mRNA COVID-19 vaccines in young children: Summary and Work Group interpretation

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cdc.gov/coronavirus
Clinical trial structure
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- Trial conducted from December 2021 through February 2022
- Children ages 6 months–5 years in the United States randomized 3:1 vaccine to saline placebo
  - Analyses performed separately for ages 6–23 months and 2–5 years
  - Results pooled for a combined estimate for ages 6 months–5 years
- Two doses of 25µg separated by 28 days
- Median follow-up time post-dose 2: 2.5 months
Clinical trial structure
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- **Efficacy and safety populations:**
  - 6–23 months: ~2300 children; 1700 vaccine and 600 placebo
  - 2–5 years: ~4000 children; 3000 vaccine and 1000 placebo
  - TOTAL 6 months–5 years: ~6400 children; 4800 vaccine and 1600 placebo

- **Immunogenicity population:**
  - 6–23 months: 230 children
  - 2-5 years: 264 children
Efficacy data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- Efficacy endpoint\textsuperscript{1,2}: Subjects with or without evidence of prior infection
  - 6–23 months: 50.6\% (21.4–68.6\%)
  - 2–5 years: 36.5\% (12.5–54.0\%)
  - Overall 6 months–5 years: 41.5\% (23.8–55.0\%)

- Higher confidence in the estimate, based on 181 COVID-19 cases in vaccine group and 97 COVID-19 cases in placebo group

- Efficacy in the trial consistent with post-authorization vaccine effectiveness for Moderna COVID-19 vaccine in adults 18–64 years during Omicron
  - Effectiveness against infection 2 months after dose 2 was 35\% (24–45\%)

\textsuperscript{1}CDC definition: At least 1 prespecified clinical symptom and a positive RT-PCR
\textsuperscript{2}Efficacy estimates presented represent the manufacturer analysis. For GRADE, estimates based on relative risks will be presented
Immunogenicity data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- Antibody levels measured 28 days after the second dose for participants without prior infection
- Antibody responses after two 25µg doses in children ages 6 months–5 years compared to two 100µg doses in individuals ages 18–25 years
  - Ratio for 6–23 months: 1.28 (1.12–1.47)
  - Ratio for 2–5 years: 1.01 (0.90–1.17)
Safety data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- **No deaths** were reported in any trial participants

- **Serious adverse events (SAE) rare overall**
  - SAEs occurred in 0.5% of vaccine recipients and 0.2% of placebo recipients
  - One vaccine recipient had 2 SAEs (fever and febrile seizure) that are possibly related to the vaccine*

- **No cases of myocarditis in any trial participants**

- **No cases of vaccine-associated anaphylaxis in any trial participants**

*As determined by FDA
Safety data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- **Local** reactions occurring within 7 days were common
  - Pain at the injection site most common

- **Systemic** reactions within 7 days were common
  - Fatigue and headache most common in children ages 2–5 years
  - Irritability and sleepiness more common in children ages 6–23 months

- Symptom onset was usually **1–2 days** post-vaccine receipt

- Most symptoms were mild and resolved after **2–3 days**
Safety data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- **Fevers** were more common after vaccine than placebo, and more common after dose 2 than dose 1
- Most fevers were reported on day 1 and 2 after either dose and lasted for a median of 1 day
- Fevers after other routine vaccines given at this age can be ~30%
- One febrile seizure possibly related to vaccine noted (3 days after dose 1)

<table>
<thead>
<tr>
<th>Fever post-dose 2</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fever</td>
<td>730/4532 (16.1%)</td>
<td>107/1483 (7.2%)</td>
</tr>
<tr>
<td>Grade 4 fever (104°F or higher)</td>
<td>10/4532 (0.2%)</td>
<td>0/1483 (0%)</td>
</tr>
</tbody>
</table>
Safety data reviewed by Work Group
Moderna COVID-19 vaccine: Children ages 6 months–5 years

- Imbalances were noted with some respiratory infections
  - Overall, events were rare (occurred in <1% of trial participants)

- No pattern for respiratory infections noted, and the clinical characteristics were typical and consistent with seasonal respiratory infections
  - Testing not performed systematically; testing for additional respiratory pathogens may have varied by results of COVID-19 testing

- Lymphadenopathy (axillary or groin) noted in 9% of vaccine recipients, compared to 2% of placebo recipients
Conclusions
Modernna COVID-19 vaccine: Children ages 6 months–5 years

- Efficacy seen after two doses of Moderna COVID-19 vaccine in children ages 6 months–5 years of age consistent with real-world vaccine effectiveness in all other ages during Omicron predominance

- Antibody levels after 2 doses in children ages 6 months–5 years produces similar antibody levels after 2 doses in individuals ages 18–24 years

- Reactogenicity post-vaccine consistent with other recommended vaccines in this age group
Pfizer-BioNTech COVID-19 vaccine
Children ages 6 months–4 years
Clinical trial structure
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- Trial conducted from June 2021 through April 2022
- Children ages 6 months–4 years in the United States randomized 2:1 vaccine to saline placebo
  - Analyses performed separately for 6–23 months and 2–5 years
  - Results pooled for a combined estimate for 6 months–5 years
- Three doses, 3µg each: Dose 1 and dose 2 separated by **21 days**
  Dose 2 and dose 3 separated by at least **8 weeks**
  - Interval between dose 2 and dose 3 in the trial longer than authorized interval:
    - ~**16 weeks** (range 8–32 weeks) for children ages 6–23 months
    - ~**11 weeks** (range 8–34 weeks) for children ages 2–4 years
- Median follow-up time post-dose 3: **1.3 months**
Ages 2–4 years, initial cohort

First doses: June 21, July 21, August 21
Second doses: June 21, July 21, August 21, September 21
Unblinding: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22
Third doses: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22, March 22

Per protocol, unblinding began 6 months after dose 2.

