ORIGINAL ARTICLE

Evaluation of mRNA-1273 Vaccine in Children 6 Months to 5 Years of Age

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ABSTRACT

BACKGROUND

The safety, reactogenicity, immunogenicity, and efficacy of the mRNA-1273 coronavirus disease 2019 (Covid-19) vaccine in young children are unknown.

METHODS

Part 1 of this ongoing phase 2–3 trial was open label for dose selection; part 2 was an observer-blinded, placebo-controlled evaluation of the selected dose. In part 2, we randomly assigned young children (6 months to 5 years of age) in a 3:1 ratio to receive two 25-μg injections of mRNA-1273 or placebo, administered 28 days apart. The primary objectives were to evaluate the safety and reactogenicity of the vaccine and to determine whether the immune response in these children was noninferior to that in young adults (18 to 25 years of age) in a related phase 3 trial. Secondary objectives were to determine the incidences of Covid-19 and severe acute respiratory syndrome coronavirus 2 infection after administration of mRNA-1273 or placebo.

RESULTS

On the basis of safety and immunogenicity results in part 1 of the trial, the 25-μg dose was evaluated in part 2. In part 2, 3040 children 2 to 5 years of age and 1762 children 6 to 23 months of age were randomly assigned to receive two 25-μg injections of mRNA-1273; 1008 children 2 to 5 years of age and 593 children 6 to 23 months of age were randomly assigned to receive placebo. The median duration of follow-up after the second injection was 71 days in the 2-to-5-year-old cohort and 68 days in the 6-to-23-month-old cohort. Adverse events were mainly low-grade and transient, and no new safety concerns were identified. At day 57, neutralizing antibody geometric mean concentrations were 1410 (95% confidence interval [CI], 1272 to 1563) among 2-to-5-year-olds and 1781 (95% CI, 1616 to 1962) among 6-to-23-month-olds, as compared with 1391 (95% CI, 1263 to 1531) among young adults, who had received 100-μg injections of mRNA-1273, findings that met the noninferiority criteria for immune responses for both age cohorts. The estimated vaccine efficacy against Covid-19 was 36.8% (95% CI, 12.5 to 54.0) among 2-to-5-year-olds and 50.6% (95% CI, 21.4 to 68.6) among 6-to-23-month-olds, at a time when B.1.1.529 (omicron) was the predominant circulating variant.

CONCLUSIONS

Two 25-μg doses of the mRNA-1273 vaccine were found to be safe in children 6 months to 5 years of age and elicited immune responses that were noninferior to those in young adults. (Funded by the Biomedical Advanced Research and Development Authority and National Institute of Allergy and Infectious Diseases; KidCOVE ClinicalTrials.gov number, NCT04796896.)

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This article was published on October 19, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2209367

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children accounted for more than 13.6 million of the documented infections in the United States as of July 2022.[1,2] Infected children may be asymptomatic or have mild symptoms but can still transmit SARS-CoV-2.[3-6] Despite social interventions to reduce coronavirus disease 2019 (Covid-19) transmission, Covid-19–related hospitalizations and deaths in children younger than 5 years of age (from October 2020 through September 2021) in the United States generally reached or surpassed the annual influenza-related rates observed in the period before the pandemic.[7-10]

Covid-19 messenger RNA vaccines, including mRNA-1273 (Moderna), are safe and efficacious in preventing illness from SARS-CoV-2 infection in adults,[11,12] adolescents, and older children (6 to 11 years of age).[13,14] The mRNA-1273 vaccine is approved in the United States for use in adults and received emergency use authorization from the Food and Drug Administration in June 2022 for persons 6 months to 17 years of age.[13,14] Although additional surges of SARS-CoV-2 infections due to emerging variants are anticipated[15,16] and efficacy among adults and children is lower against the B.1.1.529 (omicron) variant than against other variants, two mRNA-1273 injections were shown to continue to protect against hospitalization and death.[17,18]

Having a safe and effective vaccine available for infants, toddlers, and young children is critically important. Here, we report the results in children 6 months to 5 years of age in the ongoing phase 2–3 KidCOVE trial, which evaluated the safety, reactogenicity, immunogenicity, and efficacy of the mRNA-1273 vaccine.

Methods

Trial Design and Participants

The trial participants in three age cohorts (6 to 11 years, 2 to 5 years, and 6 to 23 months) were enrolled at 79 sites in the United States and 8 sites in Canada (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[14] The trial was conducted in two parts, with an open-label dose-escalation phase in part 1 and an observer-blinded, randomized, placebo-controlled expansion phase in part 2. Interim results in the cohort of 6-to-11-year-old children have been reported previously.[14] Here, we report the results of the interim analysis in the cohorts of children 2 to 5 years of age and 6 to 23 months of age through February 21, 2022.

Eligible children were healthy, but children with stable chronic conditions (e.g., asthma, diabetes mellitus) were also included. Additional inclusion and exclusion criteria and information on the trial oversight, conduct, and design are provided in the Supplementary Methods section in the Supplementary Appendix and in the protocol, available at NEJM.org.

Trial Procedures

In both parts of the trial, the vaccination regimen involved two doses of the mRNA-1273 vaccine or saline placebo administered by intramuscular injection 28 days apart. In part 1, the 25-μg and 50-μg dose levels were evaluated in children 2 to 5 years of age, and the 25-μg dose level was evaluated in children 6 to 23 months of age. After a review of safety and immunogenicity, a 25-μg dose was selected for evaluation in children in both age cohorts in part 2, and the data and safety monitoring board concurred (see the Supplementary Appendix).

In part 2 of the trial, children who were 6 months to 5 years of age were randomly assigned in a 3:1 ratio to receive two injections of mRNA-1273 (25 μg each) or placebo, administered 28 days apart. The primary objectives were to determine the safety and reactogenicity of mRNA-1273 in children 2 to 5 years of age and children 6 to 23 months of age and to infer efficacy on the basis of the noninferiority of the serum antibody geometric mean concentrations and serologic responses among these children as compared with those among young adults (18 to 25 years of age) who received two injections of mRNA-1273 (100 μg) in the phase 3 Coronavirus Efficacy (COVE) trial, which previously showed efficacy of the vaccine.[11,12] Secondary objectives were to determine the incidences of Covid-19 and SARS-CoV-2 infection, either asymptomatic or regardless of symptoms, after administration of mRNA-1273 or placebo.

Safety Assessments

In parts 1 and 2, solicited local and systemic adverse reactions that occurred within 7 days

after each injection were recorded daily. The same solicited local adverse reactions (pain, erythema, swelling, and axillary swelling or tenderness) were assessed in the two age cohorts. Among children 37 months to 5 years of age, the systemic adverse reactions assessed were fever, headache, fatigue, myalgia, arthralgia, chills, and nausea or vomiting. Among children 24 to 36 months of age and 6 to 23 months of age, fever, irritability or crying, sleepiness, and loss of appetite were assessed.

