administration by product type and TTS reports to VAERS for the 3 authorized vaccines, after 135 million doses of Pfizer-BioNTech vaccine, there have been no confirmed TTS reports to VAERS. After 110 million doses administered of Moderna vaccine, there have been no confirmed TTS reports to VAERS. After 8.7 million doses administered of the Janssen vaccine, there are 28 confirmed TTS reports to VAERS. There was one CVST with thrombocytopenia case observed in the Janssen pre-authorization clinical trials in a male 25 years of age. This case is not included in the VAERS or post-authorization confirmed case count. Some of the basic characteristics of the 28 cases are that 25 were Tier 1, 3 were Tier 2, the median age was 40, median time from vaccination to symptom onset was 9 days, all had received the Janssen COVID-19 vaccine before the pause on April 13th, there were 22 females, 6 males, 19 of the 28 TTS cases had CVST, there were no pregnant or postpartum case patients, and 5 had a past SARS-CoV-2 infection. In terms of the risk factors, it is important to note that there were no cases with a known or documented coagulation disorder. Most of the TTS cases, are occurring in the 30-49 year old age group. There have been increases in some of these age groups, which seem to be most pronounced in the 40-49 year old age group.

In terms of the treatment outcomes among the 28 TTS cases, 12 individuals received heparin. Of those 12 cases, 9 of 11 admitted before the HAN were treated with heparin and only 3/17 admitted after the HAN were treated with Heparin. Twenty-six were ultimately treated with non-Heparin anticoagulants and 18 received intravenous immune globulin (IVIG). There were 3 deaths, which is unchanged from the first presentation of the initial 6 CVST cases. Four remain hospitalized, 1 in intensive care, 2 have been discharged to post-acute care facilities, and 19 have been discharged home. None of the patients who died received heparin.

VSD is CDC's large, linked database for active surveillance and research. It includes 9 participating integrated healthcare organizations with data on over 12 million persons per year. A substantial number of doses administered of mRNA vaccines are in the VSD (3.3 million Pfizer-BioNTech, 3 million Moderna) as of April 24th. After the 6.3 million doses total, 11 total ICD-10 coded CVST diagnoses have been identified following mRNA vaccination (3 Pfizer-BioNTech and 8 Moderna). Of the 11 cases, 5 were ruled out for incident cases and 6 were considered potential CVST incident cases. All were without thrombocytopenia. There have been no confirmed cases of incident CVST with thrombocytopenia after 6.3 million doses of mRNA COVID-19 vaccines administered in the VSD. Just under 160,000 Janssen COVID-19 vaccine doses administered are in VSD through April 24th. There have been no statistical signals for any pre-specified rapid cycle analysis (RCA) outcomes and no CVST cases identified. There are 32 venous thromboembolism (VTE) and/or PE embolism cases identified in the 1-42 days following vaccination. That includes 3 cases that had both VTE and PE. Of the 32 VTE/PE cases, 29 have been quick reviewed and 3 are in progress. Of the 29 cases that have been quick reviewed, 6 were ruled out as not being VTE or PE and 23 were confirmed as VTE or PE cases. Of the 22 confirmed cases, 4 were determined to have symptom onset prior to vaccination,1 had indeterminate symptom onset, and 18 were potential VTE or PE cases with incidence following vaccination. Among the 18 cases of potential incident VTE/PE cases, 10 were female, 8 were male, ages ranged from 30-79 years, none had a history of COVID-19 infection and none had thrombocytopenia noted at the time of the VTE or PE. A fairly small number of Janssen COVID-19 vaccines administered are in the VSD, but no potential cases of TTS have been identified to date.