Ages 2–4 years, expanded enrollment*

First doses: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22
Second doses: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22, March 22

Unblinding: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22, March 22, April 22
Third doses: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22, March 22

Blinded person-time contributing to dose 3 efficacy evaluation
N=886; 606 in BNT group, 280 in placebo group

Delta predominance: June 21, July 21, August 21, September 21, October 21, November 21, December 21, January 22, February 22, March 22
Omicron predominance: February 22, March 22, April 22

* An additional safety expansion was initiation on January 31, 2022; children in the additional safety expansion would not have contributed person-time to post-dose 3 follow-up by the April 29 EUA submission.
Pfizer-BioNTech trial timeline, ages 6–23 months

Ages 6–23 months, initial cohort

- First doses: Jun 21 → Jul 21 → Aug 21 → Sep 21 → Oct 21
- Second doses: Jun 21 → Jul 21 → Aug 21 → Sep 21 → Oct 21 → Nov 21
- Third doses: Jun 21 → Jul 21 → Aug 21 → Sep 21 → Oct 21 → Nov 21

Per protocol, unblinding began 6 months after dose 2

Ages 6–23 months, expanded enrollment*


Blinded person-time contributing to dose 3 efficacy evaluation
N=570; 386 in BNT group, 184 in placebo group


Delta predominance: Jun 21 → Nov 21
Omicron predominance: Dec 21 → Apr 22
Number of children contributed *blinded* person-time to efficacy evaluation, by age group

**Ages 2–4 years**

- **Dose 1 all-available efficacy population**
  - Total: 2,750
  - Vaccine: 1,835
  - Placebo: 915

- **Dose 2 all-available efficacy population**
  - Total: 2,726 (99.1%)
  - Vaccine: 1,819 (99.1%)
  - Placebo: 907 (99.1%)

- **Dose 3 all-available efficacy population**
  - Total: 886 (32.2%)
  - Vaccine: 606 (33.0%)
  - Placebo: 280 (30.6%)

**Ages 6–23 months**

- **Dose 1 all-available efficacy population**
  - Total: 1,776
  - Vaccine: 1,178
  - Placebo: 598

- **Dose 2 all-available efficacy population**
  - Total: 1,762 (99.2%)
  - Vaccine: 1,166 (99.0%)
  - Placebo: 596 (99.7%)

- **Dose 3 all-available efficacy population**
  - Total: 570 (32.1%)
  - Vaccine: 386 (32.8%)
  - Placebo: 184 (30.8%)

32% of the overall eligible population contributed blinded person-time to the efficacy evaluation due to per-protocol unblinding after dose 2.
Efficacy data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- Efficacy endpoint\(^1,2\): Subjects with or without evidence of prior infection
  - 6–23 months: 75.5\% (-370.1–99.6\%)
  - 2–4 years: 82.3\% (-8.0–98.3\%)
  - Overall 6 months–4 years: 80.3\% (13.9–96.7\%)

- Lower confidence in the estimates, based on 3 COVID-19 cases in vaccine group and 7 COVID-19 cases in placebo group

- Post-authorization vaccine effectiveness (VE) for Pfizer-BioNTech COVID-19 vaccine in adolescents ages 12–15 years during Omicron:
  - VE against infection 2 months after dose 2 was 28.9\% (24.5–33.1\%)
  - VE against infection 2 months after dose 3 was 42.9\% (34.5–50.2\%)

\(^1\)CDC definition: At least 1 prespecified clinical symptom and a positive RT-PCR
\(^2\)Efficacy estimates presented represent the manufacturer analysis. For GRADE, estimates based on relative risks will be presented.
Efficacy data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- Post-dose 3 efficacy data are difficult to interpret
  - Limited number of cases accrued during blinded follow-up
  - Protocol specified need for 21 cases prior to formal efficacy analysis, only 10 included in current descriptive analysis
  - Dosing interval between dose 2 and dose 3 varied and are longer than authorized interval
  - Median blinded follow up time limited
    - 35 days for children ages 6–23 months
    - 40 days for children ages 2–4 years
Immunogenicity data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- Antibody levels measured 1 month post-dose 3 for participants without prior infection

- Antibody responses after three 3µg doses in children ages 6 months–4 years compared to two 30µg doses in individuals ages 16–25 years
  - Ratio for 6–23 months: \(1.19\) (1.00–1.43)
  - Ratio for 2–4 years: \(1.30\) (1.13–1.50)
  - Overall ratio for 6 months–5 years: \(1.26\) (1.13–1.40)