Safety assessments included unsolicited adverse events that occurred within 28 days after each injection and adverse events leading to nonreceipt of the second injection, discontinuation from the trial, or both; serious adverse events; medically attended adverse events; adverse events of special interest (including acute myocarditis or pericarditis and multisystem inflammatory syndrome in children [MIS-C]); and SARS-CoV-2 infection assessed from day 1 through trial completion. Surveillance for symptoms of myocarditis or pericarditis was conducted during safety telephone calls, with referral for medical assessment by a provider if needed. SARS-CoV-2 infection was assessed by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay performed at specific time points, and SARS-CoV-2 infection and Covid-19 cases were surveilled with the use of safety telephone calls and questionnaire prompts in electronic diaries completed by the parents or guardians of the participants.

IMMUNOGENICITY ASSESSMENTS

Immunogenicity assays are described in the Supplementary Methods section in the Supplementary Appendix. Neutralizing antibody geometric mean concentrations were assessed with the use of a validated pseudovirus neutralization assay in part 2 of the trial.[19,20] A serologic response was defined as an increase in the neutralizing antibody concentration from below the lower limit of quantification (LLOQ) to a concentration that was at least 4 times the LLOQ, or at least 4 times as high as the baseline value if the baseline concentration was equal to or above the LLOQ. Antispike binding antibody levels against SARS-CoV-2 variants were evaluated with the use of a Meso Scale Discovery assay.[21]

INCIDENCES OF COVID-19 AND SARS-COV-2 INFECTION

The incidence of Covid-19 was defined in accordance with the guidelines of the Centers for Disease Control and Prevention (CDC). This definition included at least one systemic or respiratory symptom and a positive RT-PCR assay for SARS-CoV-2. In a separate analysis, we used the following definition from the COVE trial: at least two systemic symptoms or at least one respiratory symptom and a positive RT-PCR assay.[11,12] As a sensitivity analysis, the incidence of Covid-19 was evaluated on the basis of any positive Covid-19 test, including home tests. SARS-CoV-2 infection (regardless of symptoms) was assessed by means of RT-PCR or Elecsys (Roche) nucleocapsid protein serologic assay (Supplementary Appendix).

STATISTICAL ANALYSIS

Details of the statistical methods are provided in the Supplementary Methods section in the Supplementary Appendix and in the statistical analysis plan (available with the protocol). The analysis populations are described in Table S1.

Safety was assessed among the participants who received at least one injection (safety population), and solicited adverse reactions were assessed among the participants in the safety population who had any data collected on solicited adverse reactions (solicited safety population); adverse reactions were assessed according to trial group and age cohort. The numbers and percentages of participants are summarized for those with solicited local and systemic adverse reactions that occurred within 7 days after each injection according to severity grade, as well as for those with unsolicited adverse events, serious adverse events, medically attended adverse events, severe adverse events, or adverse events leading to nonreceipt of the second injection or discontinuation from the trial or both. Descriptive summary statistics are reported for all other safety measures. Safety was also assessed according to baseline SARS-CoV-2 infection status at day 1 by means of virologic RT-PCR testing or serologic testing (Elecsys nucleocapsid protein serologic assay) or both.

To determine whether efficacy of the mRNA-1273 vaccine can be inferred (a primary objective), we compared the immunogenicity respons-

es in each of two cohorts defined according to age group (children 2 to 5 years of age and children 6 to 23 months of age) in the per-protocol immunogenicity population with those among young adults (18 to 25 years of age) in the COVE trial.[11,12] The per-protocol immunogenicity population included participants who had received the planned injections, were SARS-CoV-2–negative at baseline (day 1) according to both RT-PCR and serologic testing, had data available from antibody testing for day 1 and day 57, and had no major protocol deviations. Noninferiority, determined on the basis of neutralizing antibody geometric mean concentrations among children as compared with those among young adults at day 57, was indicated if the lower boundary of the 95% confidence interval for the geometric mean ratio was at least 0.67 and if the difference in the percentage of participants with a serologic response was −10 percentage points or more. We provide the geometric mean concentrations and geometric mean ratios (with 95% confidence intervals calculated according to the analysis of covariance model), the number and percentage of participants with a serologic response (with 95% confidence intervals calculated with the Clopper–Pearson method), and the between-group difference in serologic response (with 95% confidence intervals calculated with the Miettinen–Nurminen method) at day 57. The observed binding antibody levels against SARS-CoV-2 variants are also provided.

In part 2 of the trial, for the secondary efficacy objectives of determining the incidences of Covid-19 and SARS-CoV-2 infection, we evaluated all randomly assigned participants who did not have serologic or virologic evidence of SARS-CoV-2 infection at baseline and who received at least one injection of the correct dose (the modified intention-to-treat population) and participants who received both injections according to the schedule without a major protocol deviation (the per-protocol efficacy population). Incidence was calculated as the number of cases divided by the total number of person-years (defined as the total years from the first day of the analysis to the last day of trial participation, to censoring time, or to the efficacy data-cutoff date, whichever was earliest), and 95% confidence intervals were calculated with the exact method (Poisson distribution). Vaccine efficacy was estimated (1 minus the ratio of the incidence of Covid-19 or SARS-CoV-2 infection in the mRNA-1273 group as compared with the placebo group) and the 95% confidence intervals of the ratio were calculated with the exact method, conditional on the total number of cases and with adjustment for person-years. The interim results for the cohorts of children 6 to 23 months of age and children 2 to 5 years of age are provided through the data-cutoff date of February 21, 2022.

RESULTS

TRIAL POPULATION

From April 2021 through June 2021, a total of 224 children 2 to 5 years of age and 150 children 6 to 23 months of age were enrolled in part 1 of the trial (Fig. S2). Among children 2 to 5 years of age, 75 were assigned to receive the 25-μg dose of mRNA-1273, and 149 were assigned to receive the 50-μg dose; all children 6 to 23 months of age (150 participants) were assigned to receive the 25-μg dose. All participants received both injections.

In part 2 of the trial, in the cohort of children 2 to 5 years of age, 3031 of 3040 participants (99.7%) in the mRNA-1273 group and 1007 of 1008 participants (99.9%) in the placebo group received the first injection; 2960 participants (97.4%) and 970 participants (96.2%), respectively, received the second injection (Fig. 1). In the cohort of children 6 to 23 months of age, 1760 of 1762 participants (99.9%) assigned to the mRNA-1273 group and 590 of 593 participants (99.5%) assigned to the placebo group received the first injection; 1600 participants (90.8%) in the mRNA-1273 group and 529 (89.2%) in the placebo group received the second injection.

The baseline demographic and clinical characteristics of the children in the trial groups were generally balanced and were similar in part 1 (Tables S2 and S3) and part 2 (Table 1 and Table S4) of the trial. Overall, in part 2, the median age of the children in the 2-to-5-year-old cohort was 3.0 years (interquartile range, 2.0 to 4.0). A total of 76.5% of the participants in this cohort were White, 4.5% were Black, 6.0% were Asian, and 14.2% were Hispanic or Latinx. In the 6-to-23-month-old cohort, the median age was 16.0 months (interquartile range, 13.0 to 20.0). A total of 78.9% of the participants in this

cohort were White, 3.1% were Black, 4.9% were Asian, and 13.2% were Hispanic or Latinx. The underrepresentation of Black participants is acknowledged. The median duration of follow-up in the 2-to-5-year-old cohort was 103 days (interquartile range, 83 to 113) after the first injection and 71 days (interquartile range, 49 to 83) after the second injection, and in the 6-to-23-month-old cohort, the corresponding values were 98 days (interquartile range, 76 to 110) and 68 days (interquartile range, 42 to 78).

