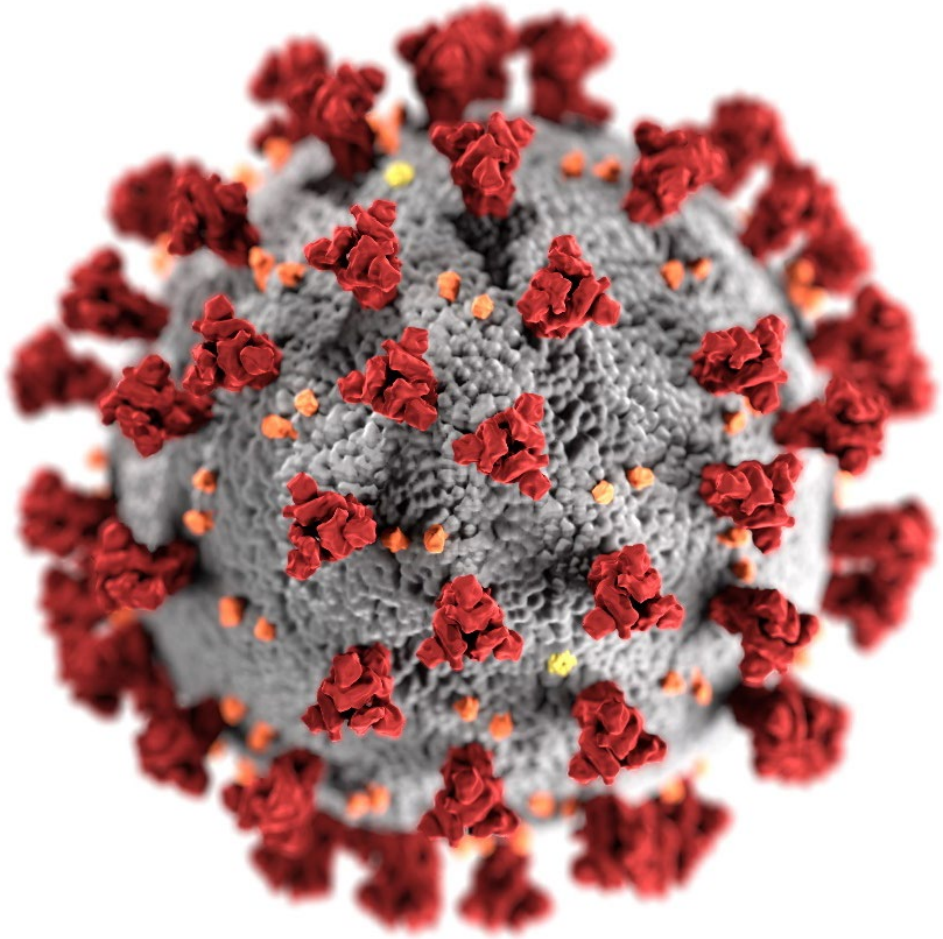
mRNA COVID-19 vaccines in young children: Summary and Work Group interpretation



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cdc.gov/coronavirus

Moderna COVID-19 vaccine

Children ages 6 months–4 years

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

- **<u>Efficacy and safety populations</u>**:
  - 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

- **<u>Immunogenicity population</u>**:
  - 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[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%)

[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

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)

Fever post-dose 2	Vaccine	Placebo
Any fever	730/4532 (16.1%)	107/1483 (7.2%)
Grade 4 fever (104^{oF} or higher)	10/4532 (0.2%)	0/1483 (0%)

