MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JUNE 17-18, 2022
EXECUTIVE SUMMARY

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MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on June 17-18, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides an Executive Summary of the meeting, which focused on the epidemiology of COVID-19 in young children; vaccine effectiveness (VE) of COVID-19 vaccines in children and adolescents; Moderna COVID-19 vaccine mRNA-1273 safety, immunogenicity, and efficacy in children 6 months through 5 years of age; safety, immunogenicity, and efficacy of Pfizer-BioNTech BNT162b2 in children ages 6 months through 4 years of age; implementation of pediatric vaccines; Evidence to Recommendations (EtR) Framework update on mRNA COVID-19 vaccines in young children; Clinical Considerations update; and votes on Moderna COVID-19 vaccine in children 6 months to 5 years of age and Pfizer-BioNTech COVID-19 vaccine in children 6 months to 4 years of age.

EXECUTIVE SUMMARY

Session Overview 6-17-22

Dr. Matthew F. Daley (WG Chair) reported that there were 85,681,615 total COVID-19 cases and 1,007,374 total deaths between January 23, 2020 – June 14, 2022. Based on cumulative total incidence, COVID-19 is the leading cause of death (COD) among infectious diseases for people ages 0-19. COVID-19 is the seventh most common of all COD for people 0-19 years of age. Among people 1-4 years of age, COVID-19 is the fifth most common of all COD. Unvaccinated people ages ≥5 years had 10 times the risk of dying from COVID-19 through March compared to people vaccinated with at least the primary series.

Among children 6 months to 4 years of age, seasonal influenzas vaccines have averted 4.3-20.1 million illnesses, 2.9-15.5 million visits, 32,000-164,000 hospitalizations, and 130-2,350 deaths. This was in the context of substantial disease burden with a seasonal incidence of about 5% to 20%, variable VE estimates ranging from 19% to 60% from 2010-2020, and consistent vaccine coverage of 63.6% to 75.2% influenza vaccine coverage among children 6 months to 4 years of age from 2010-2020.

There is no COVID-19 vaccine currently authorized for use in children less than 5 years of age. Only the Pfizer-BioNTech vaccine is currently authorized for use in children 5-17 years of age. On June 14, 2022, the Food and Drug Administration's (FDA's) Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened a meeting to review the request for Emergency Use Authorization (EUA) for the Moderna COVID-19 vaccine in children and adolescents 6-17 years of age. VRBPAC convened a meeting on June 15, 2022 to review requests for EUA for the Moderna COVID-19 vaccine in children 6 months through 5 years of age and the Pfizer-BioNTech COVID-19 vaccine in children 6 months through 4 years of age.

Between late May and early June 2022, the COVID-19 vaccine Work Group (WG) reviewed and discussed the following:

- ❑ Vaccine safety, immunogenicity and efficacy data, including both immunobridging and laboratory-confirmed direct efficacy, for the Moderna COVID-19 vaccine for children and adolescents 6 months through 5 years of age and 6 through 17 years of age
- ❑ Vaccine safety, immunogenicity, and efficacy data, including both immunobridging and laboratory-confirmed direct efficacy, for the Pfizer-BioNTech COVID-19 vaccine for children and adolescents ages 6 months through 4 years of age
- ❑ COVID-19 epidemiology and outcomes in children ages 6 months through 5 years of age
- ❑ Post-authorization VE of COVID-19 vaccines in children and adolescents ages 5 through 17 years of age
- ❑ Grading of Recommendations, Assessment, and Evaluation (GRADE) and EtR Frameworks for both Moderna and Pfizer-BioNTech COVID-19 vaccines for children ages 6 months through 5 years of age

Epidemiology of COVID-19 in Young Children

Katherine Fleming-Dutra, MD (CDC/NCIRD) presented an update on COVID-19 epidemiology in children 6 months through 4 years of age in terms of COVID-19 incidence and burden, emergency department (ED) visits, hospitalization rates and severity, COVID-19-associated mortality, Multisystem Inflammatory Syndrome in Children (MIS-C), post-COVID conditions, and other impacts of the pandemic on children and families. Children 5-11 years of age and adolescents 12-17 years of age are currently eligible for COVID-19 vaccination.

As Dr. Daley reported, there were 85,681,615 total COVID-19 cases and 1,007,374 total deaths among all ages between January 23, 2020 – June 14, 2022. COVID-19 is the leading COD among infectious diseases for people ages 0-19. COVID-19 is the seventh most common of all COD for people 0-19 years of age. Among people 1-4 years of age, COVID-19 is the fifth most common of all COD. Unvaccinated people ages ≥5 years had 10 times the risk of dying from COVID-19 through March compared to people vaccinated with at least the primary series. Among children 6 months through 4 years of age, from October 2020–September 2021, COVID-19 hospitalization rates were lower than influenza hospitalization rates during the 2017–2018 through 2019–2020 pre-pandemic influenza seasons. From October 2021–April 2022, COVID-19 hospitalization rates were as high or higher than influenza hospitalization rates during the 2017–2018 through 2021–2022 influenza seasons.

MIS-C causes severe illness in persons 0-20 years of age characterized by fever, multi-system organ involvement, laboratory evidence of inflammation, and SARS-CoV-2 infection with no alternative plausible diagnosis. Occurring 2-6 weeks after acute SARS-CoV-2 infection, 60% to 70% of patients are admitted to intensive care and 1% to 2% die. A range of new, returning, or ongoing health problems have occurred 4 or more weeks after acute SARS-CoV-2 infection in adults and children <18 years of age. Children 0-5 years of with SARS-CoV-2 infection are more likely than controls without known SARS-CoV-2 infection to experience symptoms lasting more than 4 weeks after acute infection of fatigue, loss of taste, and/or loss of smell. Evidence regarding the prevalence and spectrum of post-COVID conditions among children, especially young children, is limited by the inability of younger children to verbalize symptoms, few studies including children, lack of control groups, and symptoms frequently occurring in children without known SARS-CoV-2 infection.

Other indirect impacts of COVID-19 pandemic on children include worsening of mental or emotional health, widening of existing education gaps, decreased physical activity and increased body mass index (BMI), decreased healthcare utilization, decreased routine immunizations, and increased adverse childhood experiences (ACEs).

To summarize, as of June 12, 2022, COVID-19 has caused >570,000 cases among infants <1 year of age and >1.9 million cases among children 1-4 years of age. The Omicron surge in the US led to the highest numbers of COVID-19 cases, ED, and hospitalization rates seen during the pandemic. Children 6 months through 4 years of are at risk of severe illness from COVID-19. More than half of hospitalized children ages 6 months through 4 years had no underlying conditions. During Omicron predominance, COVID-19-associated hospitalizations among children ages 6 months through 4 years have similar or increased severity compared to older children and adolescents. The burden of COVID-19 hospitalization is similar to or exceeds that of other pediatric vaccine preventable diseases. The COVID-19 pandemic continues to have significant impact on families and increases disparities.

Updates on VE of COVID-19 Vaccines in Children and Adolescents

Ruth Link-Gelles, PhD, MPH (CDC/NCIRD) presented on COVID-19 VE during Omicron for children and adolescents. She described data from the Pediatric Research Observing Trends and Exposures in COVID-19 Timelines (PROTECT), Increasing Community Access to Testing (ICATT) Partnership, the VISION Network, and unpublished preliminary data from CDC. To summarize some of the findings, in terms of infection, 2-dose VE declined quickly in children and adolescents, following a similar pattern that occurred among adults during Omicron predominance. A booster dose in adolescents significantly improved VE initially, although there was waning. With regard to emergency department/urgent care (ED/UC) visits, 2-dose VE was higher for ED/UC visits compared to infection but declined 60 days after the second dose for adolescents. A booster dose in persons 12-15 years of age significantly improved VE. Regarding severe disease, 2-doses provided protection for both age groups, with some waning for hospitalization in adolescents. There was high VE in children and adolescents against hospitalizations and MIS-C. There were not enough data to assess waning in children 5-11 years of age or the impact of a booster dose in persons 12-15 years of age.

Moderna COVID-19 Vaccine (mRNA-1273): Safety, Immunogenicity, and Efficacy in Children 6 Months through 5 Years of Age

Rituparna Das, MD, PhD (Moderna) provided an update on the use of mRNA-1273 as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in young children 2-5 years of age and infants and toddlers 6-23 months of age where the greatest increase has been seen in the burden of hospitalization with the Omicron surge. The proposed 2 doses at the 25µg per dose level are to be administered 1 month apart. Moderna's data in these age groups comes from Study 204 in which more than 6,500 infants, toddlers, and young children were enrolled and more than 5,000 received ≥1 25µg dose of mRNA-1273. Overall, this represents a substantial safety database for these groups. The median safety follow-up times in both age groups are more than 2 months. In the early cohorts, which is the dose-finding part of the study, there are children with 7 to 8 months of median safety follow-up.

Study 204 was conducted in 2 parts for each of the age strata. Part 1 was an open-label, dose-escalation, age de-escalation study that was conducted to select a dose-level for further testing in Part 2, which was the placebo-controlled part of the trial. Both 25µg and 50µg were studied in the children 2-5 years of age. The 25µg dose was chosen for these older children. The 50µg formulation was not investigated in the younger children. Overall, the 25µg dose was chosen for both age groups because it showed an acceptable tolerability profile and demonstrated a high likelihood of meeting the pre-specified immunogenicity success criteria for this study. After Part 1 was completed, a Data and Safety Monitoring Board (DSMB) meeting was convened to ensure the committee's concurrence with the selected dose. Part 2 was designed to randomize the children in a 3:1 ratio to receive either mRNA-1273 or saline placebo. The children will be followed for 12 months after receiving their last dose of vaccine. The data presented during this session focused on the randomized phase of the study. Overall, the demographics were well-balanced between the vaccine and placebo cohorts in both age groups. The mean age was approximately 16 months in the youngest group and 3 years in the older age group. Gender, race, and ethnicity also were well-balanced.

The specific safety objectives included solicited, local, and systemic adverse events (AEs) collected for 7 days post-vaccination. Unsolicited adverse events were captured for 28 days after each vaccination. And serious AEs, medically attended AEs (MAAE), and AEs of special interest (AESI), including myocarditis, pericarditis, and MIS-C, were followed throughout the entire study. In children 2-5 years of age, pain was the most common event, with similar rates and severity following Dose 1 and Dose 2. Most local AEs, including pain, were Grade 1 or Grade 2, with few Grade 3 reactions. The median duration of local AEs in this age group was 2 to 3 days. In infants and toddlers 6-23 months of age, pain was the most common local AE, although reports of pain in this youngest group were more similar to placebo both post-Dose 1 and post-Dose 2 compared to the older age group. Systemic adverse reactions were evaluated according to age. Young children's events were fever, headaches, fatigue, myalgia, arthralgia, nausea, vomiting, and chills. For infants and toddlers, the events were fever, irritability, crying, sleepiness, and loss of appetite. Headache and fatigue were the most common systemic adverse reactions in the children 37 months to 5 years of age. Among the vaccine recipients, systemic adverse reactions were more frequent post-Dose 2 compared to post-Dose 1, although this difference was less pronounced than seen in older age groups. The duration was 2-3 days, which is very consistent with other age groups. Reporting rates of systemic adverse reactions were similar between Dose 1 and Dose 2. Systemic events were reported at similar rates among vaccine and placebo recipients.