SAFETY

Safety data from part 1 of the trial are available in the Part 1 Results section in the Supplementary Appendix and in Tables S5 through S13. In part 2, the incidence of solicited local adverse reactions was higher with mRNA-1273 than with placebo in both age cohorts, and in the mRNA-1273 group, the incidence was higher after the second injection than after the first injection (Fig. 2 and Tables S14 through S17). Most local adverse reactions were of grade 1 or 2 and lasted for 1 to 3 days. Grade 3 events were rare overall but were more frequent after the second injection; the most common grade 3 events were erythema, swelling, and pain among children 2 to 5 years of age and erythema and swelling among children 6 to 23 months of age.

Systemic adverse reactions after either injection were more common in the mRNA-1273 group than in the placebo group (Fig. 2 and Tables S18 and S19). The most common systemic adverse reaction among children 37 months to 5 years of age was fatigue; among children 6 to 36 months of age, the most common reactions were irritability or crying, sleepiness, and loss of appetite. The majority of systemic adverse reactions in both groups were of grade 1 or 2, and grade 3 adverse reactions were infrequent. The most common grade 3 systemic adverse reactions were fatigue and fever (temperature, ≥39.0°C) among children 37 months to 5 years of age and irritability or crying and fever of at least 39.6°C among children 6 to 36 months of age in the mRNA-1273 and placebo groups. Most systemic adverse reactions in the mRNA-1273 group occurred within 2 days after either injection and persisted for a median of 2 to 3 days. Overall, the incidences of solicited adverse reactions were similar regardless of baseline SARS-CoV-2 infection status, except for somewhat higher incidences of fever after either injection among participants who were SARS-CoV-2–positive at baseline (Figs. S3 and S4).

In the mRNA-1273 group, fever (temperature, ≥38.0°C) occurred more frequently after the second injection than after the first injection, and the median duration was 1 to 2 days after either injection in both age cohorts. The majority of fevers ranged in temperature from 38.0 to 38.9°C (Figs. S5 and S6). In the cohort of children 2 to 5 years of age, a confirmed grade 4 fever (temperature, >40°C) was noted in three participants in the mRNA-1273 group after the first injection, in five participants in the mRNA-1273 group after the second injection, and in two participants in the placebo group after the first injection. In the cohort of children 6 to 23 months of age, a confirmed grade 4 fever occurred in one participant in the mRNA-1273 group after the first injection, in three participants in the mRNA-1273 group after the second injection, and in one participant in the placebo group after the first injection. Among the participants with confirmed grade 4 fever, five in the mRNA-1273 group and one in the placebo group had concurrent adverse events suggestive of viral infections (Table S20).

Incidences of unsolicited adverse events that occurred within 28 days after any injection were similar in the mRNA-1273 group and the placebo group in both age cohorts (Tables S21 through S24). The incidence of adverse events considered by the investigator to be related to mRNA-1273 or placebo was higher in the mRNA-1273 group (9% among 2-to-5-year-olds and 17% among 6-to-23-month-olds) than in the placebo group (8% among 2-to-5-year-olds and 12% among 6-to-23-month-olds); the events were mainly attributed to reactogenicity events.

The incidence of serious adverse events was low overall and was similar in the mRNA-1273 group and the placebo group in the cohort of children 2 to 5 years of age. In the cohort of children 6 to 23 months of age, eight serious adverse events occurred in the mRNA-1273 group, and none occurred in the placebo group. No serious adverse events related to mRNA-1273 or placebo were reported in 2-to-5-year-olds within 28 days after either injection. One participant in the mRNA-1273 group in the 6-to-23-month-old cohort had fever and febrile seizure that was categorized as a serious adverse event