In summary, TTS is a rare, clinically serious, and potentially life-threatening condition. Current evidence suggests a plausible causal association with the Janssen COVID-19 vaccine. Symptom onset appears to occur from several days after vaccination up to 2 weeks, with most cases having symptom onset around 1-2 weeks. Most cases are in women, with most aged 18-49 years old. The clinical features of TTS following Janssen COVID-19 vaccination appear to be similar to what is being observed following AZ COVID-19 vaccination in Europe. It is important to recognize TTS early and initiate appropriate treatment, but cases of thrombosis with thrombocytopenia should not be treated with heparin unless heparin-PF4 ELISA HIT antibody testing is negative. TTS does not appear to be associated with mRNA COVID-19 vaccines. The US vaccine safety monitoring system is able to rapidly detect rare AEs following vaccination and quickly assess safety signals. CDC is committed to open and transparent communication of vaccine safety information. In terms of next steps, CDC will continue enhanced monitoring in VAERS, conduct surveillance in other vaccine safety systems, and update ACIP and the public as additional information becomes available. CDC's healthcare provider partners on the front lines are reminded to submit AE reports to VAERS. There are specific EUA reporting requirements and CDC encourages the reporting of any clinically significant AEs VAERS.

In the spirit the vote earlier in the day, v-safe™ is CDC's smartphone-based active safety monitoring system. It is a post-vaccination health checker that is a voluntary self-enrollment program that sends text messages with embedded web links from CDC to take respondents to secure, web-based surveys in which they can report to CDC about the post-vaccination experiences. Now that adolescent vaccination has been recommended, CDC encourages parents and guardians to enroll their vaccinated adolescents into v-safe™. Parents and guardians can complete health surveys on behalf of their adolescents, describing symptoms and health events after vaccination. CDC encourages completing the health surveys even if the vaccinated persons are feeling well and have no side effects. All of this information is important and helpful to CDC in terms of continued monitoring of the safety of COVID-19 vaccines as use is expanded into younger populations. CDC thinks that taking advantage of the post-vaccination observation period to counsel patients on v-safe™ and encourage patients and parents on behalf of their adolescents would be a good use of the waiting time during the post-vaccination observation period.

VaST Update

Dr. Grace Lee (ACIP, VaST Chair) reminded everyone that the objectives of the Vaccine Safety Technical (VaST) WG are to : 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring; 3) advise on analyses, interpretation, and data presentation; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the ACIP on COVID-19 vaccine safety.

At this point in the US vaccination program, a tremendous amount of safety data has been accumulated to date. There have been 262 million doses administered in the US, including 140 million Pfizer-BioNTech doses administered and 153 million individuals who have received at least one dose. v-safe™ has been incredibly helpful for confirming the reactogenicity profile observed in clinical trials. It includes over 110,000 individuals who self-identify as pregnant who are now being recruited for a specific pregnancy registry. This is a great example of innovation and the ability to capture enhanced data for a population where more data are needed. VAERS has been critical in the early detection of both anaphylaxis and TTS, and the CISA consultation service for COVID-19 vaccines has added tremendous value for challenging clinical questions.

Having moved further along in the vaccine program timeline, the focus is shifting to data from large link databases such as the VSD, VA, and DMSS.

Dr. Lee reviewed the timing of various ACIP recommendations, emphasizing that it has been a busy 5 months of service for the VaST members and for the vaccine safety teams who are presenting at all of these meetings. VaST on April 12-14, 2021 to address the TTS signal and the CVST cases with thrombocytopenia following the Janssen vaccine. VaST requested additional information to support evidence-based decision-making about the use of this vaccine and met numerous times before and after the April 23, 2021 ACIP meeting during which the recommendations for use of the Janssen COVID-19 vaccine was updated. ACIP concluded the benefits of resuming vaccination among persons 18 years and older outweighed the risks of the population level and reaffirmed its interim recommendation under the FDA's EUA with a new warning put into place for rare clotting events among women aged 18-49.

Since the last public ACIP meeting, VaST met 3 times to review the findings from enhanced monitoring efforts and the tiered CDC case ascertainment approach for TTS cases in VAERS. VaST also reviewed available data from the VSD RCA. An advantage of both of these vaccine safety systems is that they can implement broad electronic algorithms to capture potential CVST or TTS events, followed by a rapid review of electronic medical records (EMRs) for confirmation. This illustrates the robust system that allowed this to be done in real-time. VaST appreciates that its CDC colleagues have published what information they had available expeditiously and transparently. Dr. Lee also thanked their CDC colleagues for making the information available to providers and patients about the benefit/risk balance of using the Janssen vaccine that is easier to understand at a better health diversity level.