Fever is a particularly important event in the assessment of pediatric vaccines. In terms of fevers by increments among children 6 months through 5 years of age, fever after any dose occurred in about a quarter of the children. The distribution of temperatures was similar between the two age groups. Fevers of >40ºC (>104ºF) were rare. Fevers occurred more frequently following Dose 2 in children 2-5 years of age. It is important to note that most reports of fever were less than 39.0ºC. Fevers in infants and toddlers also are reported more commonly post-Dose 2. The rates of fever greater than 39.0ºC in this youngest group were similar to placebo. Beyond Day 2, fever rates in children receiving mRNA-1273 were similar to placebo. The median duration of fever in this age group was 1 day. It is important to note that this study was conducted during the winter months when respiratory tract infections are prevalent. This is evident by the relatively high rates of fever observed in the placebo group. A similar pattern was seen in infants and toddlers, with the peak of fever occurring on Days 1 and 2 after vaccination. On subsequent days, fevers looked similar across the vaccine and placebo groups. The higher background rate of fever is even more prominent in the infants and toddlers. There were 15 children with fever >40ºC (>104ºF) in the mRNA group and 3 in the placebo group. The peak

temperature of >40ºC had a duration of less than 1 day. Of the 15 vaccine recipients, 5 of the children also had symptoms of concurrent viral infections. There was 1 febrile seizure that occurred proximal to vaccination and was considered related by the investigator. Febrile seizures can occur in up to 5% of young children. The child in this study also had a maculopapular rash onset 2 days after the seizure and went on to have a subsequent seizure associated with another fever approximately 6 weeks later. The child has remained in the study and received Dose 2 of the vaccine without events.

In terms of unsolicited AEs, this analysis presented events reported up to 28 days after any injection in children 2-5 years of age. The incidence of unsolicited AEs was similar among vaccine and placebo recipients. There were no SAEs considered to be related by the investigator. Incidence of MAAEs were similar and there were no AEs that led to discontinuation of the vaccine or from the study. After the data cutoff, one event of urticaria was reported on Day 1 post-vaccination that did lead to discontinuation. There were no events of death or AEs of MIS-C or myocarditis. Among the infants and toddlers, the incidence of unsolicited AEs overall and the MAAEs were similar among vaccine and placebo recipients. There was 1 SAE within 28 days that was considered related to vaccination as described in the fever discussion. Since the data cut of Moderna's submission in late February, the SAEs were pooled from the live database in early May to provide further reassurance of the long-term safety of mRNA-1273. The updated analysis did not identify any new safety signals and there were no SAEs considered by the investigator to be related to vaccination.

Turning to immunogenicity data, VE was successfully inferred by meeting the pre-defined co-primary immunogenicity objectives that were agreed to with the FDA. These included geometric mean concentration (GMC) and the difference in seroresponse. In each age group, immune responses were compared to the subset of persons 18-25 years of age in the immunogenicity subset from Study 301 in which primary efficacy of the vaccine against any and severe COVID-19 disease was demonstrated. Immunogenicity for children 2-5 years of age compared to young adults was 1.01 (0.88, 1.17). The seroresponse rates were close to 100%, with a difference of -0.4% (-2.7,1.5). For infants and toddlers 6-23 months of age, both co-primary immunogenicity endpoints also were met. The ratio compared to young adults was 1.28 (1.12, 1.47). In addition, the seroresponse rate was 100%. The group difference was 0.7% (-1.0, 2.5). The immune response to mRNA-1273 has been remarkably consistent across age cohorts despite administering lower doses to young children. Across all age groups from young adults 18-25 years of age through the youngest children in the pediatric program of infants and toddlers 6-23 months of age, the geometric mean ratio (GMR) ranged from 1.01 through 1.28, successfully meeting all primary immunogenicity hypotheses in all age groups. Additionally, support for VE was provided through assessments of efficacy in the study demonstrated that in all age groups, there was comparable effectiveness to adults when the variants were matched. Although no serious severe cases of COVID-19 were seen in the children at the time of data cutoff, this consistency led Moderna to believe that protection against severe disease will be comparable to adults, which will be evaluated in post-authorization effectiveness studies. To expand upon this, the studies were conducted as the SARS-CoV-2 in the pandemic was changing. This is important when interpreting the efficacy results in the 2 youngest age cohorts. The enrollment and efficacy follow-up in the youngest children was conducted when the Omicron variant was predominant. From December 2021 through March 2022, the US incidence of SARS-CoV-2 infections rose from fewer than 200,000 per day to a peak of 1.4 million cases per day, which was when these youngest cohorts were followed.

While the study was not powered for assessment of efficacy, it was possible to get good efficacy estimates given the high rates of community SARS-CoV-2 transmission when these randomized cohorts were conducted. There were 2 case definitions for COVID-19 used, the CDC case definition that required at least 1 symptom and the Study 301 case definition that required 2 systemic symptoms or 1 respiratory symptom. The CDC case definition was considered primary because children tended to have less severe symptoms of COVID-19 than adults. Of note, both definitions required a nasal swab positive by reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 and a comprehensive approach was taken to capturing cases. Efficacy estimates in the young children are based on 180 cases captured over 71 days post-Dose 2. Beginning with the children 2-5 years of age, there was a lower incidence of COVID-19 by both definitions in children who received vaccines compared to those who received placebo. Statistically significant VE of 36.8% was observed using the CDC definition. With the Study 301 case definition, number of cases was reduced, but efficacy of 46.4% was observed. This also was demonstrated by the cumulative incidence curve for COVID-19 by the CDC case definition. For infants and toddlers 6-23 months of age, efficacy estimates were based on 85 cases captured over 71 days post-Dose 2. There was statistically significant efficacy in this cohort of 50.6% when the CDC definition is used. With the Study 301 definition, the point estimate was directionally similar and the confidence intervals were wider due to the drop in the number of cases.

At the start of the Omicron wave, parents were reluctant to bring their youngest children into the study site for illness visits. Instead, they were calling in results of positive home antigen tests. Given that the home antigen test results also were captured, a sensitivity analysis was done that defined COVID-19 either by positive PCR or home antigen tests. With the increased number of cases captured, the confidence intervals narrowed and the point estimates for efficacy were 53.5% and 43.7%, with the confidence intervals excluding zero. This also was demonstrated in the cumulative incidence curve for COVID-19 by the CDC case definition in the younger age groups. For context of the efficacy, real-world effectiveness in adults during the Omicron surge was assessed to help interpret VE from the pediatric program. For real-world effectiveness data against Omicron after a 2-dose primary series among adults, data were used from Moderna's collaboration study with the Kaiser Permanente health system. VE of mRNA-1273 against COVID-19 was 44% when the Omicron variant was predominant. In Study 304 in infants and young children, efficacy of mRNA-1273 was consistent with effectiveness observed in adults. While VE against any infection was lower during Omicron, the benefits of mRNA-1273 continued to be seen against hospitalization. Two doses of mRNA-1273 were shown to be 84% effective against hospitalization during the Omicron period. This is important because the same level of protection would be expected in children, given the consistency of the immune response and the efficacy with adults. Study 204 is ongoing and safety follow-up will continue for all participants. All children will be offered a booster dose after their second dose, and they will be boosted either with mRNA-1273 or Moderna's bivalent Omicron-containing vaccine.

In summary, mRNA-1273 was well-tolerated. Local and systemic reactions were seen less frequently in the youngest age groups. Solicited adverse reactions were mostly Grade 1 or 2 and slightly more common after Dose 2. Fever was reported in about a quarter of children and most commonly seen on Day 1 or 2 after each dose and resolved within 1 day. No deaths, myocarditis, pericarditis, or MIS-C were reported among vaccine recipients. There was 1 related SAE of febrile seizure within 28 days of any vaccination. The primary immunogenicity objectives were met and demonstrated that 2 doses of mRNA-1273 were immunogenic. GMCs and seroresponse rates were non-inferior to young adults. VE can, therefore, be successfully inferred based on immunogenicity. In both age groups, direct efficacy against COVID-19 was observed during the Omicron period. This is consistent with effectiveness observed in adults.

Based on the information shown during this session, Moderna has demonstrated that the benefit-risk profile for mRNA-1273 is strongly favorable in children 6 months through 5 years of age.

Safety, Immunogenicity, and Efficacy of BNT162b2 (COVID-19 Vaccine, mRNA) in Children 6 Months through 4 Years of Age

William C. Gruber, MD, FAAP, FIDSA, FPIDS (Pfizer, Inc.) presented data supporting BNT162B2 (COVID-19 Vaccine, mRNA) in children 6 months through 4 years of age with a focus on Phase 2/3 clinical data on safety, immunogenicity, and efficacy and an assessment of benefit-risk. In terms of the clinical data that supports recommendations for this age group beginning with children 5-11 years of age, nearly 19% of children 2 to <5 years of age who received 10µg developed fevers after the first and second doses. Of these fevers, 1/3 were severe. This could be poorly accepted by parents, reducing adherence to the primary 3-dose series. In contrast, the 3µg doses had a much better tolerability profile combined with comparable to better immune responses to the SARS-CoV-2 reference strain. Therefore, the 3µg doses level was advanced into Phase 2/3.

To infer efficacy in the pediatric population in the pivotal study, immunological non-inferiority to persons 16-25 years of age for whom efficacy was established was assessed in addition to safety to satisfy EUA immune response criteria and infer efficacy. Although not required for EUA approval, COVID-19 surveillance was conducted, permitting an early evaluation of VE. Children were administered 2 doses 21 days apart. A third dose was administered at least 60 days later. Current follow-up includes 1-month post-Dose 3 serology and efficacy to the data cutoff of April 29, 2022. All safety data presented was from the blinded placebo-controlled follow-up period for children 2 to <5 years of age and then 6 months to <2 years of age. Demographics in the 2 to <5 age group were balanced between the vaccine and placebo groups in terms of gender, race, ethnicity, SARS-CoV-2 exposure, and comorbidities.

Local reactions captured by eDiary over 7 days were mostly mild to moderate in severity, somewhat higher in vaccine recipients compared to placebo recipients, and did not show an increase from Dose 2 to Dose 3. Local reactions were higher or similar in frequency and severity in those with evidence of prior SARS-CoV-2 infection at baseline and all were within a well-tolerated range. There were no Grade 4 local reactions. Systemic symptoms solicited by eDiary were mostly mild to moderate and comparable after each dose. Fever, fatigue, or other symptom rates were remarkably similar to those seen in placebo recipients at each of the 3 doses and much lower than those in older age groups immunized with a higher dose level. Fever rates were comparable or lower than for other childhood vaccines. Only 3, or less than 0.2%, of BNT162B2 participants recorded fever greater than >40.0°C after Dose 1 or 2 starting on Day 2, Day 4, or Day 6. All returned to normal 6 to 7 days after the dose, one of whom had a presentation suggestive of a viral exanthem. None of these required hospitalization and all resolved quickly. Systemic symptoms were higher or similar in frequency and severity in those with evidence of prior SARS-CoV-2 infection at baseline and all were within a well-tolerate range. This highly favorable tolerability profile for the Pfizer-BioNTech vaccine should be reassuring to parents and care providers.

In children 2 to <5 years of age, blind and safety follow-up occurred from the time of Dose 2 to Dose 3 or cutoff date for a median of 4.0 months and for Dose 3 to the cutoff date for a median of 1.4 months. Overall, unsolicited AEs related to AEs, SAEs, withdrawals were infrequent and comparable between the vaccine and placebo groups. There were 3 (0.2%) subjects in the vaccine group who were withdrawn from the study due to AEs (e.g., pyrexia considered related,

status epileptic considered unrelated, and urticaria considered unrelated). There was 1 participant in the placebo group who was withdrawn due to facial swelling and rash that were considered related. There were no deaths reported in this age group. AEs, as defined by system organ class (SOC), were comparable between vaccine and placebo group.

Now looking at children 6 months to <2 years of age, the demographics were balanced between the vaccine and placebo groups related to gender, race, ethnicity, prior SARS-CoV-2 infection, and comorbidity. Local reactions in this age group, with and without prior SARS-CoV-2 infection, were mild to moderate with incidence somewhat higher in vaccine recipients. Local reactions were somewhat higher or similar in frequency and severity in those with evidence of prior SARS-CoV-2 infection at baseline and all were within a well-tolerated range. There were no Grade 4 events and frequency remained relatively the same after each dose, which is consistent with a well-tolerated vaccine. Fever, decreased appetite, drowsiness, and irritability were mostly mild to moderate, similar to placebo rates, lower than those observed in older children and adults, and comparable to those after other childhood vaccines. Fever >40.0 °C was recorded by only 3 vaccine recipients (<0.1%) for each dose starting on Day 1, Day 2, or Day 3. All returned to normal 5 to 6 days after Dose 2 among those who had a concurrent viral infection. One fever >40.0 °C was reported by a placebo recipient after the first dose. None of these required hospitalization and all resolved quickly. Systemic symptoms were somewhat higher or similar in frequency in severity in those with evidence of prior SARS-CoV-2 infection at baseline and all were within a well-tolerated range. The overall incidence at low severity of systemic symptoms speaks to a favorable tolerability profile, which should be reassuring to parents and care providers.