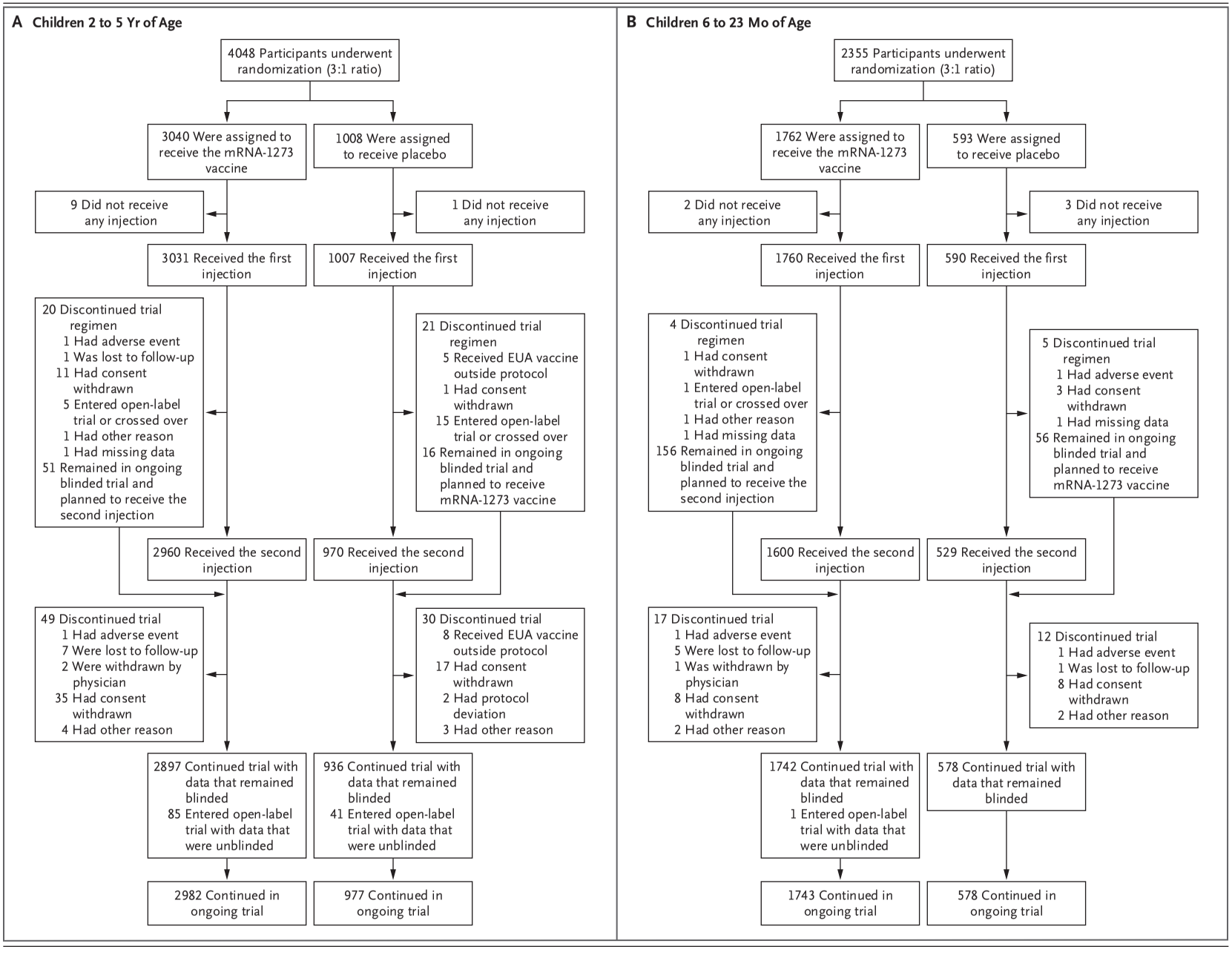

A Children 2 to 5 Yr of Age
4048 Participants underwent randomization (3:1 ratio)
3040 Were assigned to receive the mRNA-1273 vaccine
1008 Were assigned to receive placebo
9 Did not receive any injection
1 Did not receive any injection
3031 Received the first injection
1007 Received the first injection
20 Discontinued trial regimen
1 Had adverse event
1 Was lost to follow-up
11 Had consent withdrawn
5 Entered open-label trial or crossed over
1 Had other reason
1 Had missing data
51 Remained in ongoing blinded trial and planned to receive the second injection
21 Discontinued trial regimen
5 Received EUA vaccine outside protocol
1 Had consent withdrawn
15 Entered open-label trial or crossed over
16 Remained in ongoing blinded trial and planned to receive mRNA-1273 vaccine
2960 Received the second injection
970 Received the second injection
49 Discontinued trial
1 Had adverse event
7 Were lost to follow-up
2 Were withdrawn by physician
35 Had consent withdrawn
4 Had other reason
30 Discontinued trial
8 Received EUA vaccine outside protocol
17 Had consent withdrawn
2 Had protocol deviation
3 Had other reason
2897 Continued trial with data that remained blinded
85 Entered open-label trial with data that were unblinded
936 Continued trial with data that remained blinded
41 Entered open-label trial with data that were unblinded
2982 Continued in ongoing trial
977 Continued in ongoing trial
B Children 6 to 23 Mo of Age
2355 Participants underwent randomization (3:1 ratio)
1762 Were assigned to receive the mRNA-1273 vaccine
593 Were assigned to receive placebo
2 Did not receive any injection
3 Did not receive any injection
1760 Received the first injection
590 Received the first injection
4 Discontinued trial regimen
1 Had consent withdrawn
1 Entered open-label trial or crossed over
1 Had other reason
1 Had missing data
156 Remained in ongoing blinded trial and planned to receive the second injection
5 Discontinued trial regimen
1 Had adverse event
3 Had consent withdrawn
1 Had missing data
56 Remained in ongoing blinded trial and planned to receive mRNA-1273 vaccine
1600 Received the second injection
529 Received the second injection
17 Discontinued trial
1 Had adverse event
5 Were lost to follow-up
1 Was withdrawn by physician
8 Had consent withdrawn
2 Had other reason
12 Discontinued trial
1 Had adverse event
1 Was lost to follow-up
8 Had consent withdrawn
2 Had other reason
1742 Continued trial with data that remained blinded
1 Entered open-label trial with data that were unblinded
578 Continued trial with data that remained blinded
1743 Continued in ongoing trial
578 Continued in ongoing trial

Figure 1 (facing page). Randomization of Participants 2 to 5 Years of Age and Participants 6 to 23 Months of Age in Part 2 of the Trial.

Discontinuation of the trial regimen indicates that a participant who received the first injection did not receive the second injection. In the cohort of 2-to-5-year-olds (Panel A), 51 participants in the mRNA-1273 group and 16 in the placebo group had planned to receive the second injection, but the injection was delayed because of adverse events, illness, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (the majority of these participants had coronavirus disease 2019 [Covid-19] or SARS-CoV-2 infection); these participants continued in the ongoing trial, and their data remained blinded. Among the participants who discontinued the trial, 15 in the mRNA-1273 group and 6 in the placebo group received one injection, and 34 and 24 participants, respectively, received the second injection. Among the 2982 participants who continued in the ongoing trial, 2897 had data that remained blinded, and 85 had data that were unblinded (5 received the second injection after unblinding, 79 received a second injection before unblinding, and 1 had not yet received the planned second injection) and were entered in the open-label trial. In the cohort of 6-to-23-month-olds (Panel B), among the participants who discontinued the trial, 3 in the mRNA-1273 group and 5 in the placebo group received the first injection, and 14 and 7 participants, respectively, received the second injection. A total of 156 participants in the mRNA-1273 group and 56 in the placebo group had planned to receive the second injection, and their data remained blinded; most of these participants had not reached day 29 after the first injection by the data-cutoff date (February 21, 2022). EUA denotes emergency use authorization.

2 days after the first injection, and a maculopapular rash developed in the participant 2 days later, suggesting a concomitant viral infection (Table S25); the participant subsequently received the second injection without recurrence.

Adverse events of special interest that were considered to be related to the trial regimen occurred in two participants in the mRNA-1273 group in the 2-to-5-year-old cohort, in two participants in the mRNA-1273 group in the 6-to-23-month-old cohort, and in one participant in the placebo group in the 2-to-5-year-old cohort (Table S26). During the entire trial period, one participant in the mRNA-1273 group and no participants in the placebo group had nonreceipt of the second injection because of adverse events that were considered to be related to the trial regimen. No deaths or cases of myocarditis or pericarditis or MIS-C occurred before the data-cutoff date.

IMMUNOGENICITY

In the per-protocol immunogenicity population in part 2, the neutralizing antibody geometric mean concentrations at day 57 were 1410 (95% confidence interval [CI], 1272 to 1563) among 2-to-5-year-olds (assessed in 264 participants) and 1781 (95% CI, 1616 to 1962) among 6-to-23-month-olds (assessed in 230 participants), as compared with 1391 (95% CI, 1263 to 1531) among the young adults in the COVE trial (Table 2, Table S27, and Fig. S7). In comparisons of the two age cohorts in the current trial with the young adults in the COVE trial, the geometric mean ratios (1.0 [95% CI, 0.9 to 1.2] among 2-to-5-year-olds and 1.3 [95% CI, 1.1 to 1.5] among 6-to-23-month-olds) as well as the differences in the percentages of participants with a serologic response (–0.4 percentage points [95% CI, –2.7 to 1.5] among 2-to-5-year-olds and 0.7 percentage points [95% CI, –1.0 to 2.5] among 6-to-23-month-olds) met the criteria for noninferiority with respect to the primary immunogenicity objective.

In both age cohorts, the neutralizing antibody geometric mean concentrations at day 57 were higher among participants who were SARS-CoV-2–positive at baseline than among those who were negative (Fig. S8). Regardless of age, the two-injection primary series of mRNA-1273 elicited robust binding antibody responses to the ancestral strain and the B.1.351 (beta), B.1.617.2 (delta), and omicron variants (Fig. S9).