To summarize the VaST assessment, there are no confirmed TTS cases following mRNA vaccines. The risk of TTS following the Janssen vaccine is rare, yet remains highest in females less than 50 years of age. Risk mitigation strategies appear to be effective and should continue, including educating patients about the benefits and risks of available vaccines and ensuring that patients and providers are aware of the importance of early recognition and timely management of TTS. For example, in the data reviewed earlier in the day, recent TTS cases seem to be detected slightly earlier in the course of illness and fewer cases of TTS were treated with heparin after the HAN was released. VaST will continue to monitor TTS, thromboembolic disease, and thrombocytopenia in all available vaccine safety surveillance systems. VaST will update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and the ACIP on a regular basis.

COVID-19 WG Interpretation of the TSS Updates

Dr. Oliver (CDC/NCIRD) presented a COVID-19 WG Interpretation of the TTS updates. As mentioned several times in this session, an *MMWR* was published after the vote where ACIP reaffirmed its recommendations for all persons 18 years of age and older under the EUA that now includes the warning about clotting events and highlights the fact that patient and provider education about the risk for TTS with the Janssen vaccine, especially among women less than 50 is important, as well as the availability of alternative COVID vaccines. This information is required to guide vaccine decision-making and ensure early recognition and clinical management of TTS. Educational materials that are now on CDC's website.

In terms of how doses of Janssen COVID-19 vaccine have been used since the pause, nearly 8 million doses were used prior to the pause April 13, 2021. There was a fairly even split between males and females. Since the pause, 1.2 million doses of the Janssen COVID-19 vaccine have been administered. Doses are still being utilized for females, but in a smaller proportion since before the pause, especially in the population identified as the highest risk (females 18-49 years of age).

The risk/benefit analysis has been updated with the incidence of TTS that Dr. Shimabukuro just presented. This reviewed by the COVID-19 Vaccines WG. The WG's interpretation at this time is that the benefits still outweigh the risk and that no updates to vaccine policy are needed. The WG will continue to review TTS updates, as well as updates to the risk/benefit analysis. The WG will continue its discussions if or when the WG's assessment is that updates to recommendations for the use of the Janssen COVID-19 vaccine should be considered. The full risk/benefit analysis will be presented to ACIP again, along with potential updated policy considerations. Dr. Oliver emphasized that just because they are not bringing information forward to ACIP at every meeting, everyone can be reassured that the WG and others are continuing to look at the data and will bring it forward if and when needed.

Summary of Discussion (Shimabakuro, Lee, Oliver)

- Concern remained among ACIP members regarding the Janssen vaccine. While the warning that has been tied to the vaccine recommendation has been 18-49 years old and predominantly female, there are quite a few confirmed cases in the 50-59. With that in mind, it was suggested that perhaps the warning age range should be 18-60 years of age.

- ACIP members emphasized the importance of strong educational materials and continuing to seek better ways to ensure that everybody is being educated about all vaccines and vaccine recommendations, particularly pregnant women.

- The dynamic benefit/risk assessment is critically important in terms of understanding the status of the pandemic. ACIP praised the modeling team for a phenomenal job during the last meeting in putting numbers to the qualitative sense that everyone had.

COVID-19 Vaccine Effectiveness Studies

Dr. Katherine Fleming-Dutra (CDC/NCIRD) presented on why post-authorization vaccine effectiveness (VE) estimates are needed. It is known that real-world performance of vaccines can vary from that seen in the controlled trial setting due to implementation differences that can occur in widespread vaccination programs in terms of adherence to cold-chain requirements; a broader population that is eligible to receive the vaccine, such as persons with certain underlying health conditions who may not have been included in the trials; and the potential for the timing and coverage of the second dose of a 2-dose series to vary from what was studied or even from what is recommended. Post-authorization VE studies build on evidence from clinical trials to better understand VE in groups experiencing disproportionate impacts of COVID-19, especially since in the trials the number of individuals from various groups may have been limited; to understand the VE against severe disease for SARS-CoV-2 infection and transmission; and to better understand the duration of protection.