Safety follow-up in children 6 months to <2 years of age included blinded follow-up from the time of Dose 2 to Dose 3 or the cutoff date for a median of 6.3 months and from Dose 3 to the cutoff date for a median of 1.3 months. Any AEs, related AEs, SAEs, and withdrawals were infrequent and comparable between the vaccine and placebo groups. Three participants (0.3%) in the BNT162B2 group were withdrawn from the study due to AEs that all were related. Of these, 2 were due to fever >40.0 °C and had a viral exanthem that was unrelated. One participant was withdrawn due to a generalized rash on the face and trunk. There were no deaths reported in this age group. AEs defined by SOC were comparable between vaccine and placebo recipients.

Few AESIs were recorded among children 6 to <5 years of age. Predominant categories with potential angioedema and hypersensitivity comprising mainly urticarias and rashes were balanced between groups. No CDC-defined AESIs were observed. The carefully selected dose level of 3µg for the BNT162B2 vaccine was shown to have a favorable safety profile and was well-tolerated in infants, toddlers, and very young children. Vaccine reactions were mostly mild to moderate and were short-lived with systemic reactions comparable to placebo. Reactions were comparable after Doses 1, 2, and 3. The unsolicited AE profile mostly reflected reactogenicity or common childhood illness. Favorable safety profiles should encourage vaccine adherence for each of the 3 doses.

Demonstration of non-inferior immune response in children <5 years of age compared to immune response in persons 16-25 years of age after 2 doses was judged by the FDA to be sufficient to meet immunologic success criteria for EUA. The immunobridging criteria for children 2 to <5 years of age were not met for GMR, but were met for seroresponse after Dose 2. GMR children 2 to <5 years of age compared to those in persons 16-25 years of age after Dose 2 was 0.61(0.53, 0.70), which failed to meet the immunobriding criteria. However, the difference in seroresponse in these groups of -0.9 (-4.3, 2.3) the lower bound of the 95%

confidence interval for the percentage difference is greater than -10. Success was not declared due to not meeting the GMR criterion. However, in consultation with the FDA, a similar comparison was made between GMTs in children 2 to <5 compared to persons ≥65 year of age in the pivotal efficacy trial. In this case, the GMR was 1.92 at the lower bound of 1.56, which was well above the 0.679 inferior criterion. Although this was a post-hoc analysis, VE in persons ≥65 years of age was 94.5%, so the non-inferior immune response seen in children 2 to <5 years of age is likely to predict efficacy. Notably, 45.9% efficacy was observed in children 2 to <5 years of age after the second dose. Despite the likely benefit of a level of 35.9% efficacy after Dose 2, based on the growing importance of Omicron, Pfizer judged the 3-dose series as important to provide improved protection just as is required for every other age group. The immunobridging criteria for children 6 months to <2 years of age compared to persons 16-25 years of age were both met. Immunobridging criteria were met for both the GMR at 1.03 (0.90, 1.19) and a difference in seroresponse at 1.7% (-1.4, 5.2). Based on observed efficacy data, Pfizer judged that in an Omicron-predominant environment, a 3-dose series would prove necessary for a high level of protection.

Immunobridging criteria in children 2 to <5 years of age were met for both GMR and seroresponse comparing post-Dose 3 responses to post-Dose 2 responses in persons 16-25 years of age, which infers VE after Dose 3 in this age group. The median dosing time between Dose 2 and Dose 3 was 10.7 weeks. The GMR observed was 1.30 with a lower bound of 1.13, which was well above the 0.67 success criteria. Likewise, the difference in seroresponse was 1.2% with a lower bound of -1.5%, which was well above the -10% non-inferiority success criteria. Among children 6 months to <2 years of age, immunobridging criteria were met for both GMR and seroresponse, which infers VE in this age group. Median dosing time between Dose 2 and Dose 3 was 12.9 weeks. GMR was 1.19 with a lower bound of 1.00, well above the 0.67 required success criteria. The difference in seroresponse was 1.2% with a lower bound of -3.4, which was well above the -10% required success criteria. For both the younger children and older children, immunobridging criteria were met, inferring VE.

Given that most current COVID-19 cases are caused by Omicron, Pfizer also evaluated the ability of 2- and 3-dose immune sera in children 6 months to <5 years of age to neutralize Omicron compared to sera from adults 24-74 years of age in the sentinel cohorts from the licensing trial. Immune responses to Omicron were compared to those of the reference vaccine strain using a plaque reduction neutralization test (PRNT). There were comparable immune responses across all 3 age groups to the reference strain and Omicron. However, as reported by several groups, Omicron responses after only 2 doses were uniformly low across the pediatric and adult age groups. Low Omicron neutralization titers after 2 doses seems to correlate with lower efficacy against 2 vaccine doses of Omicron. However, this changes when serum samples after 3 doses are being evaluated. In this dataset, an adult comparative group was used who received the third dose at a similar time interval after the second dose in the pediatric group at about 11 to 13 weeks. The neutralizing antibody responses were measured using a fluorescent focused neutralization assay. For children 6 months to less <2 years of age and children 2 years to <5 years of age, the Omicron-specific neutralization titers after 3 doses were far higher than those after 2 doses. The Omicron-specific titers were very similar across age groups. Most importantly, the pediatric group titers were essentially the same as in the adult group, predicting that similar efficacy could likely be observed for children 6 months of age to <5 years of age after Dose 3.

Regarding the immunogenicity conclusion in children 6 months to <5 years of age, immunobridging criteria were partially met after Dose 2. All immunobridging criteria post-Dose 3 in young children required for an EUA were met for both age groups, inferring effectiveness. Omicron neutralization titers were low after 2 doses for pediatric and adult cohorts, but increased substantially after a third dose in children 6 months to <5 years of age similar to the levels observed in adults.

In terms of what has been learned from the adult and pediatric experiences about potential VE against COVID-19, the Delta surge ended prior to the third dose so no children were exposed to Delta after the third dose. Observed efficacy against Delta post-Dose 2 is favorable across all age groups post-Dose 2. The emergence of Omicron presented a new challenge. For children 6 months to <5 years of age post-Dose 2, efficacy was 21.8% (-1.7, 39.7). This is consistent with the antibody response after the second dose. Cases post-Dose 3 in this clinical study were confirmed to be Omicron. Efficacy rose to 80.3% overall and was correspondingly high for the respective age groups. This is consistent with the higher antibody response seen after the third dose against Omicron, like that of older children and adults, and is consistent with corresponding higher efficacy in older children and adults after a third dose against Omicron.

Overall, VE observed over the period of blinded observation after Dose 2 in children 2 to <5 years of age was 35.9% in those without prior evidence of SARS-CoV-2 infection and 34.3% in those with or without prior evidence of SARS-CoV-2 infection. For children 2 to <5 years of age, there appeared to be increasing efficacy over 210 days. The interval is important in terms of observation after Dose 1 and is largely driven by the efficacy after the second dose since cases after the third dose represent a small minority of total cases. This supports a likely benefit after the second dose in this age group. The potential benefit of the second dose is not as readily apparent in children 6 months to <2 years of age. Some VE after Dose 2 is likely to be inferred by the observed 35% efficacy in at least children 2 years to <5 years of age. However, the immune response data shared during this session and the descriptive efficacy show that 3 doses of the BNT162B2 vaccine are in the best interest of children to provide a high level of protection against Omicron, observed to be 80.3% with lower bound of 95% confidence interval of 13.9 in children 6 months to <5 years of age.

With regard to what can be concluded about efficacy for children 6 months to <5 years of age, as demonstrated in other pediatric and adult age groups, 2 doses of BNT162b2 are protective against variants of concern such as Delta, but do not provide adequate protection against Omicron. As demonstrated in other pediatric and adult age groups, a third dose is necessary to provide high protection against Omicron. Ongoing pharmacoepidemiology, including 5 pediatric studies, and proactive risk mitigation and pharmacovigilance will be extended to this younger age group. The potential benefits of vaccinating children 6 months to <5 years of age outweigh the known potential risk. This age group is currently unprotected. Protection against COVID-19 is critical, particularly given the unpredictability of potential new waves and emergence of new variants of concern. Available safety, immunogenicity, and efficacy information support a highly favorable benefit risk profile for administration of 3 doses of BNT162B2 at 3µg to children 6 months to <5 years of age.

mRNA COVID-19 Vaccines in Young Children: Summary and WG Interpretation

Sara Oliver, MD, MSPH (CDC/NCIRD) briefly summarized the COVID-19 Vaccine WG's interpretation of the data presented from Moderna and Pfizer on mRNA COVID-19 vaccines in young children. As a reminder, the Moderna trial among children 6 months through 5 years of age was conducted from December 2021 through February of 2022, with case accrual after a second dose at the height of the Omicron surge. Children 6 months through 5 years of age in the US and were randomized 3:1 vaccine to saline placebo. The analyses were performed separately for children 6-23 months of age and 2-5 years of age. The results were pooled for a combined estimate of children 6 months through 5 years of age. The Moderna schedule is 2 doses of 25µg separated by 28 days. The median follow-up time post-Dose 2 was 2.5 months.

For the overall population, there were over 6,000 children included in the efficacy and safety analyses who were randomized 3:1. A subset of nearly 500 children were included in the immunogenicity analysis. For the efficacy endpoint among subjects with or without evidence of prior infection, VE was 50.9% (21.4-68.6%) for children 6-23 months of age and 36.5% (12.5-54.0%) for children 2-5 years of age. The overall VE for children 6 months to 5 years of age was 41.5% (23.8–55.0%). There is higher confidence in this estimate based on 181 COVID cases in the vaccine group and 97 cases in the placebo group. In addition, efficacy in this trial is consistent with a post-authorization VE for the Moderna vaccine in adults 18-64 years of age during Omicron for whom VE against infection 2 months after Dose 2 was 35% (24%-45%).

Regarding immunogenicity data, the antibody levels were measured 28 days after the second dose for participants without prior infection. The antibody responses after 2 doses at 25µg each in children 6 months to 5 years of age compared to 2 doses at 100µg each in individuals 18-25 years of age met inferiority criteria with a ratio of 1.28 (1.12–1.47) in children 6-23 months of age and a ratio of 1.01 (0.90–1.17) in children 2-5 years of age. Regarding safety data, no deaths were reported in any trial participants. SAEs were rare overall, occurring in 0.5% of vaccine recipients and 0.2% of placebo recipients. One vaccine recipient had 2 SAEs, a fever and febrile seizure, that were deemed possibly related to the vaccine by FDA. No cases of myocarditis or anaphylaxis were noted in any trial participants.

Local reactions, such as pain at the injection site, were common. Systemic reactions also occurred in the children 2-5 years of age. Fatigue and headache were the most common. In the younger children 6-23 months of age, irritability and sleepiness were most common. Symptoms typically started 1 to 2 days post-vaccine and resolved after 2 to 3 days. Fevers were more common after vaccine in the placebo group and were more common after Dose 2 than Dose 1. Most fevers were reported in the first few days after vaccine and lasted for around 1 day. Fevers after the second dose were 16%. However, fevers for other routine vaccines given at this age, such as the pneumococcal vaccine, can be around 30%. There was 1 febrile seizure that was possibly related to the vaccine.