EFFICACY

In the 2-to-5-year-old cohort, there were 119 cases of Covid-19 among 2594 participants (4.6%) in the mRNA-1273 group and 61 cases among 858 participants (7.1%) in the placebo group that met the CDC definition; the estimated vaccine efficacy at 14 or more days after the second injection in the per-protocol population was 36.8% (95% CI, 12.5 to 54.0). With respect to cases that met the definition of Covid-19 from the COVE trial, there were 71 cases among 2594 participants (2.7%) in the mRNA-1273 group and 43 cases among 858 participants (5.0%) in the placebo group; the estimated vaccine efficacy was 46.4% (95% CI, 19.8 to 63.8) (Fig. 3, Table S28, and Fig. S10). In the 6-to-23-month-old cohort, there were 51 cases among 1511 participants (3.4%) in the mRNA-1273 group and 34 cases among 513 participants

Table 1. Demographic and Clinical Characteristics of the Participants in the Safety Population at Baseline (Part 2 of the Trial), Stratified According to Age Cohort and Trial-Group Assignment.*

Characteristic	Children 2–5 Yr of Age		Children 6–23 Mo of Age	
	mRNA-1273, 25 μg (N=3031)	Placebo (N=1007)	mRNA-1273, 25 μg (N=1761)	Placebo (N=589)
Age — mo or yr				
Mean	3.0±0.9	3.0±0.9	15.8±5.0	15.9±4.5
Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	16.0 (12.0–20.0)	16.0 (13.0–20.0)
Age group — no. (%)				
≥6 to <12 mo	—	—	375 (21.3)	124 (21.1)
≥12 to <24 mo	—	—	1373 (78.0)	462 (78.4)
≥24 mo†			13 (0.7)	3 (0.5)
<2 yr†	24 (0.8)	12 (1.2)		
≥2 to <4 yr	2057 (67.9)	655 (65.0)	—	—
≥4 to <6 yr	950 (31.3)	340 (33.8)	—	—
≥24 to <37 mo	999 (33.0)	345 (34.3)	—	—
≥37 mo to <6 yr	2032 (67.0)	662 (65.7)	—	—
Sex — no. (%)				
Male	1543 (50.9)	510 (50.6)	910 (51.7)	290 (49.2)
Female	1488 (49.1)	497 (49.4)	851 (48.3)	299 (50.8)
Race or ethnic group — no. (%)‡				
White	2297 (75.8)	792 (78.6)	1390 (78.9)	466 (79.1)
Black	142 (4.7)	38 (3.8)	57 (3.2)	16 (2.7)
Asian	191 (6.3)	51 (5.1)	79 (4.5)	35 (5.9)
American Indian or Alaska Native	12 (0.4)	3 (0.3)	4 (0.2)	0
Native Hawaiian or other Pacific Islander	7 (0.2)	4 (0.4)	0	0
Multiracial	322 (10.6)	99 (9.8)	186 (10.6)	64 (10.9)
Other and not reported	56 (1.8)	20 (2.0)	40 (2.3)	7 (1.2)
Unknown	4 (0.1)	0	5 (0.3)	1 (0.2)
Hispanic or Latinx — no. (%)‡				
Yes	433 (14.3)	142 (14.1)	227 (12.9)	84 (14.3)
No	2579 (85.1)	856 (85.0)	1517 (86.1)	498 (84.6)
Not reported	14 (0.5)	8 (0.8)	15 (0.9)	6 (1.0)
Unknown	5 (0.2)	1 (0.1)	2 (0.1)	1 (0.2)
Race and ethnic group — no. (%)‡				
White non-Hispanic	1975 (65.2)	678 (67.3)	1221 (69.3)	393 (66.7)
Communities of color	1054 (34.8)	327 (32.5)	538 (30.6)	194 (32.9)
Missing data	2 (<0.1)	2 (0.2)	2 (0.1)	2 (0.3)
Weight — kg				
Mean	16.1±3.2	16.0±3.0	10.9±2.1	10.9±2.1
Median (IQR)	15.7 (14.1–17.7)	15.6 (14.1–17.6)	10.8 (9.6–12.1)	10.8 (9.6–12.1)
SARS-CoV-2 status — no. (%)§				
Negative	2695 (88.9)	898 (89.2)	1575 (89.4)	530 (90.0)

Table 1. (Continued.)

Characteristic	Children 2–5 Yr of Age		Children 6–23 Mo of Age	
	mRNA-1273, 25 μg (N=3031)	Placebo (N=1007)	mRNA-1273, 25 μg (N=1761)	Placebo (N=589)
Positive	266 (8.8)	82 (8.1)	106 (6.0)	38 (6.5)
Missing data	70 (2.3)	27 (2.7)	80 (4.5)	21 (3.6)

* Plus–minus values are means ±SD. The data-cutoff date was February 21, 2022. Shown are data for the participants in the safety population. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Some participants 6 to 23 months of age and some participants at least 24 months of age were included in both age cohorts, most likely because of coincident enrollment of both age cohorts, entry errors at the time of randomization, and other limitations of the interactive response technology system.

‡ Race and ethnic group were reported by the parents or guardians of the participants. Participants could be included in more than one category. Communities of color was a composite variable that included all races and ethnic groups (other than white non-Hispanic) among the participants with available data.

§ Baseline severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status was positive if there was immunologic or virologic evidence of previous coronavirus disease 2019, as defined by a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test or a positive Elecsys (Roche) nucleocapsid protein serologic assay at day 1. Negative is defined as a negative RT-PCR test and negative Elecsys assay at day 1.

(6.6%) in the placebo group that met the CDC definition; the vaccine efficacy was 50.6% (95% CI, 21.4 to 68.6). With respect to cases that met the definition of Covid-19 from the COVE trial, there were 37 cases among 1511 participants (2.4%) in the mRNA-1273 group and 18 cases among 513 participants (3.5%) in the placebo group; the vaccine efficacy was 31.5% (95% CI, –27.7 to 62.0). Vaccine efficacy was also shown against any SARS-CoV-2 infection regardless of symptoms and against asymptomatic infection in both age cohorts. The efficacy findings in the modified intention-to-treat population were similar to those in the per-protocol population (Fig. 3 and Table S29).

The results of the sensitivity analysis in which the incidence of Covid-19 was evaluated on the basis of any positive Covid-19 test, including home tests, were similar to those in which the incidences of Covid-19 were evaluated on the basis of confirmed positive RT-PCR assays (Table S30). The estimated efficacy against Covid-19 as defined by the CDC was 28.5% (95% CI, 5.9 to 45.3) among children 2 to 5 years of age and 53.5% (95% CI, 32.4 to 67.8) among children 6 to 23 months of age, and the estimated efficacies against Covid-19 as defined in the COVE trial were 37.5% (95% CI, 11.8 to 55.3) and 43.7% (95% CI, 8.5 to 64.8), respectively; the lower boundaries of the 95% confidence intervals were greater than 0 in each of these estimations. Among the Covid-19 cases in the per-protocol population that met the CDC definition and had available sequence information (December 2021 through February 2022), 78 of 79 cases in the 2-to-5-year-old cohort and 44 of 44 cases in the 6-to-23-month-old cohort were of omicron BA.1 and BA.1.1 lineages.