This team's priorities have been developed based on the results of internal and external input to focus on the information that will be most useful for guiding policy. The most immediate priority after introduction of COVID-19 vaccines has been to answer the question, "Does vaccine protect against symptomatic diseases as expected from the clinical trials?" Subsequent priorities include: 1) estimating VE against the key outcomes of severe disease, non-severe disease, and infection and transmission; 2) estimating VE in groups experiencing disproportionate impact of COVID-19 (e.g., adults ≥65 years, those living in LTCF, people with key underlying health conditions, and racial and ethnic minority groups experiencing disproportionate impact of COVID-19; 3) estimating the VE for regimen-related questions for 2-dose products; 4) understanding viral evolution and whether genome changes impact VE; 5) understanding duration of protection; and 6) comparison of VE across products.

In terms of the overall landscape of the COVID-19 mRNA VE literature globally, Dr. Fleming-Dutra focused on mRNA vaccines. Because the of the products that are currently in use in the US, the vast majority of real-world literature is from mRNA vaccines. It is very important to address the caveats of the literature. The literature is rapidly evolving and growing exponentially by the day. A wide variety of methods, populations, and definitions are being used. Most of the VE literature is currently in pre-press form and there are few peer-reviewed publications. The quality of the literature varies widely among studies. Meta-analyses and formal comparisons are not appropriate at this time due to these caveats. Dr. Fleming-Dutra shared a graph (slide 6) to illustrate the complexity of the literature examining the VE of the 2-doses of the Pfizer-BioNTech vaccine.[37] To summarize the literature, there is very high and relatively consistent VE across all of these studies and even across the outcomes, with the possible exception of asymptomatic infections. These consistent results are very reassuring. The VE literature for two doses of mRNA vaccines comes from populations that were using both the Moderna and Pfizer products. There were fewer studies in this category, all of which were from the US. Again, there is reassuringly high and relatively consistent VE across these studies.

Turning to the CDC VE studies, Dr. Britton and colleagues from CDC, Connecticut Department of Health, and Yale School of Medicine, published an *MMWR* on March 15, 2021 on the effectiveness of the Pfizer-BioNTech vaccine among residents of two skilled nursing facilities (SNF). These facilities were experiencing COVID-19 outbreaks that began just after the vaccine was introduced in these facilities. This offered an early opportunity to assess VE in this population. During this investigation, the researchers found that a partial regimen of the Pfizer-BioNTech vaccine from 14 or more days after the first dose and 7 days after the second dose provided significant protection against infection, with a VE of 63% (33%-79%). They conducted a couple of sensitivity analyses that excluded residents with prior SARS-CoV-2 infection and examined time windows of 14 more days after Dose 1 up to the receipt of Dose 2 and from 14 or more days after Dose 1 through 14 days following Dose 2. The sensitivity analyses yielded very similar VE results. These findings are comparable to other first dose VE findings among the broader adult population, community-dwelling older adults, and adults with multiple comorbidities.[38]

[37] Figure courtesy of Dr. Minal Patel, World Health Organization, Individual studies results only
[38] https://www.cdc.gov/mmwr/volumes/70/wr/mm7011e3.htm?s_cid=mm7011e3_w

On March 29, 2021, Dr. Thompson and colleagues published an *MMWR* with the interim estimates of VE of the Pfizer-BioNTech and Moderna mRNA vaccines in preventing SARS-CoV-2 infection and among HCP, first responders, and other essential and front line workers in 8 US sites. This is an ongoing cohort study. This interim analysis found the adjusted VE against infection for partial immunization status, meaning 14 days after the first dose through receipt, to be 80% (59%-90%). VE against infection for full immunization, starting 14 days after the second dose, was 90% (68%-97%).[39]

On April 28, 2021, Dr. Tenforde and colleagues published an MMWR on the effectiveness of the Pfizer-BioNTech and Moderna vaccines against COVID-19 among hospitalized adults aged 65 years or older in multiple sites across the US. This is also an ongoing study. This interim analysis used a test-negative design by enrolling hospitalized adults aged 65 years or older. Those who tested positive for COVID-19 by PCR were cases and those who tested negative were controls. In these interim results, VE against hospitalization of full vaccination was 94% (44%-99%). Additionally, the investigators looked at any vaccination. Partial or full vaccination status had a VE of 71% (44%–85%) and partial vaccination status alone had a VE of 64% (28%-82%).[40]