The WG also noted imbalances with some respiratory infections, such as respiratory syncytial virus (RSV). However, in the context of all respiratory infections, including COVID, no imbalances were noted. The events were rare in less than 1% of trial participants. In addition, there was no patterning or clustering of the cases. The clinical characteristics were typical and consistent with seasonal respiratory infections. In addition, testing was not performed systematically for all patients and was at the discretion of the clinician evaluating the patient. Because of this, testing for additional respiratory pathogens may have varied by the results of COVID-19 testing. Lymphadenopathy was a solicited AE. Lymphadenopathy, either in the

axillary region or the groin, was noted in 9% of vaccine recipients compared to 2% of placebo recipients.

In conclusion, the efficacy seen after 2 doses of the Moderna COVID-19 vaccine in children 6 months through 5 years of age is consistent with real-world VE in other ages during Omicron predominance. The antibody levels after 2 doses in children 6 months through 5 years of age produces similar antibody levels seen after 2 doses in individuals 18-24 years of age. Reactogenicity post-vaccine is consistent with other recommended vaccines in this age group.

Moving now to the Pfizer-BioNTech COVID-19 vaccine in children 6 months to 4 years of age, the clinical trial was conducted from June 2021 through April 2022. Children 6 months to 4 years of age in the US were randomized 2:1 vaccine to a saline placebo. The analyses were performed separately for the 2 age groups and were then pooled for a combined analysis. This series is 3 of 3µg each, with Dose 1 and Dose 2 separated by 21 days and Dose 2 and Dose 3 separated by at least 8 weeks. Note that the interval between Dose 2 and Dose 3 in the trial was longer than the authorized interval. Among children 6-23 months of age, the interval was 16 weeks with a range of 8-32 weeks. For children 2-4 years of age, the interval was 11 weeks with a range of 8-34 weeks. In addition, the median follow-up time post-Dose 3 was 1.3 months.

In terms of timing in the Pfizer trial, children 2-4 years of age began receiving their first doses in June and second doses in July. However, per protocol, the investigators began unblinding participants 6 months after the second dose around December 2021 and into January and February 2022. Based on analyses after the second dose, the protocol was amended in February 2022 and third doses were given. However, by then, many of the initial cohort from the trial were unblinded and placebo crossover had already occurred. After FDA's request to expand the size of the trial, expanded safety enrollment began. This cohort began receiving doses in October and November, with third doses starting in February and March. Blinded-person time contributing to the Dose 3 efficacy and safety evaluation was from February through April, which was when the cases began declining after the Omicron surge. For children 6-23 months of age, the same phenomenon occurred in which participants were unblinded 6 months after the second dose. In terms of the impact unblinding had on the total number of participants who contributed blinded-person time to the efficacy and safety evaluations, there were about 2,700 children 2-4 years of age and about 1,700 children 6-23 months of age. By Dose 3, much of the population had been unblinded, with 32% of the overall eligible population contributing blinded-person time to the efficacy and safety evaluations.

Efficacy estimates after the third dose in subjects with or without evidence of prior infection were 75.5% (-370.1–99.6%) among children 6-23 months, 82.3% (-8.0–98.3%) among children 2-4 years of age, and 80.3% (13.9–96.7%) overall among children 6 months through 4 years of age. However, the confidence intervals were wide. There is lower confidence in these estimates based on 3 COVID-19 cases in the vaccine group and 7 COVID-19 cases in the placebo group. For comparison and context, post-authorization VE against infection for the Pfizer COVID-19 vaccine in adolescents 12-15 years of age during Omicron was 29% 2 months after Dose 2 and 43% 2 months after Dose 3. Overall, the WG felt that the post-Dose 3 efficacy data are difficult to interpret. There were a limited number of cases during the blinded follow-up. In addition, the protocol specified a need for 21 cases prior to the formal efficacy analysis and only 10 were included in the interim descriptive analysis. Importantly, the dosing intervals between Dose 2 and Dose 3 varied and are longer than the authorized interval. The median blinded follow-up time is limited, with the median time of 35 days for children 6-23 months of age and 40 days for children 2-4 years of age.

Antibody levels were measured 1-month post-Dose 3 for participants without prior infection. Antibody responses after three 3µg doses in children 6 months to 4 years of age compared to two 30µg doses in individuals 16-25 years of age met the non-inferiority criteria. The ratio for children 6-23 months of age was 1.19 (1.00–1.43), the ratio for children 2-4 years of age was 1.30 (1.13–1.50), and the overall ratio for children 6 months through 5 years of age was 1.26 (1.13–1.40). The immunogenicity population was comprised of 82 children 6-23 months of age and 143 children 2-5 years of age for a total of 225 children. For comparison and context, the WG reviewed the results that were seen after Dose 2. For children 6-23 months of age, VE was minimal VE 14.5% (-24.9–41.0%). However, the non-inferiority criteria were met. Some protection was noted for children 2-4 years of age with a VE of 33% (9.1–51.3%), but the non-inferiority criteria were not met.

From a safety standpoint, no deaths were reported in any trial participants. SAEs were rare overall and occurred in 1% of vaccine recipients and 1.5% of placebo recipients. One vaccine recipient had 2 SAEs, fever and pain in an extremity requiring hospitalization that were possibly related to the vaccine. However, the FDA felt the symptoms were potentially consistent with viral myositis. No cases of myocarditis or anaphylaxis were noted in trial participants. Local reaction, such as pain or tenderness at the injection site, occurred within 7 days and were common. Fatigue was the most common systemic symptom in children 2-4 years of age. Irritability and drowsiness were more common in children 6-23 months of age. Overall, the reactions were comparable after Doses 1, 2, and 3. Most symptoms were mild and resolved after 1 to 2 days. Fevers were reported with similar frequency after both vaccine and placebo and after Doses 1, 2, and 3. Most fevers were reported on Days 1 and 2 after any dose and lasted for a median of 1 day.

In conclusion, antibody levels after the 3 doses of Pfizer-BioNTech COVID-19 vaccine in children ages 6 months through 4 years of age produce similar antibody levels after 2 doses in individuals 16-24 years of age. Reactogenicity post-vaccine was similar after each of the 3 vaccine doses and similar to reactions seen in placebo recipients. However, the efficacy estimates after 3 doses are difficult to interpret given the small numbers and limited follow-up time. The WG noted that the impact of the longer intervals in the trial between Dose 2 and Dose 3 on efficacy, reactogenicity, and safety are unknown.

Regarding the WG's interpretation in total, the mRNA COVID-19 vaccine clinical trials in young children were both conducted during Omicron predominance but at different months and incidence levels. In addition to differences in the number of participants in the efficacy analyses and differences in follow-up time, these incidence levels impacted COVID-19 case accrual and certainty in the efficacy estimates. Because of this, the efficacy estimates for these 2 mRNA vaccines cannot be directly compared. However, both vaccines met the non-inferiority criteria from neutralizing antibody levels. Notably, the current data are for either a 2-dose or 3-dose primary series. To achieve the criteria set by FDA for authorization, 2 doses for Moderna or 3 doses of the Pfizer vaccine were required. For individuals 5 years of age and older, 2 doses achieved the preset efficacy requirements or the required antibody levels for immunobridging. A booster was then provided to optimize the immune response and address waning of antibody titers detected after completion of the primary series. Post-authorization effectiveness studies can help determine the subsequent timing and need for boosters after a 2-dose series with Moderna or a 3-dose series with Pfizer. That booster would then be a third dose for the Moderna vaccine and a fourth dose for the Pfizer vaccine in this age group. However, it is known that in other age groups during Omicron, mRNA COVID-19 vaccine post-authorization VE was lower against infection, but higher protection was noted against severe disease. While the clinical trials were not powered to detect efficacy against severe disease in this young

population, similar patterns in this age group are expected to what is seen in everyone 5 years of age and over.

In terms of next steps, Dr. Oliver noted that the EtR framework, including the GRADE summary of the data, would be presented the next day at which time the WG would be discussing 2 separate policy questions:

> "Should vaccination with Moderna COVID-19 vaccine (2-doses, 25µg, IM) be recommended for children 6 months – 5 years of age, under an Emergency Use Authorization?"
>
> "Should vaccination with Pfizer-BioNTech COVID-19 vaccine (3-doses, 3µg, IM) be recommended for children 6 months – 4 years of age, under an Emergency Use Authorization?"

These 2 vaccines will not be compared. Instead, the comparison would be of each vaccine to no vaccine.

Session Overview 6-18-22

Dr. Matthew F. Daley (WG Chair) reminded everyone that on June 16, 2022, FDA granted EUA for the following:

- ❑ 2-dose Moderna COVID-19 vaccine primary series for administration to individuals ages 6 months through 5 years
- ❑ 3rd primary series dose to individuals ages 6 months through 5 years with certain kinds of immunocompromise
- ❑ 3-dose Pfizer-BioNTech COVID-19 vaccine primary series for administration to individuals ages 6 months through 4 years
- ❑ 2-dose Moderna COVID-19 vaccine primary series for administration to individuals ages 6 through 17 years
- ❑ 3rd primary series dose to individuals ages 6 through 17 years with certain kinds of immunocompromise

On June 17, 2022, the ACIP heard presentations on the epidemiology of COVID-19 in young children; COVID-19 VE in children and adolescents; safety and immunogenicity of the Moderna COVID-19 vaccine 2-dose primary series in children 6 months through 5 years of age; safety and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine 3-dose primary series in children 6 months through 4 years of age; and an ACIP COVID-19 Vaccine WG interpretation of safety, immunogenicity, and efficacy of Moderna and Pfizer-BioNTech COVID-19 vaccine primary series data.

The agenda for the second day of the meeting included presentations on implementation of pediatric COVID-19 vaccines; the EtR Framework on mRNA COVID-19 vaccines in young children; an update on Clinical Considerations; and votes on Moderna COVID-19 vaccine in children 6 months through 5 years of age and Pfizer-BioNTech COVID-19 vaccine in children 6 months to 4 years of age.

Implementation of Pediatric Vaccines

Kevin Chatham-Stephens, MD, MPH, FAAP (CDC/NCBDDD) discussed pediatric COVID-19 vaccine planning for children 6 Months through 4 years of age, explaining that this very important vaccine rollout for children <5 years of age mimics the overarching goal in children 5-11 years of age and the adolescent vaccine programs to ensure that all children have access to the vaccine. Similar to the vaccine rollout for children 5-11 years of age, the plan is to ensure that vaccine is widely available in different locations throughout communities through primary care providers (PCPs), urgent care facilities, hospitals, Federally Qualified Health Centers (FQHCs), Rural Health Centers (RHCs), commercial pharmacies, federal entities (e.g., DoD, IHS), public health programs in jurisdictions, and Head Start and other Early Care and Education (ECE) systems.

However, there also will be some key differences between the rollout for children 5-11 years of age and the rollout for children <5 years of age. For example, approximately a third of children 5-11 years of age were vaccinated in pharmacies and just under 10% were vaccinated in school-located vaccination clinics. Those settings are anticipated to be less prominent in the vaccine program for children <5 years of age in that pediatricians and family practice doctors in the medical home (e.g., private pediatric clinics, FQHCs, local health departments, et cetera) will play a larger role, especially for the younger children in this age group. Pharmacies are still anticipated to play a critical role in having the vaccine available at nights, on weekends, and on holidays when clinics may be closed. In local health departments, especially in rural areas, federal partners such as Indian Health Service (IHS), and Health Resources and Services Administration (HRSA) FQHCs, and RHC will continue to serve critical roles in contributing to vaccine equity. ECE programs like Head Start and other support programs such as Women, Infants, and Children (WIC) will play more prominent roles in this vaccine program given their roles as trusted messengers to families of children in this age group.

To estimate how well a network of likely pediatric vaccine providers would cover children <5 years of age, a mapping analysis was conducted to assess the proportion of children <5 years of age who reside within 5 miles of a likely vaccine provider. There are approximately 18,000 non-pharmacy providers that have administered vaccines to children <5 years of age and about 4,000 pharmacies that have expressed interest in offering vaccines to children <5 years of age. The mapping analysis found that when these 2 sets of providers are combined, approximately 85% of children <5 years of age reside within 5 miles of likely vaccine providers and 94% live with 10 miles.

