VRBPAC Meeting: Pfizer COVID-19 Vaccine for Children 5-11

October 26, 2021

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VRBPAC AGENDA (October 26, 2021)

VOTING QUESTION: Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5 through 11 years of age?

VOTE: **17 YES - 1 ABSTAIN Motion passes**

FDA - Introduction of Topic and Background OVERVIEW EUA REQUEST

- **Purpose of this section:** FDA representatives presented an overview of Pfizer's EUA request, a brief risk/benefit analysis leading to today's meeting, and a summary of today's meeting.

- **Key Points:**
    - Considerations on data to support EUA of COVID-19 vaccines for use in pediatric age groups were discussed at the June 10, 2021 VRBPAC meeting.
    - Benefits of vaccination in pediatric age groups is assessed via clinical endpoint efficacy data and immune bridging data.
    - Pfizer EUA Request: Pfizer submitted data to the FDA on October 6, 2021. The proposed dose and regimen is a primary series of 2 doses (0.2 mL each, 10 µg of mRNA), 3 weeks apart, administered intramuscularly in individuals 5-11.
        - Clinical package includes safety and immunogenicity data ~1,500 vaccine recipients with 2 months or more safety follow-up, post-dose 2 and ~1,600 vaccine recipients with about 2 weeks safety follow-up, post-dose 2

CDC - Epidemiology of COVID-19 in Children COVID IN CHILDREN 5-11 SLIDES

- **Purpose of this section:** Review of real world data on COVID-19 infection/hospitalization/death in children 5-11

- **Key Points:**
    - During recent months, children 5-11 years are making up a greater proportion of total cases: 10.6% of cases the week of October 10, 2021. Children consistently have higher seroprevalence estimates than adults. Age 5–11 have the highest seroprevalence, but confidence intervals overlap with other pediatric age groups.
        - Age 5–11 seroprevalence increased from 13% in Nov–Dec 2020 to 42% in May–June 2021

- Seroprevalence data suggest infections in children less likely to be reported compared with adults. Children are at least as likely as adults to be infected with SARS-CoV-2 Seroprevalence in children continues to increase.
- Minority children 5-11 are more disproportionately impacted by COVID-19 disease. Underlying conditions related to more severe disease of note are obesity and feeding tube dependence. There have been a total of 94 deaths in children 5-11 associated with COVID disease.
- MIS-C is the most concerning and dangerous severe adverse events. There have been 5,217 MIS-C cases reported to national surveillance as of October 4, 2021, with the median age of onset at 9 years. 39% of cases occurred in children 6-11 years and 61% occurred in children who are Hispanic/Latino or Black, Non-Hispanic.

- **Discussion:**
  - The committee brought up a number of safety concerns, including the age range of MIS-C related to COVID infection in younger children. A few committee members noted that obesity as an independent risk factor for hospitalization is important to consider when thinking about safety concerns.
  - Other committee members asked about the long term effects of COVID, such as chronic fatigue syndrome etc. Overall, the long term effects of COVID need to be studied in more depth, but there are preliminary findings that kids 5-11 are experiencing long term effects.
  - Regarding seroprevalence surveillance, the committee was interested in recent data vs. pre-Delta data. Some members noted that seroprevalence rates for 5-11 is likely an underestimate.

CDC - Known safety signals (Myocarditis in adolescents/young adults) SLIDES

- **Purpose of this section:** CDC representatives presented data on myocarditis from numerous studies, demonstrating that myocarditis is a series cardiovascular condition that continues to be monitored

- **Key Points:**
  - MIS-C related to COVID-19 disease is more strongly correlated with myocardial infarctions than myocarditis related to mRNA vaccines.
  - There are a total of 826 cases of myocarditis reported in the U.S. related to the mRNA vaccines. The majority are young men, and the majority fully recover.
  - The 5-11 age group has the lowest cases of myocarditis compared to the entirety of the pediatric population. Hormone levels, especially in young males, may play a role in higher rates of myocarditis in adolescent/teenaged men.
  - Myocarditis is a rare but important adverse event following COVID-19 vaccination. Not all myocarditis is the same and early follow-up results of COVID-19 vaccine-associated myocarditis are sparse. Ongoing follow-up is in progress.

- **Discussion:**
    - One committee member brought up the dosing interval between a first a second dose of mRNA COVID vaccines, questioning whether the closeness of the dosing interval influences rates of vaccine related myocarditis.
    - There were concerns that rates of more mild myocarditis and pericarditis are underestimated and fail to be reported (due to children not being hospitalized). Overall, there is not strong data on this group with mild myocardial infractions.

Sponsor Presentation - Pfizer BioNTech PFIZER SLIDES

- **Purpose of this section:** Pfizer BioNTech presented their Phase 1, 2, and 3 study data on their mRNA vaccine for children 5-11; reviewed safety and efficacy data of Pfizer's new formulation for the younger pediatric population