On April 30, 2021, Dr. Cavanaugh and colleagues from Kentucky published another *MMWR* that included VE during a COVID-19 outbreak associated with a SARS-CoV-2 R.1 lineage variant in a SNF. During this outbreak investigation, it was estimated that VE against symptomatic disease was 87%(66%-95%) among residents who were fully vaccinated. Among HCP in the facility who were fully vaccinated, VE was basically the same at 87% (46%-97%).[41]

Dr. Fleming-Dutra shared a summary table previewing the work that is still ongoing, including the VE priority, prospective data collection, and type of analyses (slides 18). Work has been done to harmonize and coordinate across various platforms, the COVID-19 response, and across the US government. Because this meeting was focused primarily on the pediatric population, she highlighted the ongoing work that will include adolescents and children (slide 19).

The OVERCOMING2 platform will focus specifically on adolescents and children. This is the VE arm of the OVERCOMING COVID-19 surveillance system. OVERCOMING2 will be assessing VE against COVID-19 and MIS-C among hospitalized children less than 19 years of age. This platform is based on an ICU network assessing influenza VE against critical illness in pediatric patients. During 2020, OVERCOMING2 enrolled all MIS-C patients and ICU patients with COVID-19 at about 57 US pediatric hospitals. The primary objectives for the VE portion of this network will be to: 1) assess the VE against any hospitalized COVID-19 in MIS-C among two control groups (test-negative acute respiratory illness and non-acute respiratory illness hospitalizations); and 2) assess the VE by several subgroups (variant, vaccine type, age, race/ethnicity, sex, time since vaccination, partial vaccination).

Another critical question that CDC is assessing is, “Do viral genome changes impact VE?” Selected prospective platforms will be collecting specimens from cases where possible for whole genome sequencing (WGS). It is important to note that this will not be performed in real-time and may not be powered for variant-specific VE assessment. The Vaccine Evaluation Unit (VEU) also has a team assessing vaccine breakthrough cases with hospitalization or death, and also is collaboration with the Emerging Infections Program (EIP) to compare the frequency of

[39] https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e3.htm?s_cid=mm7013e3_w
[40] https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e1.htm?s_cid=mm7018e1_w
[41] https://www.cdc.gov/mmwr/volumes/70/wr/mm7017e2.htm?s_cid=mm7017e2_w

variants among vaccinated and unvaccinated persons that may help shed light on this question. This work is part of the broader CDC efforts to monitor the impact of SARS-CoV-2 variants. Dr. Fleming-Dutra shared a summary table delineating current VE assessments for genomic characterization (slide 22).

Another important VE priority is to understand the duration of protection provided by COVID-19 vaccines. This will help inform the question about the potential need for a booster or booster doses. To better understand duration of protection, it is important to take into account into account changes in the circulating variants over time. The work to assess the duration of protection will leverage platforms that can be used on an ongoing basis to assess VE with increasing time since vaccination. Dr. Fleming-Dutra shared a summary table previewing VE assessments including duration of protection (slide 24).

In terms of the VE estimates that were calculated from the COVID-19 outbreaks in Connecticut and Kentucky and published in the *MMWR*, COVID-19 outbreaks in defined populations may provide opportunities to estimate VE around important questions. The Vaccine Effectiveness team is currently working with state and local health departments and other federal partners to conduct VE assessments in outbreak settings among residents of long-term care facilities (LTCF) and among incarcerated and detained persons and staff in corrections facilities. They are actively looking for COVID-19 outbreaks in congregate settings, but the investigations for these outbreaks can be leveraged to assess variant-specific effectiveness, VE for Johnson & Johnson's Janssen vaccine, and the VE of among adolescents and children when children are eligible for vaccine.

In conclusion, the initial COVID-19 VE estimates from recently published reports are demonstrating remarkably consistent results across studies with a variety of methods and populations, which is very reassuring. There is an urgent need for VE data to guide vaccine policy. A broad approach including a diversity of projects, methods, bias control, populations, and sample sizes strengthens the understanding of the true real-world performance of these vaccines.