It is known that vaccinating in the medical home is incredibly important, as the medical home provides comprehensive primary care that facilitates partnerships between children's families and clinicians, and routine immunizations typically occur in the medical home. For instance, approximately 80% of children 6 months through 4 years of age received influenza vaccine for the 2020-2021 influenza season in their doctor's office. This is compared to the very low percentages of children this age group who are vaccinated at a pharmacy, including less than 1% of children 6-23 months of age and approximately 4% of children 2-4 years of age. In addition to vaccination, the medical home is a location in which children also receive recommended screenings for a variety of issues (e.g., such as development, autism, vision, iron deficiency, lead poisoning) and are provided guidance that helps them thrive in a healthy and safe environment (e.g., nutrition, injury prevention, and chronic disease management).

To better understand COVID-19 vaccine practices and intention to vaccinate children <5 years of age, CDC surveyed thousands of Vaccines for Children (VFC) providers in March 2020. Dr. Chatham-Stephens presented some of the preliminary unpublished results for all providers, as well as results by urban or rural location. Of note, these results were limited to those who were enrolled in the COVID-19 vaccination program. Most VFC (85%) providers have administered a COVID-19 vaccine to children 5-17 years of age and almost three quarters (73%) of all providers intend to offer COVID-19 vaccination to children <5 years of age. This percentage is higher for urban providers at 76% compared with rural providers at 67%. Since not all clinics will have the vaccine and not all children have a medical home, CDC also asked whether the practice intends to offer COVID-19 vaccination to children who are not currently patients of the practice. Approximately half of all providers said they would offer COVID-19 vaccination to children who are not currently patients of their practice. The percentage is higher for rural providers at 58% compared with urban providers at 49%.

In terms of some of the select activities CDC has conducted to support health departments, clinicians, and others, the agency disseminated an *Operational Planning Guide* over the past several months that includes characteristics of the vaccines, key planning assumptions, and a planning checklist. They also are We are also working on a “Dear Colleague” letter for VFC providers that emphasizes the importance of their role in this vaccination program and provides various tips and resources. CDC also has engaged in a variety of vaccine confidence bootcamps, which are great interactive trainings to provide partners and participants with strategies for building vaccine confidence in their communities. Examples that are particularly relevant in this discussion include bootcamps with the National Association of School Nurses (NASN), early care and education partners, and YMCA. The agency also has shared jurisdiction-specific maps of likely vaccine providers for children <5 years of age. Jurisdictions have been able to use these maps to identify and then address gaps in provider availability. CDC’s communications experts continue to release resources to promote COVID-19 vaccine for children and teens, including social media graphics, videos, and customizable materials in various web pages available at https://www.cdc.gov/vaccines/covid-19/planning/children/resources-promote.htm.

The vaccines.gov site enables the public to identify nearby providers with vaccine in stock and make an appointment, and it enables providers to report their COVID-19 vaccine inventory. To prepare for the rollout of vaccines for children <5 years of age, a new function will be added that enables the minimum age that can be vaccinated at a location in months and years to be displayed. Providers can report these data now. The CDC will be monitoring inventory as the vaccines are delivered to clinics, pharmacies, and other clinical settings starting on Monday, June 20, 2022. In addition to vaccines.gov, parents and caregivers can reach out to their child’s pediatrician or family practice doctor, local health department, pharmacy, et cetera to ask if they have the vaccine. It is important to understand that not every clinic or pharmacy will receive their vaccine on June 20, 2022. Some vaccine providers were waiting for the EUAs and CDC’s recommendations before ordering the vaccine. They wanted to see the data to help them decide which of the 2 vaccines to order. CDC expects the vaccine provider network to expand as these providers order their vaccine post-EUA or post-ACIP voting.

EtR Framework: mRNA COVID-19 Vaccines in Young Children

Sara Oliver, MD, MSPH (CDC/NCIRD) provided a combined EtR Framework presentation on both Moderna COVID-19 vaccine in children 6 months through 5 years of age and Pfizer-BioNTech COVID-19 vaccine in children 6 months through 4 years of age in order to offer a comprehensive review of the entire program for both vaccines in this age group, given that they will rollout at the same time—something that has not occurred in the COVID-19 program to date. As a reminder, the EtR Framework is a structure to describe information considered in moving from evidence to an ACIP vaccine recommendation. This process provides transparency around the impact of additional factors on deliberations when considering a recommendation. These 2 policy questions for this EtR framework were as follows:

> "Should vaccination with Moderna COVID-19 vaccine (2-doses, 25µg, IM) be recommended for children 6 months–5 years of age, under an Emergency Use Authorization?"
>
> "Should vaccination with Pfizer-BioNTech COVID-19 vaccine (3-doses, 3µg, IM) be recommended for children 6 months–4 years of age, under an Emergency Use Authorization?"

In terms of the overall PICO (population, intervention, comparison, outcomes) for this analysis, the population was young children 6 months through 5 years of age or children 6 months through 5 years of age depending upon the vaccine focus. The comparison group for both vaccines was to no vaccine. These 2 vaccines were not compared to each other. The outcomes of interest included symptomatic laboratory confirmed COVID-19, hospitalization due to COVID-19, MIS-C, asymptomatic SARS-CoV-2 infection, SAEs, and/or reactogenicity of Grade ≥3.

For the public health problem domain, as of June 14, 2002, there were more than 85 million total recorded cases of COVID-19 in the US. Since April 2022, there has been an increasing number of cases, although perhaps with a slight decrease at the end of May 2022. At this point, the 7-day moving average was just over 100,000 cases. During the pandemic, over 570,000 cases have occurred among infants and more than 1.9 million cases have occurred among children 1-4 years of age. Regarding COVID-19-associated hospitalization rates per 100,000 population among children and adolescents 6 months through 17 years of age from CDC's COVID-NET surveillance system, as with COVID-19 cases and ED visits, hospitalization rates increased during the Omicron surge to the highest rates seen during the pandemic. During 2022, the hospitalization rates were the highest among children 6 months through 4 years of age followed by children 5-11 years of age and adolescents 12-17 years of age.

Cumulative COVID-19-associated hospitalizations in the same age groups further illustrate this point. During the Omicron surge among children 6 months through 4 years of age, the slope of the cumulative hospitalization rate increased more than it did for older children and adolescents. By March 2022, it was higher among this age group than among adolescents. During the Omicron surge, both children 5-11 years of age and 12 to 17 years of age were eligible for vaccination. Data from the National Center for Health Statistics (NCHS) showing the number of COVID-19 deaths in children from January 1, 2020 through May 11, 2022 are based on death certificate reporting. Among children 6 months through 4 years of age, there were 202 COVID-related deaths, which made up 1.7% of all deaths among children in this age group. COVID-19 is the leading cause of death among children <1 year of age and 1-4 years of age and adolescents 5-19 years of age. The cumulative COVID-19 deaths rank among the top 5 causes

of death in children <1 year of age and 1-4 years of age and is the only infectious cause of death throughout the March 1, 2020 through April 30, 2022 timeframe.

Not all COVID-19 cases are captured using traditional surveillance methods because some cases are asymptomatic, not diagnosed, or not reported. Tracking the proportion of the population with SARS-CoV-2 antibodies (e.g., seroprevalence) can improve understanding of the population level incidence of COVID-19. Data from national commercial laboratory surveillance from September 2021 through February 2022 show that seroprevalence from infection-induced SARS-CoV-2 antibodies increased substantially during Omicron. The largest increase was among children 6 months through 4 years of age who have not been eligible for vaccination to date. There are now 2 additional months of data that show a less steep rise in seroprevalence between February and the combined March and April timepoint. Seroprevalence in this age group is now estimated at 71%.

Then look further at what is known about infection in children and adults who are seropositive, a study among Quebec residents from December 2021 through March 2022 in persons ≥12 years of age showed that those with prior infection who were not vaccinated had the lowest effectiveness or protection against reinfection. Similar data were found for effectiveness of vaccination from mRNA vaccine against COVID-19 hospitalization among adults previously infected. Antibodies produced by previous SARS-CoV-2 infection in the pediatric population may not neutralize the currently circulating Omicron variant, leaving them potentially susceptible to reinfection with Omicron. In a study by Tang and colleagues among children, COVID-19 vaccines were shown to induce a broader neutralizing antibody response against variants of concern (Alpha, Beta, Gamma, Delta, and Omicron) compared with natural immunity induced following the SARS-CoV-2 infection. This study highlights the importance of vaccinating children with prior infection to prevent both severe disease and future infections.

To summarize the public health problem, COVID-19 has caused over 2 million cases among children 6 months through 4 years of age. Children in this age group are at risk of severe illness from COVID-19. More than half of hospitalized children in this age group had no underlying medical conditions, can have similar increased severity compared to older children and adolescents, and the burden of COVID-associated death is similar to or exceeds that of other pediatric vaccine-preventable diseases. Prior infection may not provide broad protection against newer SARS-CoV-2 variants, and the COVID-19 pandemic continues to have significant impact on families. Overall, the WG felt that COVID-19 among children 6 through 4 or 5 years of age is a public health problem.

Now moving to the domain of benefits and harms. As a reminder from the presentation the previous day, data from the Moderna COVID-19 vaccine comes from 1 Phase 2/3 randomized controlled trial (RCT) conducted in the US. Participants were randomized 3:1 vaccine to saline placebo. Per protocol, the 2 co-primary endpoints for immunobridging were GMR and seroresponse. Efficacy data also were provided for symptomatic infection. Relative risks were calculated from cases in the study population, and VE for GRADE was calculated based on these relative risks. In addition, a sensitivity analysis of VE was performed to include COVID-19 cases that were identified using home testing but RT-PCR confirmation. First looking at the prevention of symptomatic laboratory-confirmed COVID-19 with pooled results among children 6 months through 5 years if age, using the CDC case definition VE was 40.3% among those who were seronegative at baseline and 37.8% when those who were seropositive at baseline were included. In a sensitivity analysis, including home tests, the VE was 36.6%. The VE of 37.8 using the CDC case definition among seropositive or seronegative is the outcome that was used in GRADE.

The Phase 2/3 trial also was designed to use immunobridging to evaluate efficacy. Immunobridging studies are used to compare immunogenicity for a group of interest, here children 6-23 months and children 2-5 years of age, with a comparison group in which efficacy has been demonstrated in clinical trials. In this case, the comparison group was adults 18-25 years. The immune response to vaccine was evaluated using a GMR of adults to young children to young adults. Non-inferiority criteria are met when the lower bound of the 95% confidence interval for the ratio comparing the geometric mean neutralizing antibody titers for the 2 groups is not less than a preset value, which for this evaluation was 0.67. In both age groups, children 6-23 months and children 2-5 years of age, the immune response to vaccine was non-inferior to that observed in those aged 18-25 years of age, with a GMR of 1.28 in the younger age groups and 1.01 in children 2-5 years of age.

The GRADE assessment for the outcome of symptomatic laboratory-confirmed COVID-19 using the direct efficacy, the relative risk was 0.62 (0.49, 0.79). There were no serious concerns in the certainty estimate and the final evidence certainty was Type I (high). GRADE also was performed for symptomatic laboratory-confirmed COVID-19 using immunobridging. Among both age groups (6–23 months and 2–5 years), the non-inferiority criteria were met. There were serious concerns of indirectness because immunogenicity is a surrogate marker of efficacy, so the final evidence certainty was Type 2 (moderate).

The next outcome of interest was asymptomatic SARS-CoV-2 infection. For this trial, it was identified by absence of symptoms and at least 1 of the following: 1) binding antibodies against SARS-CoV-2 nucleocapsid protein negative at Day 1 that became positive post-baseline; or 2) a positive PCR test post-baseline at a scheduled or unscheduled visit. Participants who were PCR-positive at baseline were excluded. Among children 6 months through 5 years of age, the VE against asymptomatic infection was 16% (-18.5%, 40.5%). This is the outcome that was used for GRADE. In addition, when home antigen tests were included, the VE estimate was 21% (4.5 to 35). For the GRADE assessment of this outcome, the relative risk was 0.84 (0.60, 1.19). There were serious concerns of indirectness because asymptomatic SARS-CoV-2 PCR testing on the full cohort occurred only once, and serology was not done on all participants. There also were serious concerns of imprecision due to the wide confidence interval. The final evidence certainty was Type III (low).