DISCUSSION

In children 6 months to 5 years of age, a two-injection primary series of mRNA-1273 at a dose of 25 μg had an acceptable safety profile and elicited immune responses that were consistent with those observed in clinical trials that involved higher doses of this vaccine in older children, adolescents, and adults.[11-14] In addition, vaccine efficacy against Covid-19 was shown, albeit at a lower values than those observed in previous mRNA-1273 trials[11,12,14] involving older age cohorts that were conducted before the emergence of omicron — a finding consistent with reduced vaccine effectiveness against omicron observed among adults and adolescents.[17,18]

The 25-μg mRNA-1273 dose, established in part 1 of the trial, elicited mild-to-moderate, transient reactogenicity in both age cohorts in part 2. No trial pause rules were met, and no safety concerns were identified. Apart from fevers, the reactogenicity in these young children was generally lower than that observed for mRNA-1273 in adults, adolescents, and older children (6 to 11 years of age).[11-14] The incidence

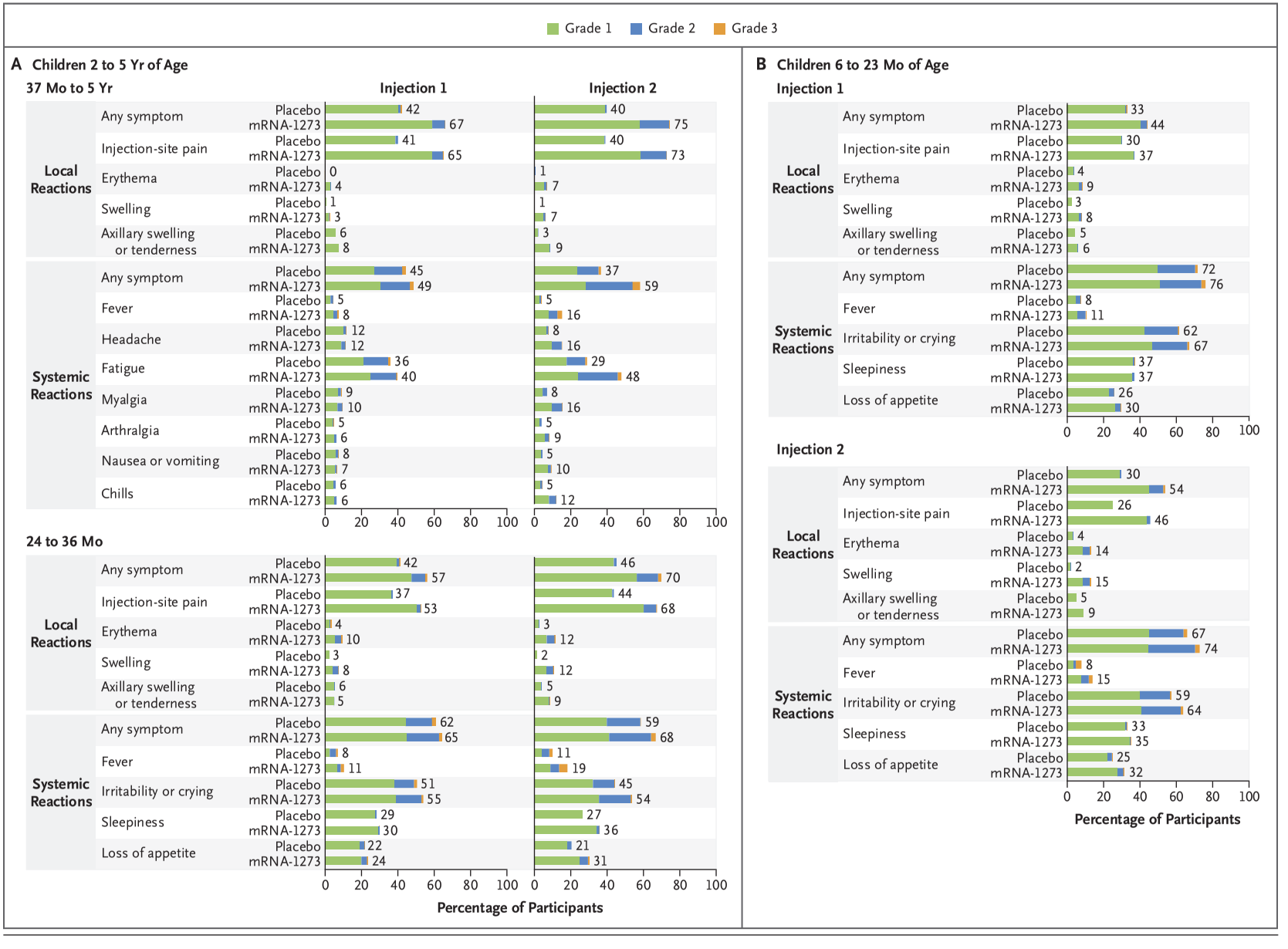

Grade 1
Grade 2
Grade 3
A Children 2 to 5 Yr of Age
37 Mo to 5 Yr
Injection 1
Injection 2
Local Reactions
Any symptom
Placebo 42
mRNA-1273 67
Placebo 40
mRNA-1273 75
Injection-site pain
Placebo 41
mRNA-1273 65
Placebo 40
mRNA-1273 73
Erythema
Placebo 0
mRNA-1273 4
Placebo 1
mRNA-1273 7
Swelling
Placebo 1
mRNA-1273 3
Placebo 1
mRNA-1273 7
Axillary swelling or tenderness
Placebo 6
mRNA-1273 8
Placebo 3
mRNA-1273 9
Systemic Reactions
Any symptom
Placebo 45
mRNA-1273 49
Placebo 37
mRNA-1273 59
Fever
Placebo 5
mRNA-1273 8
Placebo 5
mRNA-1273 16
Headache
Placebo 12
mRNA-1273 12
Placebo 8
mRNA-1273 16
Fatigue
Placebo 36
mRNA-1273 40
Placebo 29
mRNA-1273 48
Myalgia
Placebo 9
mRNA-1273 10
Placebo 8
mRNA-1273 16
Arthralgia
Placebo 5
mRNA-1273 6
Placebo 5
mRNA-1273 9
Nausea or vomiting
Placebo 8
mRNA-1273 7
Placebo 5
mRNA-1273 10
Chills
Placebo 6
mRNA-1273 6
Placebo 5
mRNA-1273 12
0 20 40 60 80 100
24 to 36 Mo
Local Reactions
Any symptom
Placebo 42
mRNA-1273 57
Placebo 46
mRNA-1273 70
Injection-site pain
Placebo 37
mRNA-1273 53
Placebo 44
mRNA-1273 68
Erythema
Placebo 4
mRNA-1273 10
Placebo 3
mRNA-1273 12
Swelling
Placebo 3
mRNA-1273 8
Placebo 2
mRNA-1273 12
Axillary swelling or tenderness
Placebo 6
mRNA-1273 5
Placebo 5
mRNA-1273 9
Systemic Reactions
Any symptom
Placebo 62
mRNA-1273 65
Placebo 59
mRNA-1273 68
Fever
Placebo 8
mRNA-1273 11
Placebo 11
mRNA-1273 19
Irritability or crying
Placebo 51
mRNA-1273 55
Placebo 45
mRNA-1273 54
Sleepiness
Placebo 29
mRNA-1273 30
Placebo 27
mRNA-1273 36
Loss of appetite
Placebo 22
mRNA-1273 24
Placebo 21
mRNA-1273 31
0 20 40 60 80 100
Percentage of Participants
B Children 6 to 23 Mo of Age
Injection 1
Local Reactions
Any symptom
Placebo 33
mRNA-1273 44
Injection-site pain
Placebo 30
mRNA-1273 37
Erythema
Placebo 4
mRNA-1273 9
Swelling
Placebo 3
mRNA-1273 8
Axillary swelling or tenderness
Placebo 5
mRNA-1273 6
Systemic Reactions
Any symptom
Placebo 72
mRNA-1273 76
Fever
Placebo 8
mRNA-1273 11
Irritability or crying
Placebo 62
mRNA-1273 67
Sleepiness
Placebo 37
mRNA-1273 37
Loss of appetite
Placebo 26
mRNA-1273 30
0 20 40 60 80 100
Injection 2
Local Reactions
Any symptom
Placebo 30
mRNA-1273 54
Injection-site pain
Placebo 26
mRNA-1273 46
Erythema
Placebo 4
mRNA-1273 14
Swelling
Placebo 2
mRNA-1273 15
Axillary swelling or tenderness
Placebo 5
mRNA-1273 9
Systemic Reactions
Any symptom
Placebo 67
mRNA-1273 74
Fever
Placebo 8
mRNA-1273 15
Irritability or crying
Placebo 59
mRNA-1273 64
Sleepiness
Placebo 33
mRNA-1273 35
Loss of appetite
Placebo 25
mRNA-1273 32
0 20 40 60 80 100
Percentage of Participants

Figure 2 (facing page). Solicited Local and Systemic Adverse Reactions in the Cohorts of Children 2 to 5 Years and 6 to 23 Months of Age in Part 2 of the Trial.