Summary of Discussion

- ACIP members suggested a number of additional studies they hoped might be underway or could be considered, including the following:
    - Some of the large datasets probably have enough pregnant women to examine efficacy in this population
    - More data are needed on the immunocompromised population (~4% of the US population) in terms of overall efficacy and timing of vaccination, particularly given the relatively devastating data over the past few weeks about cellular immune response in these populations and the inability to give a booster under the current EUA
    - Perhaps consideration could be given to more severe forms of the illness rather than just mildly symptomatic infection and other important factors that will stress medical systems
    - Consider modeling certain locations with varying levels of uptake of vaccination to determine the indirect protective effects in localized communities with higher uptake
    - With regard to the analysis of completing the vaccination schedule as planned, one suggestion would be to assess how many subjects had a prior COVID infection and

1 versus 2 doses with respect to VE, given that 1 dose in people with prior COVID infection may result in a sufficient antibody response
- Duration of protection and VE against variants are critically important to better understand, particularly in terms of immunocompromised populations

Update on Emerging SARS-CoV-2 Variants and Vaccine Considerations

Dr. Heather Scobie (CDC/CGH) provided an update on emerging SARS-CoV-2 variants and vaccine considerations. There are multiple SARS-CoV-2 variants circulating globally. Viruses constantly change through mutation, so new variants are to be expected. After emerging, some disappear and other persist. CDC and others are studying these variants to understand whether they spread more easily, cause milder or more severe disease, are detected by available diagnostic tests, respond to current therapeutics, or change the effectiveness of COVID-19 vaccines.[42]

A SARS-CoV-2 Interagency Group (SIG) has established definitions for classifying variants into three categories for public health action, which are described below:

- **Variant of Interest (VOI):** Genetic markers associated with changes to receptor binding, reduced antibody neutralization, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity

- **Variant of Concern (VOC):** Evidence of increased transmissibility, more severe disease, significant reduction in neutralization by antibodies, reduced effectiveness of treatments or vaccines, or diagnostic detection failures

- **Variant of High Consequence (VOHC):** Clear evidence that prevention measures or medical countermeasures have significantly reduced effectiveness [None yet]

US classifications may differ from those of the WHO since the importance of variants may differ by location. Currently, there are 8 VOIs. B.1.526 and B.1.526.1 were first detected in New York. B.1.525 was first detected in the United Kingdom (UK) and Nigeria and P.2 was first detected in Brazil. The previous week, 4 VOIs were detected. B.1.617 was first detected in India and B.1.617.1, 2, and 3 also were added as variants of interesting in India. The variants have independently evolved shared mutations in the receptor binding domain of the spike protein, which can reduce the efficacy of antibody therapies and vaccines.

Three variants have global consensus as VOCs. These include B.1.1.7 first detected in the UK, B.1.351 first detected in South Africa, and P.1 first detected in Brazil and Japan. Both B.1.1.7 and B.1.351 are estimated to be 50% more transmissible and have become the dominant strains in some areas. The Brazil and South Africa strains share a cluster of three mutations in the receptor binding domain that have the largest known impact on VE, with the E484K mutation being the most problematic. More recently, the US classified the California variants B.1.427 and B.1.429 as VOCs. These variants appear to be 20% more transmissible.

[42] https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html

Turning to genomic surveillance and the epidemiology of the variants, US SARS-CoV-2 sequences are submitted in two public repositories, the National Center for Biotechnology Information (NCBI) and GISAID starting in January 2020 to the present. As a result of efforts by CDC and partners to improve genomic surveillance, the number of published sequences has substantially increased during 2021. Overall, 6%-9% of SARS-CoV-2 positive cases were sequenced weekly.

National estimates of the proportions of circulating SARS-CoV-2 variants are available from CDC's COVID data tracker. To provide more accurate estimates, proportions are adjusted with weights to correct for non-random sampling. The previous week, CDC started producing NOWCAST projections and prediction intervals that account for a limited data availability during the 3-4 week lag between sample collection and sequencing results. This allows estimation for a more recent time period. For the 2 weeks ending May 8th, B.1.1.7 remained the most frequent lineage, with a projected prevalence of 72%. B.1.427 and B.1.429 were projected to have decreased 1% combined. B.1.351 decreased to less than 1%, while P.1 increased to 6%. The VOIs B.1.526 and B.1.526.1 were relatively steady at 7% and 3%, and B.1.617.2 increased to 3%. Other VOIs were less than 1%. In terms of the NOWCAST projected variant proportions in each of the 10 designated HHS services regions for the 2 weeks ending May 8th, while B.1.1.7 predominated in each region, the distribution of other lineages varied. For example, B.1.526 and B.1.526.1 were highest in the Northeast, while B.1.427 and B.1.429 were highest on the West Coast. P.1 was projected to have increased in all regions, but was highest at around 10% in regions 1, 5, and 9. B.1.617.2 was greater than 10% in regions 2 and 8.