- Immunogenicity population:
  - 6–23 months: \(82\) children
  - 2–5 years: \(143\) children
For comparison, results after dose 2 are shown

<table>
<thead>
<tr>
<th></th>
<th>Dose 2(^1) Efficacy(^2,3)</th>
<th>Dose 2 Immunobridging(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–23 months</td>
<td>14.5% (-24.9–41.0%)</td>
<td>Non-inferiority criteria <strong>met</strong></td>
</tr>
<tr>
<td>2–4 years</td>
<td>33.6% (9.1–51.3%)</td>
<td>Non-inferiority criteria <strong>not met</strong></td>
</tr>
</tbody>
</table>

\(^1\)Seven days after dose 2 to before dose 3  
\(^2\)**CDC definition**: At least 1 prespecified clinical symptom and a positive RT-PCR  
\(^3\)Efficacy estimates presented represent the manufacturer analysis. For GRADE, estimates based on relative risks will be presented  
\(^4\)Antibody responses after two 3µg doses in children ages 6 months–4 years compared to two 30µg doses in individuals ages 16–25 years
Safety data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- **No deaths** were reported in any trial participants
- Serious adverse events (SAE) **rare** overall
  - SAEs occurred in 1.0% of vaccine recipients and 1.5% of placebo recipients
  - One vaccine recipient had 2 SAEs (fever and pain in extremity requiring hospitalization) possibly related to the vaccine*
- No cases of myocarditis in any trial participants
- No cases of vaccine-associated anaphylaxis in any trial participants

*Investigator considered it possibly related; FDA considered the events potentially consistent with symptoms due to viral myositis*
Safety data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- **Local** reactions occurring within 7 days were common
  - Pain or tenderness at the injection site most common

- **Systemic** reactions within 7 days were common
  - Fatigue most common in children ages 2–4 years
  - Irritability and drowsiness more common in children ages 6–23 months

- Reactions were comparable after dose 1, 2, and 3

- Most symptoms were mild and resolved after **1–2 days**
Safety data reviewed by Work Group
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- **Fever**s were reported with similar frequency after both vaccine and placebo, and similar frequencies after doses 1, 2, and 3.
- Most fevers were reported on day 1 and 2 after either dose and lasted for a median of 1 day.

<table>
<thead>
<tr>
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<th>Fever post-dose 2</th>
<th>Fever post-dose 3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine N=2926</td>
<td>Placebo N=1469</td>
</tr>
<tr>
<td>Any fever</td>
<td>173 (5.9%)</td>
<td>82 (5.7%)</td>
</tr>
<tr>
<td>Grade 4 fever (104°F or higher)</td>
<td>3 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vaccine N=917</td>
<td>Placebo N=432</td>
</tr>
<tr>
<td>Any fever</td>
<td>53 (5.8%)</td>
<td>21 (4.9%)</td>
</tr>
<tr>
<td>Grade 4 fever (104°F or higher)</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions
Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- Antibody levels after 3 doses in children ages 6 months–4 years produces similar antibody levels after 2 doses in individuals ages 16–24 years
- Reactogenicity post-vaccine similar after each of the 3 vaccine doses, and similar to reactions seen in placebo recipients
- Efficacy estimates difficult to interpret given small numbers and limited follow-up time
  - Impact of longer interval in the trial between dose 2 and dose 3 on efficacy, reactogenicity or safety are unknown
Work Group Interpretation
Work Group interpretation:
mRNA COVID-19 vaccines in young children

- mRNA COVID-19 vaccine clinical trials in young children both conducted during Omicron predominance, but different months and incidence levels
  - In addition to differences in number of participants in the efficacy analyses and differences in follow up time, the incidence levels impacted COVID-19 case accrual and certainty in efficacy estimates

- Efficacy estimates for these two mRNA vaccines cannot be directly compared

- Both vaccines met non-inferiority criteria for neutralizing antibody levels
Current data are for a **2-dose** or **3-dose primary series**

To achieve criteria set by FDA for authorization, 2 doses for Moderna or 3 doses of Pfizer-BioNTech COVID-19 vaccine were required

- For ages 5 years and over, 2 doses achieved the required antibody levels for immunobridging. A booster was then provided to optimize immune response and address waning of antibody titers detected after completion of primary series

Post-authorization effectiveness studies can help determine subsequent timing and need of **booster**s after 2-dose (Moderna) or 3-dose (Pfizer-BioNTech) primary series
Work Group interpretation:
mRNA COVID-19 vaccines in young children

- In other age groups during Omicron, mRNA COVID-19 vaccine post-authorization vaccine effectiveness was lower against infection, but **higher** protection against **severe disease**

- Clinical trials were not powered to detect efficacy against severe disease in young children, but similar patterns in this age group are expected to what is seen in everyone ages 5 years and older
Next Steps: mRNA COVID-19 vaccines in young children

- Evidence to Recommendation (EtR) Framework, including GRADE summary will be presented tomorrow

Policy questions for EtR

- 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?
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