Shown are the percentages of participants in the two age cohorts (2-to-5-year-olds [Panel A] and 6-to-23-month-olds [Panel B]) in the part 2 solicited safety population (all participants who received at least one injection and had any data collected on solicited adverse reactions) who had a solicited local or systemic adverse reaction within 7 days after the first or second injection. Local adverse reactions of injection-site pain, erythema, swelling (hardness), and axillary or groin swelling or tenderness were assessed in both age cohorts. Among participants 37 months to 5 years of age, the solicited systemic adverse reactions were fever, headache, fatigue, myalgia, arthralgia, nausea or vomiting, and chills. Among participants 6 to 36 months of age, the solicited systemic adverse reactions were fever, irritability or crying, sleepiness, and loss of appetite. The data-cutoff date was February 21, 2022.

of fever after either mRNA-1273 injection in both age cohorts was similar (22 to 23%) to that previously reported (24%) among 6-to-11-year-olds who received 50-μg of mRNA-1273 in this trial[14] and to that after other routinely recommended vaccinations.[22,23] Few grade 4 fevers (temperature, >40.0°C) were reported in the mRNA-1273 and placebo groups. No myocarditis, pericarditis, or MIS-C and no deaths occurred through the analysis-cutoff date. No safety issues were identified in participants who had SARS-CoV-2 infection before or during the trial; however, longer-term safety monitoring will continue.

The efficacy of mRNA-1273 was inferred on the basis of having met prespecified criteria for immunobridging, the approach used for authorization and approval in Covid-19 vaccine studies

Table 2. Immunogenicity of the mRNA-1273 Vaccine in Part 2 of the Trial.*

Variable	Children 2–5 Yr of Age mRNA-1273, 25 μg (N=264)	Children 6–23 Mo of Age mRNA-1273, 25 μg (N=230)	Young Adults 18–25 Yr of Age mRNA-1273, 100 μg (N=295)
Baseline			
No. of participants with available data	264	230	294
GMC (95% CI)†	7.7 (7.2 to 8.2)	7.9 (7.4 to 8.5)	11.1 (10.6 to 11.7)
Day 57			
No. of participants with available data	264	230	291
GMC (95% CI)†	1410 (1272 to 1563)	1781 (1616 to 1962)	1391 (1263 to 1531)
GMR vs. young adults (95% CI)‡	1.0 (0.9 to 1.2)	1.3 (1.1 to 1.5)	—
Serologic response			
No. of participants/total no. (%)§	261/264 (98.9)	230/230 (100.0)	289/291 (99.3)
95% CI¶	96.7 to 99.8	98.4 to 100.0	97.5 to 99.9
Difference in serologic response vs. young adults — percentage points (95% CI)‖	–0.4 (–2.7 to 1.5)	0.7 (–1.0 to 2.5)	—

* The data-cutoff date was February 21, 2022. The neutralizing antibody geometric mean concentrations (GMCs) shown are the observed values. The data for young adults are from the mRNA-1273 group in the Coronavirus Efficacy (COVE) trial.[11] Antibody values were assessed by means of pseudovirus neutralizing antibody assay. Values that were below the lower limit of quantification (LLOQ) (10.0) are replaced by 0.5 times the LLOQ. Values greater than the upper limit of the ULOQ (281,600) are replaced by the ULOQ if the actual values were not available. GMR denotes geometric mean ratio.

† The 95% confidence interval was calculated on the basis of the t-distribution of the log-transformed values for the observed GMC and then back-transformed to the original scale for presentation.

‡ The log-transformed antibody levels were analyzed with the use of an analysis of covariance model (primary approach) with the group variable (children and young adults in the COVE trial) as a fixed effect. The resulting least-squares means, difference in least-squares means, and 95% confidence intervals were back-transformed to the original scale for presentation.

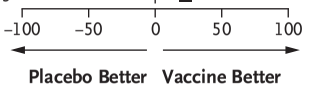
§ A serologic response in a participant was defined as an increase in GMCs from below the LLOQ to GMCs that were at least 4 times the LLOQ, or at least 4 times as high as the baseline value if the baseline concentrations were equal to or above the LLOQ. Percentages were based on the number of participants with nonmissing data at baseline and the corresponding time point (N1).

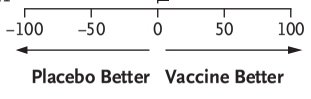
¶ The 95% confidence intervals were calculated with the use of the Clopper–Pearson method.

‖ The 95% confidence intervals were calculated with the use of the Miettinen–Nurminen (score) confidence limits.

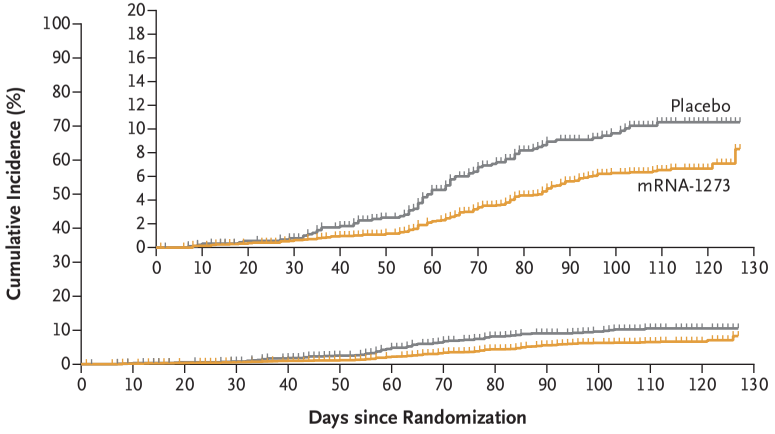
A Incidence of Secondary End-Point Events ≥14 Days after Second Injection, Per-Protocol Population