- **Key Points:**
    - Dosage: 10ug dose level was selected as optimal to elicit robust immune responses with an acceptable safety profile (2 doses, 3 weeks apart)
    - Data: Meets all safety data expectations, immunobridging criteria comparing 5 to <12 yo to 16 to 25 yo subjects,90.7% efficacy was observed, and plans for active safety follow up under EUA
        - There were two cohorts in the Phase 2/3 studies, and they vary by followup time: the first cohort had 2+ months of followup, and the second had approximately 2 weeks of followup (focused on safety). Each cohort was about the same size.
        - Immunobridging success criteria were met for 5 to <12 year olds at 10 µg dose level
    - Why do we need this vaccine? COVID-19 causes additional long-term sequelae in children (ie. 50% of MIS-C in 5−13 year-olds), severe outcomes are unpredictable and can occur in healthy children (ie. 1 in 3 hospitalizations occur among children without comorbidities), and vaccinating children has other societal benefits (ie. transmission)
    - Reactions to Vaccine: The most common vaccine reactions were pain, swelling, and redness around the injection site. Rates of *fever and chills for the 5-11 cohort were lower than the 16-25 cohort*
        - *No deaths or serious SAEs and adverse events were comparable with placebo and study recipients.*
        - All SAEs considered unrelated to the vaccine
        - Reactogenicity was mostly mild to moderate, and short lived
    - No severe cases of COVID-19 or cases of MIS-C were reported.

- **Discussion:**
    - A committee member questions why there were 3 cases of COVID despite vaccination. Pfizer responded that older children may have more exposure due to increased social activity.

- Another member noted that perhaps a lower dose (ie. 10ug) may be safety, equally as efficacious, and have less side effects for the 12-17 adolescent population.
- Some committee members felt that we may be missing the impact of disease by only addressing symptomatic infection in the efficacy/immunogenicity analysis.
- Data is limited because of short followup time (max ~2 months), which made some members question whether or not COVID-19 vaccines for 5-11 are really needed.

FDA Presentation - COVID Vaccines 5-11

EFFICACY/SAFETY
BEST SAFETY MONITORING SYSTEM
BENEFIT RISK ANALYSIS

- **Purpose of this section:** Review of FDAs independent analysis of Pfizer Phase 1,2, and 3 data, demonstrating safety and efficacy for the 5-11 population
- **Key Points:**
  - Phase 1 data demonstrated that a 10 ug dose was optimal compared to 20 ug and 30 ug. Phase 2/3 studies involved the two dose series, 3 weeks apart of the Pfizer vaccine. There were two cohorts in the Phase 2/3 studies, and they vary by followup time: the first cohort had 2+ months of followup, and the second had approximately 2 weeks of followup (focused on safety). Each cohort was about the same size.
  - Vaccine efficacy was 90.7% effective against symptomatic COVID-19 infection and included “participants without evidence of infection prior to 7 days after dose 2.”Immunobridging success criteria for both the GMT ratio and seroresponse were met.
  - The most common reactions were pain at the injection site, fatigue, and headache. The most common SAE was lymphadenopathy and SAEs occurred at a frequency of 0.1% and 0.2%, respectively, in vaccine recipients, and in 0.1% and 0% in placebo recipients, respectively.
  - There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths.There were more than double participants in the safety data base for the Pfizer 5-11 age group compared to the 12-15 age group.
  - **FDA Biologics and Effectiveness Safety (BEST)** System is monitoring the safety of COVID-19 vaccines in near-real time surveillance. The pediatric population will be monitored in FDA BEST
  - Benefits clearly outweigh the risk in the five scenarios presented during the benefit risk analysis.

	EUA 5-11 years	EUA 12-15 years
Dose/regimen	Two 10 µg doses 3 weeks apart	Two 30 µg doses 3 weeks apart
Safety Endpoints	Solicited local and systemic ARs, unsolicited, SAEs, AESIs	Solicited local and systemic ARs, unsolicited, SAEs, AESIs
Immunobridging approach	GMT ratio and seroresponse 1 month post dose 2 compared with young adults 16-25 years of age in C4501001 efficacy study	GMT ratio 1 month post dose 2 compared with young adults 16-25 years of age in C4501001 efficacy study (seroresponse analysis was descriptive only)
Efficacy Endpoints	Secondary descriptive	Secondary descriptive
Safety database (vaccine recipients)	~3000	~1131
Length of follow up	1444 with ≥2 months of follow up	660 with ≥2 months of follow up

Final Discussion, and Vote

- The committee brought up a number of safety concerns related to myocarditis and pericarditis. There were concerns that cases of mild myocarditis and pericarditis are underestimated and fail to be reported.
- Data is limited for children in this age group with mild myocardial infarctions, and voting members felt that further surveillance of myocarditis/pericarditis is needed. However, many members noted that myocarditis related to MIS-C from COVID infection leads to much higher rates of myocarditis than an mRNA vaccines.
- Overall, the committee felt that the benefits outweigh risks when voting to recommend authorization. The committee brought up a number of concerns, including the unpredictable course of the pandemic, limitations in assumptions of sustained immunity, and lack of consideration to asymptomatic infection in the analysis.
- Some members expressed reservations on widespread use/implementation for the entirety of the 5-11 cohort. Some voting members felt that due to overall low rates of deaths/hospitalization and natural immunity levels, children 5-11 may not need a COVID-19 vaccine.
- Other members (as well as Peter Marks) noted that approving this vaccine is essential to prevent *any* deaths and to increase equity. Failing to approve this vaccine under EUA deprives parents the choice to vaccinate their children, and will deny this vaccine to children who may need protection from COVID disease in one way or another.
- Some members felt strongly that if/when this vaccine is approved under FDA EUA and recommended by CDC ACIP, it should not be mandated in schools, etc. due to limited safety data and short followup time in phase 2 and 3 clinical trials.
- **VOTING QUESTION:** Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5 through 11 years of age?
    - **VOTE:** **17 YES - 1 ABSTAIN Motion passes.**