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

Moderna 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

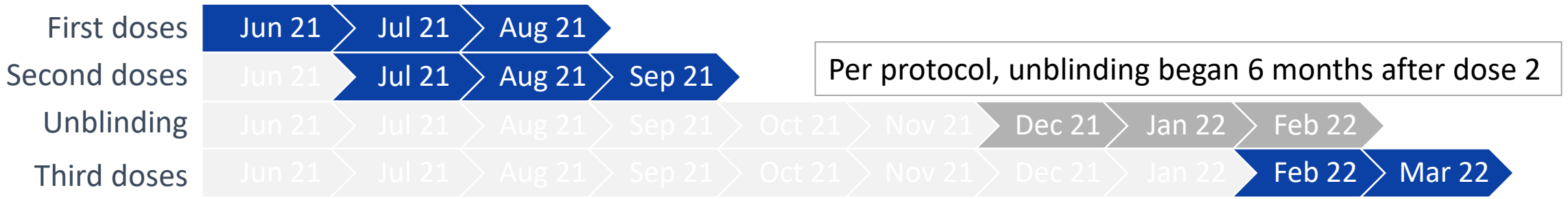
Clinical trial structure

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**

Pfizer-BioNTech trial timeline, ages 2–4 years

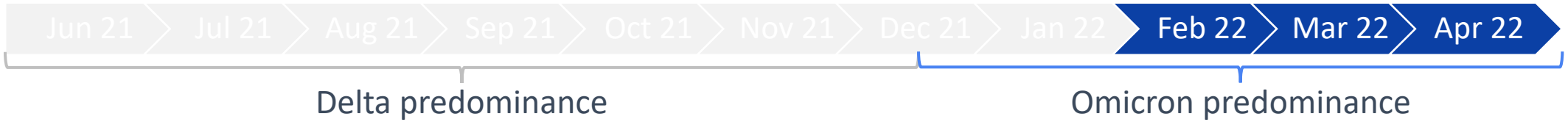
Ages 2–4 years, initial cohort



Ages 2–4 years, expanded enrollment*

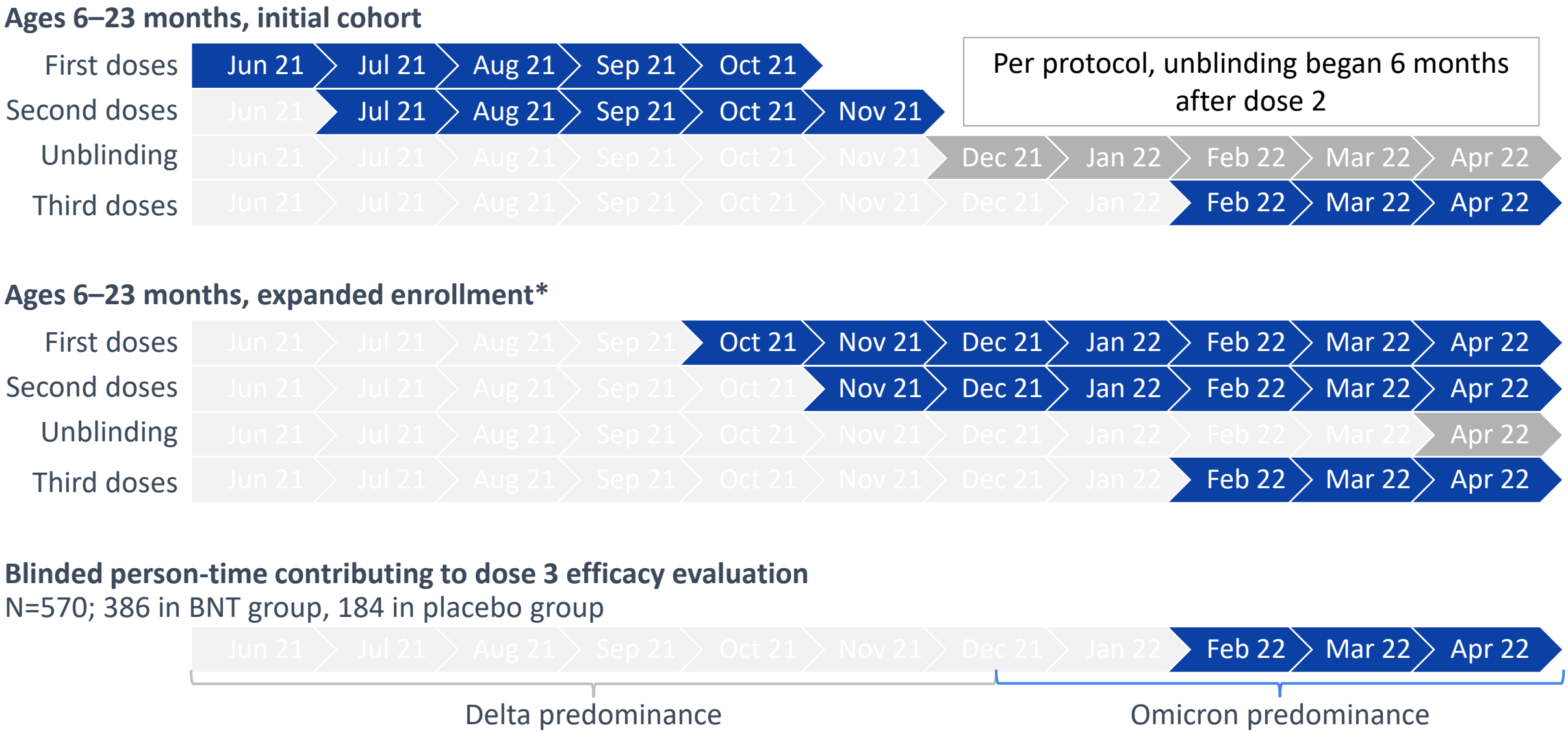
Blinded person-time contributing to dose 3 efficacy evaluation