For the critical outcome of SAEs, 24 participants in the Phase 2/3 trial among both age groups experienced 28 events among the 4,800 children in the vaccine group and 3 participants experienced 4 events out of 1,600 in the placebo group for a comparison of 0.50% to 0.19%. One participant experienced 2 SAEs of fever and febrile seizure that were considered possibly related by FDA. No deaths were reported. For GRADE for SAEs, there was serious concern of indirectness due to the short duration of follow-up of 2 months after Dose 2. There also were very serious concerns for study size and the width of the confidence interval. The final evidence certainty was Type IV (very low).

In terms of the outcome of severe reactogenicity of Grade 3 or 4, the overall main criteria for Grade ≥3 or higher is typically a symptom that prevents daily activity. Overall, 7.7% of vaccine recipients and 4.1% of placebo recipients reported a local or systemic reaction of Grade ≥3. The majority of these events were Grade ≥3. There were 15 fevers of >40.0 °C in the vaccine group and 3 in the placebo group. The GRADE assessment for reactogenicity relative risk was 1.87 (1.44 to 2.42). There were no serious concerns in the certainty assessment, so the final evidence certainty was Type 1 (high).

In conclusion, efficacy seen after 2 doses of the Moderna vaccine in children 6 months through 5 years of age in the trial is consistent with the real-world VE of other ages in Omicron. The comparison of antibody levels met the immunobridging criteria, and the reactogenicity post-vaccine is consistent with other recommended vaccines in this age group.

Moving now to the GRADE evaluation for the Pfizer vaccine among children 6 months through 4 years of age, the Pfizer Phase 2/3 trial was conducted in the US, Finland, Poland, and Spain. Participants were randomized 2:1 vaccine to saline placebo. The interval between Dose 1 and Dose 2 was 21 days and the interval between Dose 2 and Dose 3 varied, with a median of 11 to 16 weeks. Direct efficacy and immunobridging, the per protocol primary endpoints, were evaluated. The median follow-up after Dose 3 was 1.3 months. VE from relative risk also was calculated. While most of the randomized participants received the first 2 doses, only 32.9% of the vaccine arm and 30.7% of the placebo arm went on to receive a blinded third dose as the protocol specified unblinding at 6 months after the second dose.

The 3-dose VE estimate for symptomatic laboratory-confirmed COVID-19 among participants 6-23 months was 76% (-161.2, 97.8). For participants 2-4 years of age, the3-dose VE was 81% (5.3, 96.4). The combined efficacy estimate was 80% (22.8, 94.8). The immune response to vaccine in children 6-23 months of age and those 2-4 four years of age was non-inferior to that observed in young adults 16-25 years of age, with a GMR of 1.19 (1.00, 1.43) in children 6-23 months of age and 1.3 (1.13, 1.50) in children 2-4 years of age. For context, the trial was originally designed to be evaluated as a 2-dose primary series. The 2-dose VE for participants 6-23 months of age was 15% (-19.4, 40.0) and non-inferiority criteria for immunobridging were met. The VE for children 2-4 years of age was 32% (10.0, 49.6). However, non-inferiority criteria for immunobridging were not met for this age group.

The GRADE assessment for the outcome of symptomatic laboratory-confirmed COVID-19 was assessed using direct efficacy. There was serious concern for indirectness due to the short duration of follow-up of 1.3 months and very serious concern for imprecision due to the study size. The final evidence certainty was Type 4 (very low). In addition to direct efficacy, a GRADE assessment was conducted for the outcome of symptomatic laboratory-confirmed COVID-19 assessed using immuno-bridging. There were serious concerns for indirectness because immunogenicity is a surrogate measure of efficacy. The final evidence certainty for this outcome was Type 2 (moderate).

For the evaluation of SAEs, the safety population included all randomized participants who received at least 1 dose of vaccine. This included approximately 1700 children 6-23 months of age and approximately 2700 children 2-4 years of age. The median follow-up after Dose 3 was 1.3 months for children 6-23 months of age and 1.4 months for children 2-4 years of age. The pooled SAEs among all participants aged 6 months through 4 years of age included 29 events out of 3,000 participants in the vaccine arm and 22 events out of 1,500 participants in the placebo arm for comparison of 1% to 1.5%. One vaccine participant had 2 SAEs, fever and pain in an extremity that required hospitalization that were considered possibly related by the investigator. FDA considered the events potentially consistent with symptoms due to an unspecified viral myositis. No deaths were reported in trial participants.

Regarding the GRADE assessment for SAEs, there was very serious concern for indirectness due to the short duration of follow-up 1-month post-Dose 3 and because only 32% of trial participants received Dose 3 in the blinded follow-up, which limited the ability to detect SAEs that could occur at a higher rate after Dose 3. There were also serious concerns of imprecision due to study size. The final evidence certainty was Type 4 (very low). For reactogenicity of

Grade ≥3 symptoms that interfered with daily life, among participants 6 months through 4 years of age, GRADE ≥3 local reactions or systemic events after any dose was reported in 4.3% of participants in the vaccine arm and 3.6% of participants in the placebo arm. The majority of these events were GRADE 3. There were 6 fevers of >40.0 °C among vaccine recipients and 1 among placebo recipients. For GRADE, there was a relative risk of 1.2 (0.88, 1.64). Serious concern for indirectness was noted because only 31% of trial participants received Dose 3, limiting the ability to detect severe reactogenicity that would occur specifically after Dose 3. The final evidence certainty was Type 2 (moderate).

In summary for Pfizer, the conclusions from the trial were that the antibody levels seen after 3 doses in children 6 months to 4 years of age produce similar antibody levels after 2 doses in individuals 16-24 years of age. Reactogenicity post-vaccine was similar for each of the 3 vaccine doses and similar to the reaction seen in the placebo recipients. Efficacy estimates are difficult to interpret given the small numbers and limited follow-up time and because the impact of the longer interval in the trial between Dose 2 and Dose 3 on efficacy, reactogenicity, or safety are unknown.

Other considerations for benefits and harms of mRNA vaccines in young children include COVID-19 vaccines and seropositivity, myocarditis in young children, cardiac complications after SARS-CoV-2 infections, vaccine-associated myocarditis in children and adolescents, and the numbers needed to vaccinate (NNV) analysis. In terms of COVID-19 vaccines and seropositivity, Omicron wave-surges of pediatric COVID-19 hospitalization occurred even with high seroprevalence, suggesting that this alone is not sufficient to provide broad protection. Many millions of seropositive individuals have been vaccinated without safety concerns. Vaccination remains the safest strategy for preventing complications from SARS-CoV-2 infection and offers additional protection against reinfection. Prior infection may not provide broad protection against newer SARS-CoV-2 variants. However, the Clinical Consideration state that people who recently had a SARS-CoV-2 infection may consider delaying their COVID vaccine by 3 months from symptom onset or a positive test. An increased time between infection and vaccination may result in an improved immune response to vaccination. A low risk of reinfection has been observed in the weeks following infection.

Then thinking through myocarditis in young children, before the COVID-19 pandemic, peaks in myocarditis hospitalizations were seen in infants and in adolescents. In adolescents, myocarditis is typically viral in etiology and male predominance is observed. In infants, many cases can represent cardiomyopathy with a congenital or genetic component. It also is possible to infer what is known regarding cardiac complications due to SARS-CoV-2 infection in young children. Cardiac complications in the setting of acute SARS-CoV-2 infection in young children are uncommon. Most cardiac complications post-SARS-CoV-2 infection in infants are related to MIS-C, of which about 1.8% cases are children 6-11 months of age. However, infants <1 year of age with MIS-C have severe cardiovascular involvement in about 55% to 65% of cases. This is contrasted to around 80% in the adolescent populations.

As Dr. Shimabukuro showed during the last ACIP meeting, reporting rate to the Vaccine Adverse Event Reporting System (VAERS) for myocarditis following the Pfizer vaccine in male children 5-11 years of age after Dose 2 of the primary series is slightly elevated when compared to the background incidence. Otherwise, reporting rates are within the background incidence. In addition, to date myocarditis and pericarditis have not statistically signaled in Vaccine Safety Datalink (VSD) surveillance in children 5-11 years of age. Overall, the risk of myocarditis after mRNA COVID-19 vaccination, if any, in young children is unknown. No cases occurred during the clinical trials and there were almost 8,000 who had at least 7 days of follow-up. However,

the trials were not powered to detect rare AEs. Based on the epidemiology of classic myocarditis and what is known from safety monitoring in children 5-11 years of age, myocarditis after mRNA COVID-19 vaccination in young children is anticipated to be rare. This is likely due to multiple factors, including the underlying epidemiology of myocarditis fundamentally being different in infants. In addition, the dose used in young children is even lower than the dose used in children 5-11 years of age.

During the previous day, Dr. Link-Gelles summarized that in older children and adolescents, there are real-world VE data to show that 2 doses can provide good protection against severe disease and against MIS-C. The NNV was calculated using the following methods. Benefits were calculated per 1 million fully vaccinated with an mRNA vaccine, focusing on the age group 6 months through 4 years of age and using pandemic average age-specific incidence rates with hospitalization rates from COVID-NET and case rates from case-based surveillance. VE against hospitalization was assumed to range from 42% to 84% and VE against symptomatic infection was assumed to range from 30% to 60%. A120-day time horizon was used. Among children 6 months through 4 years, 600 to 1,300 vaccinations are needed to prevent 1 case, and 6,100 to 12,000 vaccinations are needed to prevent 1 hospitalization over a 120-day period.

To put these numbers into context, the NNV to prevent 1 hospitalization for COVID-19 were compared to influenza. To make the methods comparable, COVID-19 rates were used from the influenza season from October 1 through April 29 and the time horizon was extended out to 6 months. The VE assumptions remained the same as for the COVID-19 calculation. Making this set of assumptions comparable between COVID-19 and influenza, the NNV to prevent 1 COVID-19 hospitalization ranged from 1,600 to 3,300 in comparison and the NNV to prevent 1 influenza hospitalization in this similar age group ranged from 1,000 to 6,800.

In summary for the known and potential benefits, the clinical trials provide data for protection against symptomatic infection. The clinical trials were not powered to detect efficacy against severe disease in young children, but similar patterns are expected those seen in everyone 5 years of age and older, with higher protection against severe disease. Emerging data in adults suggest that post-COVID conditions may be less likely to occur in vaccinated individuals, and vaccination in this age group also may provide parents with increased confidence to return to pre-pandemic activities, improving social interactions for young children.

To summarize the known and potential harms, the clinical trial data provided safety data in nearly 8,000 vaccinated young children. This is a larger safety database than any of the prior pediatric age groups for COVID-19 vaccines. There are also post-authorization safety data after almost 600 million doses of COVID-19 vaccines given in the US. Post-authorization safety data for children ages 5-11 years of age are very reassuring. The reporting rates of myocarditis in males are only slightly elevated compared to the background incidence, which is likely related to both underlying epidemiology of myocarditis and dose de-escalation.

To summarize benefits and harms, these are the first COVID-19 vaccine clinical trials conducted exclusively during the Omicron predominance. Post-authorization VE studies have shown a lower effectiveness during Omicron compared to the previous SARS-CoV-2 variants. Both mRNA COVID-19 vaccines for young children met the non-inferiority criteria for neutralizing antibody levels. Differences have been noted in the certainty of efficacy estimates for each of the mRNA vaccines, and their efficacy estimates cannot be directly compared. Importantly, receipt of a primary COVID-19 vaccine series can provide protection against COVID-19 disease and severe outcomes. Therefore, reviewing the totality of this data, the benefits of the COVID vaccines in young children outweigh possible risks. The WG felt that the desired anticipated

effects were moderate to large risk, reflecting some uncertainty with regard to the efficacy estimates, and that the undesirable anticipated effects were minimal to small. In terms of the judgment for Moderna, the WG felt that the desirable effects outweigh the undesirable effects. For the Pfizer vaccine, the WG felt that the desirable effects outweighed undesirable effects.