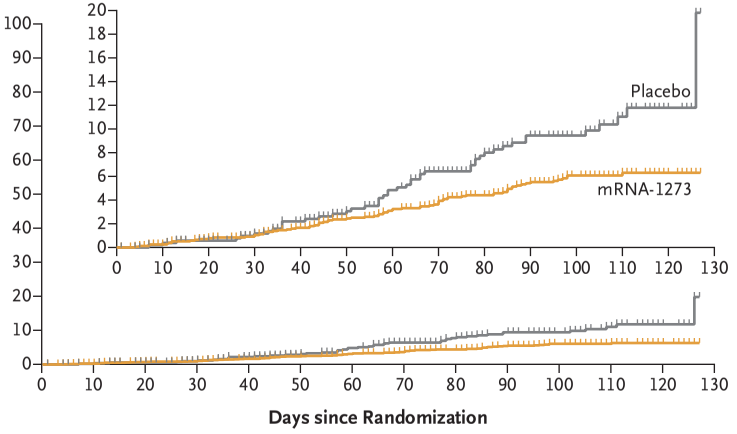
End Point	2–5 Yr of Age: mRNA-1273 (N=2594)	2–5 Yr of Age: Placebo (N=858)	2–5 Yr of Age: Vaccine Efficacy (95% CI)	6–23 Mo of Age: mRNA-1273 (N=1511)	6–23 Mo of Age: Placebo (N=513)	6–23 Mo of Age: Vaccine Efficacy (95% CI)
	no. of participants with event		%	*no. of participants with event*		%
Covid-19 (CDC definition)	119	61	36.8 (12.5 to 54.0)	51	34	50.6 (21.4 to 68.6)
Covid-19 (COVE trial definition)	71	43	46.4 (19.8 to 63.8)	37	18	31.5 (–27.7 to 62.0)
SARS-CoV-2 infection regardless of symptoms	198	93	31.5 (11.4 to 46.7)	81	45	40.5 (12.3 to 59.2)
Asymptomatic SARS-CoV-2 infection	79	33	22.9 (–19.5 to 49.3)	32	11	3.8 (–111.5 to 52.8)





B Covid-19 (CDC Definition), Modified Intention-to-Treat Population





No. at Risk

Placebo	898	890	882	876	847	804	775	711	634	589	435	289	85	0
mRNA-1273	2693	2681	2650	2633	2593	2472	2423	2242	2046	1875	1417	929	285	0

Placebo	530	519	508	492	468	441	425	391	348	306	213	125	40	0
mRNA-1273	1574	1538	1501	1463	1411	1348	1318	1250	1122	998	691	417	114	0

Figure 3 (facing page). Secondary Efficacy End Points.
Panel A shows the incidences of secondary end points in the cohorts of 2-to-5-year-olds and 6-to-23-month-olds in the per-protocol efficacy population, which included all participants who received both injections per schedule, had no virologic or serologic evidence of SARS-CoV-2 infection at baseline, and had no major protocol deviations. A case of Covid-19 was defined by the Centers for Disease Control and Prevention (CDC) as at least one systemic or respiratory symptom and a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was defined in the Coronavirus Efficacy (COVE) trial[11] as at least two systemic symptoms or at least one respiratory symptom and a positive RT-PCR assay. Vaccine efficacy for secondary end points of the incidence of Covid-19 and SARS-CoV-2 infection regardless of symptoms and asymptomatic infection in the per-protocol efficacy population was defined as 1 minus the ratio of incidence rate (mRNA-1273 vs. placebo). The 95% confidence interval of the ratio was calculated with the use of the exact method, conditional on the total number of cases, with adjustment for person-years. Panel B shows the cumulative incidence of Covid-19 (according to the CDC definition) starting from randomization among the children 2 to 5 years of age and those 6 to 23 months of age in the modified intention-to-treat population, which included all randomly assigned participants who did not have serologic or virologic evidence of SARS-CoV-2 infection at baseline and who received at least one injection of the correct dose. The tick marks indicate censored data. The insets show the same data on an enlarged y axis. The data-cutoff date was February 21, 2022.

involving adolescents and older children.[13,14,24-26] Two-injections of 25 μg of mRNA-1273 in these younger children elicited neutralizing antibody concentrations similar to those in 18-to-25-year-olds who received two 100-μg injections in the COVE trial.[11,12] These data suggest that the benefits of mRNA-1273 vaccination in the prevention of Covid-19 also extend to children and infants as young as 6 months of age.

Incidences of SARS-CoV-2 infections and Covid-19 were assessed as secondary end points in the trial during a period when omicron was the predominant circulating variant, particularly among young children. Among participants with available sequencing data, nearly all had confirmed omicron (BA.1 and BA.1.1) sequences. Nonetheless, primary vaccination with two 25-μg doses of mRNA-1273 was protective against confirmed Covid-19, as defined by the CDC or in the COVE trial, in both age cohorts. The estimated vaccine efficacy was lower than that reported in previous mRNA-1273 trials conducted when other variants were predominant[11-14] and similar to that reported in effectiveness studies of the two-dose mRNA-1273 series involving adults during circulation of the omicron variant.[17,18,27] The vaccine also elicited robust binding antibody levels against a broad range of variants including previous variants of concern and the delta and omicron variants. In addition, primary vaccination offers protection against hospitalization and death.[18,27,28] The previously authorized vaccine for 5-to-11-year-olds showed excellent effectiveness in preventing Covid-19–related hospitalizations and MIS-C, including during peak circulation of delta.[28-30] Although declines in vaccine effectiveness against omicron infection have been observed, the vaccines remain effective in preventing hospitalizations.[17,18]

Important limitations to this trial should be considered. Generally healthy children and children with stable medical conditions were enrolled. Additional work may be necessary to understand the effect of immunosuppressive conditions on vaccine immunogenicity in children. The trial was powered to detect rare adverse events (at approximately 0.1%); however, wider-scale use of the vaccine in children after authorization may identify other less frequent or more serious adverse events, and continued monitoring of safety after emergency use authorization is ongoing.[31] The vaccine efficacy was shown on the basis of cases of Covid-19 and SARS-CoV-2 infection reported as of the data-cutoff date, and longer-term evaluation of the efficacy and durability of protection continues in the ongoing trial.

In children 6 months to 5 years of age, two 25-μg injections of the mRNA-1273 vaccine had acceptable reactogenicity, safety, and effectiveness during a period when omicron was the predominant circulating variant, a finding consistent with that observed previously in children 6 to 11 years of age, adolescents, and adults.[11-14] Active and passive safety surveillance will continue during the postauthorization period in large global safety networks to detect any new safety signals. The longer-term effectiveness and durability of mRNA-1273 will also continue to be assessed in clinical trials and through its postauthorization use.

Supported by the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and

Development Authority (contract number, 75A50120C00034), and the National Institute of Allergy and Infectious Diseases (grant numbers, UM1AI148576, UM1AI148452, UM1AI148689, UM1AI148450, UM1AI148372, and UM1AI148575).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants and their families; the staff at the trial sites for implementing the protocol; members of the data and safety monitoring board (David Bernstein, M.D. [chair], Cincinnati Children's Hospital Medical Center; Michael Polis, M.D., M.P.H., Medical Consulting; and Anne Chang, Ph.D., M.P.H.T.M., M.B., B.S., Children's Health Queensland Hospital, Australia); David C. Montefiori, Ph.D., and the Immune Assay Team at Duke University Medical Center for performing the neutralization assays in part 1 of the trial; PPD Laboratories for performing the neutralization assays in part 2 of the trial and the Meso Scale Discovery multiplex binding antibody assays in parts 1 and 2 of the trial; and Frank Dutko, Ph.D. (a Moderna contractor), for editorial support with an earlier version of the manuscript.

APPENDIX

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