N=886; 606 in BNT group, 280 in placebo group

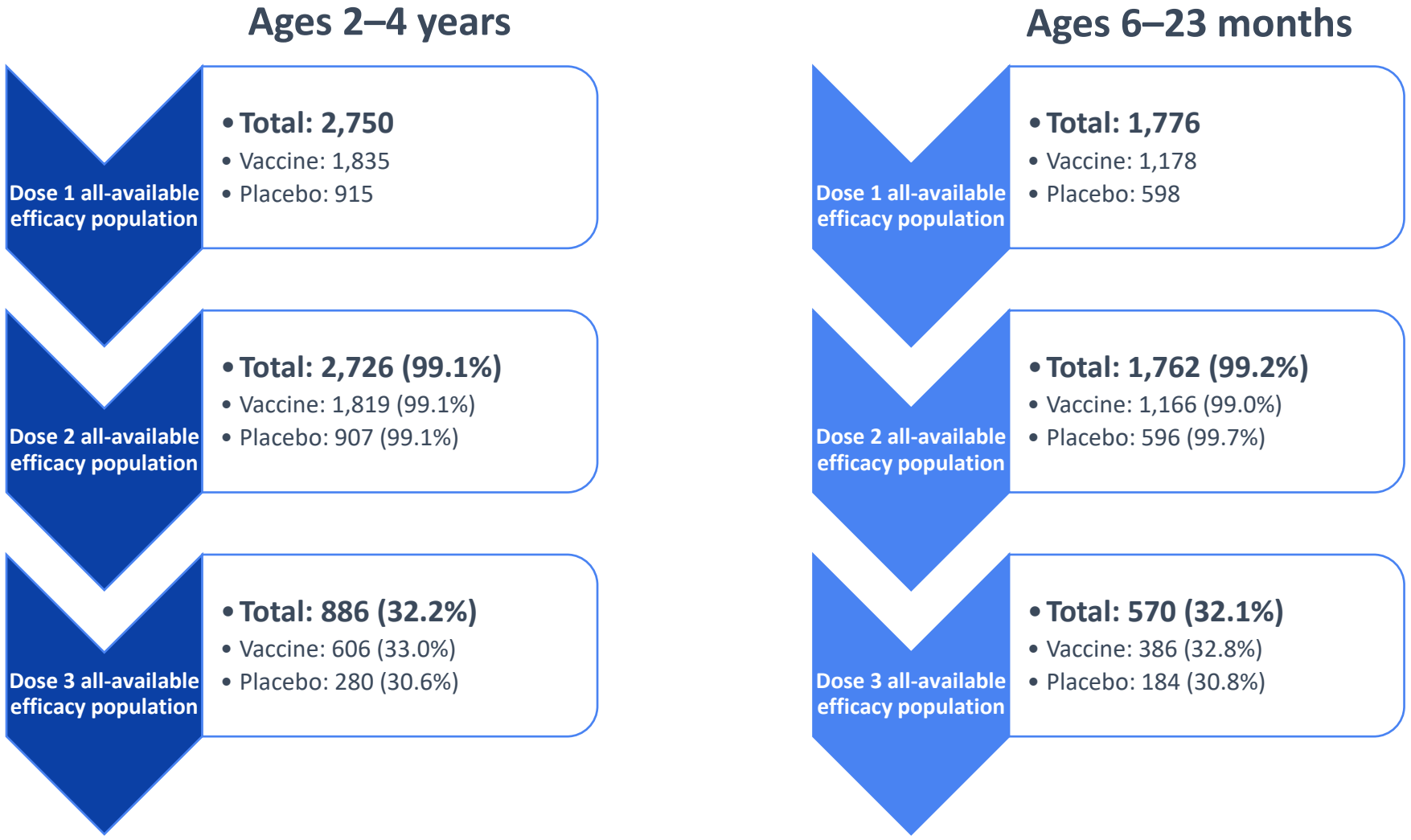


* An additional safety expansion was initiation on January 31, 2022; children in the additional safety expansion would not have contributed person-time to post-dose 3 follow-up by the April 29 EUA submission.

Pfizer-BioNTech trial timeline, ages 6–23 months



Number of children contributed *blinded* person-time to efficacy evaluation, by age group



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**

Data reviewed by Work Group

Pfizer-BioNTech COVID-19 vaccine: Children ages 6 months–4 years

- For comparison, results after dose 2 are shown

	Dose 2[1] Efficacy[2,3]	Dose 2 Immunobridging[4]
6–23 months	14.5% (-24.9–41.0%)	Non-inferiority criteria **met**
2–4 years	33.6% (9.1–51.3%)	Non-inferiority criteria **not met**