Moving now to the domain of values, a survey was designed by CDC, the University of Iowa, and RAND Corporation to assess parental beliefs and attitudes toward pediatric COVID-19 vaccines among children 6 months through 4 years of age that was administered February 2-10, 2022. At that time, around half of parents of children 6 months through 4 years of age said that they would definitely or probably vaccinate their child once they become eligible. A third of parents of children 6 months through 4 years of age said they definitely or probably would not vaccinate their child once eligible. Only a fifth of respondents said that they would get their child vaccinated within 3 months after becoming eligible, but additional respondents said that they would vaccinate with subsequent time. Parents also were asked about preference for a 2-dose or a 3-dose series, with some uncertainty around the timing availability. There was a slight preference for a 2-dose series, but with no data on VE or timing of when these vaccines would be available, there was no strong preference either way at the time of the survey. The percentage of parents of children 6 months through 4 years of age who definitely or probably would vaccinate their child when eligible varied by gender of the parent, race, ethnicity, and education.

Based on data from the National Immunization Survey-Child COVID Module (NIS-CCM) from December 2021 – May 2022, over time the population that reported that they would definitely get their child vaccinated had declined to 33% in May. This could be due to a variety of factors, including a declining sense of urgency with the pandemic. In May, 17% of parents reported that they definitely would not get their child vaccinated. Looking at this by age subgroups, a smaller percent of parents of children 6-23 months tended to have their child vaccinated compared to parents of children 2-4 years of age. A Kaiser Family Foundation (KFF) survey showed that 1 in 5 parents of children <5 years of age were eager to vaccinate their child and would do so right away once a COVID-19 vaccine was authorized. Almost 4 in 10 parents said they wanted to wait and see before getting their child vaccinated. Another 4 in 10 said they were reluctant to get their child vaccinated, with 11% saying they would only do it if they were required and 27% saying they would definitely not get their child vaccinated. Lack of information may be a factor in parents' reluctance to have their younger children vaccinated right away. A majority of parents of children <5 years of age at the time of the KFF survey said that they did not have enough information about the safety and effectiveness of COVID-19 vaccines. Notably, this survey was conducted in April, which was prior to having information on the safety and efficacy of COVID-19 vaccines in young children.

In summary of the available evidence for the values domain, half of parents of children 6 months through 4 years of age definitely or probably would get their child vaccinated once eligible and 1 in 5 parents of children in this age group are eager to vaccinate and plan to do so right away once the vaccine is available. However, nearly a third of parents of children 6 months through 4 years of age definitely or probably would not vaccinate their child once eligible. In a survey conducted prior to available data, parents of children under 5 years of age said they did not have enough information. This highlights the importance of communicating these data broadly to parents. The WG felt that whether the target population feels the desirable effects are large relative to the undesirable effects varies, and that there is important or probably important uncertainty or variability.

Regarding the domain of acceptability, a child's pediatrician or HCP remains the top trusted source for vaccine information for parents. The involvement of the VFC program, with many of the VFC providers being enrolled as COVID-19 providers, will be especially important for the population of young children. A variety of other programs also will be important to engage in order to reach children in this young age group, including the IHS, Tribal and Urban Indian Health Programs, and HRSA programs. The goal is an efficient rollout resulting in equitable vaccine access for young children in the initial weeks when demand is likely to be higher. Also head earlier was the goal of over 85% of children living within 5 miles of a vaccine provider. In summary of the acceptability domain, the child's HCP continues to be the top trusted source of information, with a variety of programs to facilitate this rollout and acceptability among providers. The WG felt that the mRNA COVID-19 vaccines would be acceptable to stakeholders.

For the domain of feasibility, the Moderna vaccine product for children 6 months through 5 years of age ships at -20°C and has a different color border (magenta). It is a different concentration than the adult primary series. It will have a new National Drug Code (NDC) code, and it does not require a diluent. The Pfizer vaccine for children 6 months through 4 years of age ships at -80°C and has a different color cap (maroon). It has a different amount of diluent added and a new NDC code. The product configurations for both products currently are 10-dose vials in cartons of 10 vials each for a total of 100 doses total. The minimum order quantity is 100 doses per product. Ancillary supplies will be provided for both vaccine products, including pediatric-specific needles. Diluent will be provided with the Pfizer orders.

To summarize the feasibility domain, the Pfizer vaccine for children 6 months through 4 years of age has a similar product configuration to other Pfizer pediatric products. The maroon cap may be more familiar to pediatric HCP. The long-term storage requires an ultra-low temperature freezer and requires diluent. The Moderna vaccine for children 6 months through 5 years of age may be less familiar to pediatric HCP. The product is able to be stored at traditional freezer temperatures and does not require diluent. Overall, the WG felt the Moderna vaccine would be feasible to implement. The WG also felt that the Pfizer vaccine would be feasible to implement. However, discussions among the WG highlighted that the lack of diluent and other storage issues may make the Moderna vaccine more feasible to implement, especially for new providers to the COVID vaccine program.

In terms of the resource domain, no studies were found that evaluated cost-effectiveness of COVID-19 vaccination among children. Studies in adults have shown that COVID-19 vaccine-related healthcare costs could be billions or trillions of dollars. Given this, COVID vaccines overall are likely cost-saving. In a study conducted by Pfizer, it was estimated that the Pfizer vaccine use in individuals 12 years of age and over in 2021 may have averted 9 million cases, almost 700,000 hospitalizations, and over 100,000 deaths. This would have resulted in $30 billion of direct healthcare cost savings. At this time, a vaccine will be available at no cost to the recipient, so cost-effectiveness is not a primary driver for decision-making during the pandemic but will continue to be reassessed in the future. The WG felt that mRNA COVID vaccines in young children are a reasonable and efficient allocation of resources.

Regarding the equity domain, there was an increase in COVID-19 cases among all children during the Omicron surge. However, there were considerable increase among American Indian and Alaskan Native (AI/AN) children. Based on NIS-CCM data, parental intent varied by race, ethnicity, household income, and metropolitan area. There was lower intent among rural individuals and much higher intent among those who have previously received their influenza vaccine. HHS focus groups were conducted, some of which focused on race and ethnicity

specifically and another that focused on the overall population without a specific race and ethnicity focus. There were 18 focus groups with 4-6 participants in each group. Some groups were composed of parents who were ready to vaccinate, while others were waiting to vaccinate. Participants in the focus groups shared their thoughts and opinions about the COVID-19 pandemic regarding their child, vaccination intent, and getting their child a COVID-19 vaccine when it is authorized and available.

Black parents of children 6 months through <2 years of age noted that their child's pediatrician did not have a strong stance on receiving a COVID-19 vaccine, despite having a strong stance on vaccines in general. This made them second guess whether the COVID-19 vaccine is necessary for children. Young children cannot talk/say what is going on or how they feel, which contributed to their concerns about vaccinating childing. The only thing that will make them trust is time. COVID is such a new virus, they are still learning about it. Long-term side effects are the big concern. A child will be living a long time, and they want to know that they are safe. One person admitted that they made an intentional choice to not pay attention to the news or get information on COVID-19 because it will make them worry too much. Hispanic/Latino parents want to wait a couple of months perhaps but want the pediatrician to specifically advise it. Some parents have talked to their doctor about the options and did not get a strong recommendation. If things get worse (e.g., high cases, worse scenarios), that will motivate them to vaccinate their child. One parent felt like COVID is so new that the information medical professionals have might not be totally right. One parent would get their young child vaccinated right away based on the experience from themselves and their other child. A smaller dose makes them more comfortable. One parent would rather not get it for their child unless they had to.

In terms of what actions can be taken to improve equity regarding COVID-19 vaccines, it is known that CDC and HCP are trusted sources of information for parents. Parents want to discuss both the pros and the cons of vaccination. Advertisements need to include representative images, including diversity in racial and ethnic groups, gender, and parents (e.g., moms and dads should be shown). Public health and clinical trial research must be inclusive of all populations from before research initiation through completion and dissemination. There are ways that communities can help improve equity as well. Pediatricians and VFC providers can provide vaccines, but they will not be the only providers of these vaccines. In many areas, pharmacies, community or rural health clinics, school providers, faith-based organizations, and others could partner with others or serve as community vaccination sites. In summary, the WG interpretation was that mRNA COVID-19 vaccines in young children probably would have no impact on health equity.

In summary, the WG discussed each mRNA COVID vaccine primary series compared to no vaccine. Both mRNA COVID-19 primary series in young children met the non-inferiority endpoints, provide protection against symptomatic disease, and are expected to provide higher protection against severe disease. Two vaccine options in this population may allow parents and providers a choice, which could increase uptake and acceptability. The WG felt that for the 2 doses of 25μg of the Moderna vaccine, the desirable consequences clearly outweigh the undesirable consequences and proposed to ACIP to recommend the intervention. For the 3 doses of 3μg of the Pfizer-BioNTech COVID-19 vaccine, the WG felt that the desirable consequences clearly outweigh the undesirable consequences. While the WG noted that there was more uncertainty with this outcome, they still proposed to ACIP to recommend the intervention.

Since the beginning of the COVID pandemic, among US children 6 months through 4 years of age, there have been over 2 million cases, over 20,000 hospitalizations, and over 200 deaths. COVID-19 can cause severe disease and death among children, including children without underlying medical conditions. Future surges will continue to impact children, with unvaccinated children remaining at higher risk of severe outcomes. As with all other age groups, the priority is vaccination of unvaccinated individuals. Expansion of vaccine recommendations down to children 6 months of age would allow an additional 18.7 million children to receive a primary COVID-19 vaccine series. The current data are for a 2-dose Moderna or a 3-dose Pfizer primary series. Post-authorization VE studies will be monitored closely to help determine subsequent timing and the need for boosters, with the acknowledgement that immunocompromised children may also need additional doses for optimal protection.

Clinical Considerations Update

Sara Oliver, MD, MSPH (CDC/NCIRD) presented an update on the Interim Clinical Considerations for Pediatric COVID-19 vaccines on behalf of Dr. Hall, who had developed laryngitis. In terms of the vaccine schedules, the age ranges differ in that Moderna's age group is 6 months through 5 years of age and Pfizer's is 6 months through 4 years of age. It is important to note that "through" means "up to and including." That means the upper age ranges includes that year through the last day before their birthdate. This applies to all age ranges discussed throughout the meeting.

According to the pediatric schedule for the Moderna vaccine for people who are not moderate or severely immunocompromised, all children 6 months through 5 years of age would receive a 2-dose primary series separated by 4 to 8 weeks. Based on the schedule for people who are moderate or severely immunocompromised, all children who are 6 months through 5 years should receive a 3-dose primary series separated by 4 weeks. Just like when the other COVID-19 vaccines were first authorized by age group, only primary series doses are authorized at this time. There are not boosters currently authorized, but there may be recommendations for those in the future.

Based on the pediatric schedule for the Pfizer vaccine for children 6 months through 4 years of age, a 3-dose primary series is recommended for those who are moderate to severely immunocompromised and those who are not. For those who are not immunocompromised, Dose 1 and Dose 2 can be separated by 3 to 8 weeks and Dose 2 and Dose 3 are separated by 8 weeks. For those who are immunocompromised, Dose 1 and Dose 2 are separated by 3 weeks and Dose 2 and Dose 3 are separated by at least 8 weeks. Booster doses are not authorized to this age group, but there may be recommendations for those in the future.