Regarding the impact of variants on VE, while cellular immunity likely plays a role in protecting against SARS-CoV-2, a robust correlation has been observed between VE versus neutralizing or binding antibody titers. Current vaccines produce neutralizing antibody levels falling within a protective margin, but a precise threshold or correlative protection has not yet been determined. New vaccines may be needed for E484K and future escape mutations, which may reduce protection to near below the threshold resulting in lowered VE, increased breakthrough infections, and shortened duration of immunity.

CDC conducted a review of available studies on vaccines authorized or intending to be authorized in the US and containing data on the ability of post-vaccination sera to neutralize SARS-CoV-2 variants. In terms of the reduction in neutralization and variants relative to the wildtype or dominant strain used in each study, B.1.1.7 had a median 2-fold reduction in neutralization, B.1.351 had the largest median reduction at 7.6-fold, and P.1 had an intermediate reduction of 3.7-fold. One study assessed the other Brazil variant, P.2, and observed a similar effect to P.1. Two studies assessed a B.1.1.7 variant with an E484K change, which has been detected in the UK and the US, and found that neutralization was reduced compared to B.1.1.7 alone. The India B.1.617, California B.1.429, and New York B.1.526 variants had modest reductions of less than 3-fold, while one study of B.1.617.1 and a B.1.526 variant with an additional 484K mutation have larger reductions.

In summary, the largest impacts on neutralization were observed for B.1.351, followed by P.1. It is difficult to estimate how these results might translate into clinical protection. Some of the variation in the results presented may be explained by differences in experimental conditions. Limitations for all studies were small sample sizes and a lack of generalizability. Almost half of the studies have yet to be peer-reviewed.

With regard to VE point estimates related to the variants (slides 21, 22), a Pfizer vaccine study published the previous week from Qatar showed a high real-world VE of 90% against infection with B.1.1.7 and 75% against B.1.351. A growing number of Pfizer studies from the UK and Israel also have demonstrated high real-world VE while B.1.1.7 was prevalent. For the Janssen vaccine clinical trial, a variation in VE was observed across countries that may have been related to the high prevalence of circulating variants in Brazil and South Africa. Importantly, both the Qatar Pfizer study and Janssen clinical trial demonstrated high VE against severe critical disease regardless of circulating variants. In the Novavax and AZ vaccine clinical trials, slightly lower VEs were observed for B.1.1.7 than non-B.1.1.7 strains and more substantial reductions were observed for B.1.351. The AZ vaccine clinical trial in South Africa observed a VE of only 10% against B.1.351, but study investigators noted that only mild or moderate cases were observed in the trial.

Despite high vaccine efficacy, vaccine breakthrough cases are still expected to occur, including those caused by circulating variance. As of April 26th, among 95 million people who were fully vaccinated in the US, 9245 breakthrough infections were reported through national passive surveillance. CDC works with state health departments on case investigations and sequencing to identify variants. Starting soon, a CDC project was the emerging infections program sites should allow estimation of the frequency of SARS-CoV-2 variants among vaccinated and unvaccinated people in the US.[43]

One study from Israel assessed variants of concern and infections among Pfizer vaccinated people versus unvaccinated matched controls during a time when B.1.1.7 was predominant and B.1.351 was found in less than 1% of specimens. Investigators found that people testing positive for SARS-CoV-2 at least a week after the second vaccine dose had significantly higher odds of infection with B.1.351, while partially vaccinated persons between 2 weeks after the first dose and 1 week after the second dose had significantly higher odds of having B.1.1.7 compared with unvaccinated people. The authors concluded that breakthrough infection was more frequent for VOCs.[44] For perspective, CDC also notes that other studies from Israel have documented high VE and a dramatic decline in COVID cases despite B.1.1.7 predominance.