[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

- **Fevers** 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

	Fever post-dose 2		Fever post-dose 3	
	Vaccine N=2926	Placebo N=1469	Vaccine N=917	Placebo N=432
Any fever	173 (5.9%)	82 (5.7%)	53 (5.8%)	21 (4.9%)
Grade 4 fever (104^{oF} or higher)	3 (0.1%)	0	1 (0.1%)	0

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

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

- 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 **boosters** 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?

GRADE= Grading of Recommendations, Assessment, Development and Evaluation

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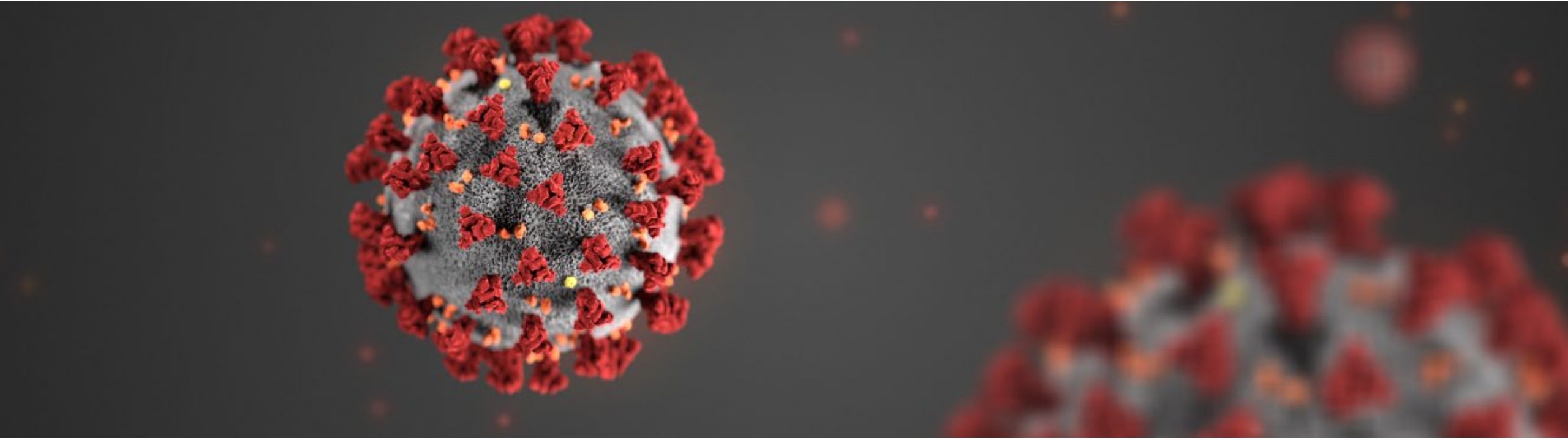

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Thank you!

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