In terms of the 3- to 8-week interval between Dose 1 and Dose 2 and when it may be appropriate to use the shorter authorized interval of 3 to 4 weeks or when it would be appropriate to use the longer 8-week interval, this can be used in anyone 6 months through 64 years of age. The benefits and risks can be weighed with individual patients based on their characteristics and situations. The shorter interval is more appropriate when the protection needs to be achieved the soonest. These situations could include being immunocompromised or living with an underlying medical condition that would put somebody at higher risk for severe disease, living with a household member who has an increased risk for severe disease who cannot be vaccinated due to contraindication or living, and/or going to school in or traveling to an area with high COVID-19 community levels. The longer interval may be more important in some situations when the priority is to reduce the myocarditis risk. Some studies in adolescents and adults have shown that the small risk of myocarditis associated with the mRNA

COVID-19 vaccines may be reduced with the longer interval. The use of this longer interval would be especially important in adolescents and young adult males where the highest risk is seen. Another instance would be to optimize VE, which may be increased with a longer interval, keeping in mind that this is balanced with a risk of remaining not fully protected for a longer period of time. Extending the interval to beyond 8 weeks has not been shown to provide additional benefit.

With regard to the new formulations, children should receive the age-appropriate vaccine formulation and follow the schedule based on their age on the day of vaccination regardless of their size or weight. If a person moves from a younger age group to an older age group during the primary series or between the primary series and receipt of a booster dose, they should receive the vaccine dosage for the older age group for all subsequent doses. However, FDA authorizations do allow for some different dosing for certain age transitions. There will be an upcoming clinician education call that will address a variety of scenarios for aging up into the next age group. Additional slides will be posted on the ACIP website that will walk through all of these possible options. Dr. Oliver reviewed the formulations and labels for the Moderna and Pfizer-BioNTech COVID-19 formulations for children. COVID-19 vaccines are not interchangeable. The same mRNA vaccine product should be used for all doses of the primary series. In exceptional situations in which the mRNA vaccine product administered for a previous dose(s) of the primary series cannot be determined or is not available, either age-appropriate available mRNA COVID-19 vaccine product may be administered at a minimum interval of 28 days between doses to complete the mRNA COVID-19 primary vaccination series.

As is currently the recommendation, the guidance will continue that COVID-19 vaccines may be administered without regard to timing of other vaccines. This includes both simultaneous administration of COVID-19 vaccine and other vaccines on the same day or at any time before or after another vaccine. Extensive experience with non-COVID-19 vaccines has demonstrated that immunogenicity and AE profiles are generally similar when vaccines are administered simultaneously as when they are administered alone. However, data assessing the outcomes of simultaneous administration of COVID-19 with other vaccines are limited currently, including any potential to increase reactogenicity when COVID-19 and other vaccines are administered at the same basis. Therefore, providers can make decisions about co-administration on a case-by-case basis. In accordance with general best practices, routine administration for all age-appropriate doses of vaccines simultaneously is recommended for children for whom no specific contraindications exist at the time of the healthcare visit.

When deciding whether to co-administer another vaccine with the COVID-19 vaccine, providers and guardians may consider whether a child is behind or at risk of becoming behind on their recommended vaccines, the likelihood of the child returning for another vaccination visit, their risk of vaccine-preventable diseases, and the reactogenicity profile of the vaccines. Best practices for multiple injections include labeling each syringe with the name and dosage of the vaccine with the lot number and initials of the preparer and the exact beyond use time, if applicable. Each injection should be administered in a different injection site, with injection sites separated by 1 inch or more if possible. COVID-19 vaccines and vaccines that may be more likely to cause a local reaction can be administered in different limbs, if possible. Additionally, vaccines that may be known to be more painful also could be administered after the other vaccine(s).

It also is important to take a closer look at the importance of catch-up vaccination and avoiding missed opportunities to vaccinate. In terms of what is known about vaccination coverage since the pandemic began, vaccination coverage among kindergarteners nationwide was lower during the 2020-to 2021 school year compared with the 2019-2020 school year. There was 94% coverage for MMR, DTaP, and varicella at a level just below the Healthy People target of 95%. Coverage for all 3 vaccines decreased in the majority of states. During the 2020-2021 school year, 10% of school principals reported that fewer students were fully vaccinated, 27% of school nurses reported that fewer students were vaccinated in that school year, and 46% of school nurses reported that school vaccination requirements were a much lower priority compared to recent years. An assessment of VFC orders for influenza vaccine components through May showed that overall, there was a dramatic decrease in orders from the 2019 baseline. Orders decreased in 2020 and 2021. To date in 2022, there has been some catch-up. However, orders are still about 4% lower than the same time in 2019 pre-pandemic. This emphasizes the gap that need to be made up with routine vaccination and the importance of opportunities with COVID-19 vaccines that could play a role in that catch-up.

In terms of patient and patent/guardian counseling on side effects, in clinical trials have shown that young children tend to experience similar but maybe fewer side effects than adolescents or young adults. Providers should counsel parents and guardians on the potential side effects. Local side effects may include pain, swelling, and redness at the injection site and/or axillary or inguinal lymphadenopathy. Systemic side effects may include fever, fatigue, headache, chills, myalgia, and arthralgia. In younger children and infants, there may be irritability, crying, sleepiness, and loss of appetite. Febrile seizures were rare in the COVID-19 clinical trials for young children. In most cases, simultaneous vaccine does not lead to higher rates of febrile seizures, although administering more than one vaccine at the same clinic visit has been associated with an increased risk of febrile seizures for some specific vaccines in young children. The impact of co-administration with COVID-19 on the risk of febrile seizures has not been specifically studied to date. Febrile seizures are not uncommon generally and can occur in infants and young children with any condition that causes a fever. Up to 5% of children younger than 5 years of age will have at least one febrile seizure. These can occur with vaccination but are uncommon. Nearly all children who have a febrile seizure recover quickly and do not have any permanent neurologic damage. CDC and FDA are going to closely monitor COVID-19 vaccines to identify any safety signals.

To wrap up the end of EtR Framework, as with all ages, post-authorization safety and effectiveness monitoring will be critical. Platforms are in place to monitor VE and the results will be communicated publicly as soon as possible. As heard to the previous day, timing of these results will depend on vaccine uptake and COVID-19 incidence. COVID-19 vaccines are being administered under the most intensive vaccine safety effort in US history. For these young children, parents can complete the surveys in v-safe[SM], the CDC smartphone-based monitoring program. Doing so will provide critical information in the post-authorization monitoring. Healthcare providers also can help by promoting v-safe[SM] in their practices through information sheets, posters, and QR codes. All of this information and tools are available on the CDC website.

Vote: Moderna COVID-19 Vaccine in Children 6 Months Through 5 Years of Age

Sara Oliver, MD, MSPH (CDC/NCIRD) presented the proposed recommendations for a Moderna vaccine series for children 6 months through 5 years of age, which read as follows:

> "A two-dose Moderna COVID-19 vaccine series (25µg each) is recommended for children ages 6 months through 5 years under the EUA issued by FDA."

Motion/Vote: Moderna COVID-19 Vaccine in Children 6 Months Through 5 Years of Age

Dr. Poehling made a motion for ACIP to adopt the verbiage of the recommendation stating that, "A two-dose Moderna COVID-19 vaccine series (25µg each) is recommended for children ages 6 months through 5 years under the EUA issued by FDA." Ms. Bahta seconded the motion. No conflicts of interest (COIs) were declared. The motion carried with 12 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

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

Vote: Pfizer-BioNTech COVID-19 Vaccine in Children 6 Months Through 4 Years of Age

Sara Oliver, MD, MSPH (CDC/NCIRD) presented the proposed recommendations for a Pfizer-BioNTech COVID-19 vaccine booster dose for children 6 months through 4 years of age, which read as follows:

> "A three-dose Pfizer-BioNTech COVID-19 vaccine series (3µg each) is recommended for children ages 6 months through 4 years of age under the EUA issued by FDA."

Motion/Vote: Pfizer-BioNTech COVID-19 Vaccine in Children 6 Months Through 4 Years of Age

Dr. Bell made a motion for ACIP to adopt the verbiage of the recommendation stating that, "A three-dose Pfizer-BioNTech COVID-19 vaccine series (3µg each) is recommended for children ages 6 months through 4 years of age under the EUA issued by FDA." Dr. Sanchez seconded the motion. No COIs were declared. The motion carried with 12 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

Dr. Bell emphasized that as oftentimes is the case about balancing benefits and harms, this is an opportunity that one does not get very often to participate in preventing the death of young children. Any deaths are a tragedy. A death in a young child is an incredible tragedy and this disease is killing children. On the harm side, all the information so far is good. There is more information than there often is for other vaccines. Anyone making an important decision about anything, especially for their children, wants to consider that balance. While they do not know everything there is to be known about this and the data may change, the bottom line is that this infection kills children and there is an opportunity to prevent that. Every parent will want to consider that calculus as well. ACIP members take their responsibility extremely Seriously and this is an opportunity to prevent a known risk. She thought they made a big step forward with these votes.

Dr. Brooks stressed that the ACIP just authorized 18.7 million children to get vaccinated. There have been over 2 million cases in these children and 200 plus deaths. While it is unknown what is coming in terms of future variants, he felt comfortable in saying that vaccinating will be a net benefit. ACIP made a decision that will help children in that they will achieve a certain level of efficacy and going forward, that will be a benefit over the next months and years. He agreed that ACIP had taken a major step forward.

Dr. Daley reminded everyone that they heard pleas to approve these vaccines through public commentary during the first day of the meeting and in the written comments submitted through the docket. They also heard pleas not to approve these vaccines. He said he wanted to explicitly state that ACIP heard those who disagreed with the decisions made during this meeting. Some people emphasized that they do not think these vaccines are effective. Data were presented showing that they are effective. Some commenters emphasized concerns that the vaccines are not safe. The safety data indicate that they have a high degree of safety. ACIP took all comments and data into consideration and made the votes that they did for the reasons articulated by Dr. Brooks and Dr. Bell—that ACIP feels like this is an opportunity to prevent severe disease and death in this in this age group. He also reiterated that the work continues and that ACIP will continue to communicate this as best they can to the public.

Dr. Lee said that she was fully confident that vaccines should be recommended. They clearly can prevent hospitalizations and deaths. She also believes they have the potential to prevent long-term complications of infections that are not yet understood. She is very concerned that the long-term implications of infection over time will be the next big public health burden that they face, particularly among children. Her hope is that these votes will allow for one step forward in the right direction and that progress will continue over time. She thanked all of her fellow committee members.

Dr. Romero thanked the ACIP voting members, liaisons, and *ex-officios* and all of the members of CDC who put time into making this decision. As someone who once sat where they all sat during this meeting, he understands how much effort goes into this and how much effort has gone forward since the end of his tenure. On behalf of NCIRD, he thanked everyone very much for doing such an incredible job of protecting the nation’s children. He wished everyone a much-deserved rest this weekend and a Happy Father’s Day to the fathers in the group.

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ACRONYMS USED IN THIS DOCUMENT

ACEs	Adverse Childhood Experiences
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI/AN	American Indian and Alaskan Native
CDC	Centers for Disease Control and Prevention
COD	Causes of Death
COI	Conflicts of Interest
DSMB	Data and Safety Monitoring Board
ECE	Early Care and Education
ED	Emergency Department
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GRADE	Grading of Recommendations, Assessment, and Evaluation
HCP	Healthcare Personnel / Provider
HHS	(Department of) Health and Human Services
HRSA	Health Resources and Services Administration
ICATT	Increasing Community Access to Testing Partnership
ICU	Intensive Care Unit
IHS	Indian Health Service
MAAE	Medically Attended Adverse Events
MIS-C	Multisystem Inflammatory Syndrome in Children
NASN	National Association of School Nurses
NDC	National Drug Code
NIS-CCM	National Immunization Survey-Child COVID Module
PCP	Primary Care Providers
PCR	Polymerase Chain Reaction
PICO	Population, Intervention, Comparison, Outcomes
PRNT	Plaque Reduction Neutralization Test
PROTECT	Pediatric Research Observing Trends and Exposures in COVID-19 Timelines
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RHC	Rural Health Center
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SOC	System Organ Class
UC	Urgent Care
US	United States

VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WIC	Women, Infants, and Children