In summary, the B.1.1.7 variant is exponentially increasing in prevalence in the US but has minimal impact of VE. However, variants with additional substitutions in their receptor binding domain, like E484K, deserve special attention. The B.1.351 variant is at low prevalence in the US, but has moderate impact on the effectiveness of some vaccines, though they may still provide protection against severe disease. P.1 has increasing prevalence in the US and has the same triple mutation in the receptor binding domain as B.1.351, which is worth watching closely. Additional data are still needed on the potential impact on VE.

Vaccine manufacturers have announced booster studies of current vaccines and their development of second generation vaccines against B.1.351. The previous week, Moderna posted preliminary results of a Phase 2 clinical trial of a single 50 µg booster dose of the previously authorized and new variant specific vaccines. At 6-8 months after the primary series, study participants had low or undetectable neutralizing antibodies for B.1.351 and P.1, while titers against wild-type virus were still likely to be productive. Both variant vaccines had acceptable safety and boosted immunity levels roughly equivalent to those after primary vaccination for all viruses tested. The variant booster was more effective than the original

[43] Tehran et al. https://www.cdc.gov/mmwr/volumes/70/wr/mm7017e1.htm
[44] Kustin et al. MedRxiv preprint (16 April 2021): https://www.medrxiv.org/content/10.1101/2021.04.06.21254882v2

vaccine at neutralizing B.1.351. Still in progress is a clinical trial for bivalent vaccine with a 1:1 mix of the original and variant vaccines.[45]

Periodic update of SARS-CoV-2 vaccines is likely to be needed. The FDA has defined the data needed to support an EUA amendment for a vaccine addressing emerging SARS-CoV-2 variants, which includes an immunogenicity study designed as a non-inferiority comparison. The SIG is developing an evaluation and risk assessment framework that defines the evidence needed to recommend whether a modified vaccine is needed. WHO will have a role in global coordination.

It is important to emphasize that the current prevention measures and authorized vaccines offer good protection against SARS-CoV-2 variants and efforts are needed to increase uptake. CDC will continue to monitor evidence on the emergence and spread of SARS-CoV-2 variants, VE, breakthrough infections in vaccinated or previously infected persons, and the ability of post-vaccinations serum to neutralize emerging variant viruses. ACIP will review evidence submitted for booster doses and any next generation vaccines if it becomes clear that they are needed to address the variants.

[45] Wu et al. medRxiv preprint (May 6, 2021): https://doi.org/10.1101/2021.05.05.21256716 https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov/ https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development

CERTIFICATION

Upon reviewing the foregoing version of the May 12, 2021 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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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
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
AFM	Acute Flaccid Myelitis
AGS	American Geriatric Society
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
CBER	Center for Biologics Evaluation and Research
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
CVST	Cerebral Venous Sinus Thrombosis
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVRPA	Division of Vaccines and Related Product Applications
DVT	Deep Vein Thrombosis
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent
EMA	European Medicines Agency
EtR Framework	Evidence to Recommendations Framework
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHCs	Federally Qualified Health Center
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAN	Health Alert Network
HCP	Health Care Personnel / Provider / Professional
HCW	Health Care Workers

HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-Induced Thrombocytopenia
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
ITP	Immune Thrombocytopenia
ITT	Immune Thrombotic Thrombocytopenia
ITT	Intention-To-Treat
IVIG	Intravenous Immune Globulin
J&J	Johnson & Johnson
LGBTQ+	Lesbian, Gay, Bisexual, Transgender, Questioning, and Others
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	*Morbidity and Mortality Weekly Report*
mRNA	Messenger Ribonucleic Acid
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	New England Journal of Medicine
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
OB-GYN	Obstetrics and Gynecology
PE	Pulmonary Embolism
PF4	Platelet Factor 4
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PIDS	Pediatric Infectious Disease Society
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHEA	Society for Healthcare Epidemiology of America
SIG	SARS-CoV-2 Interagency Group
SMEs	Subject Matter Experts
SOC	System Organ Class
SSRI	Selective Serotonin Reuptake Inhibitor

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
VITT	Vaccine-Induced Immune Thrombotic Thrombocytopenia
VOC	Variant of Concern
VOHC	Variant of High Consequence
VOI	Variant of Interest
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization