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Safety and Immunogenicity of SARS-CoV-2 Recombinant Spike Protein Vaccine in Children and Adolescents in India
A Phase 2-3 Randomized Clinical Trial

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IMPORTANCE The recombinant COVID-19 vaccine NVX-CoV2373 has demonstrated efficacy of approximately 90% in adults; however, its safety and efficacy in children is unknown.

OBJECTIVE To assess the noninferiority of SII-NVX-CoV2373 in children and adolescents compared to adults and to evaluate its safety in comparison with placebo.

DESIGN, SETTING, AND PARTICIPANTS This phase 2-3 observer-blind randomized clinical trial was conducted in 2 cohorts, children (aged 2 to 11 years) and adolescents (aged 12 to 17 years) between August 2021 and August 2022. Participants were randomized 3:1 to SII-NVX-CoV2373 or placebo and monitored for 179 days. The participants, study team, and laboratory staff were blinded. This was a multicenter study conducted across 10 tertiary care hospitals in India. Exclusion criteria included previous COVID-19 infection or vaccination, immunocompromised condition, and immunosuppressive medications.

INTERVENTIONS Two doses of 0.5-mL SII-NVX-CoV2373 or placebo were administered intramuscularly on days 1 and 22.

MAIN OUTCOMES AND MEASURES Primary outcomes were geometric mean titer ratio of both anti-spike (anti-S) IgG and neutralizing antibodies (NAbs) between both pediatric age groups to that of adults on day 36. Noninferiority was concluded if the lower bound of 95% CI of this ratio was greater than 0.67 for each age group. Both the antibodies were assessed for the index strain and for selected variants at various time points. Solicited adverse events (AEs) were recorded for 7 days after each vaccination, unsolicited AEs were recorded for 35 days, and serious AEs and AEs of special interest were recorded for 179 days.

RESULTS A total of 460 children in each age cohort were randomized to receive vaccine or placebo. The mean (SD) age was 6.7 (2.7) years in the child cohort and 14.3 (1.6) years in the adolescent cohort; 231 participants (50.2%) in the child cohort and 218 in the adolescent cohort (47.4%) were female. Both anti-S IgG and NAb titers were markedly higher in the SII-NVX-CoV2373 group than in the placebo group on both day 36 and day 180. The geometric mean titer ratios compared to those in adults were 1.20 (95% CI, 1.08-1.34) and 1.52 (95% CI, 1.38-1.67) for anti-S IgG in adolescents and children, respectively; while for NAbs, they were 1.33 (95% CI, 1.17-1.50) and 1.93 (95% CI, 1.70-2.18) in adolescents and children, respectively, indicating noninferiority. SII-NVX-CoV2373 also showed immune responses against variants studied. Injection site reactions, fever, headache, malaise, and fatigue were common solicited AEs. There were no AEs of special interest and no causally related serious AEs.

CONCLUSIONS AND RELEVANCE SII-NVX-CoV2373 was safe and well tolerated in children and adolescents in this study. The vaccine was highly immunogenic and may be used in pediatric vaccination against COVID-19.

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Supplemental content

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While children are a low-risk population for COVID-19,[1-3] severe illness and deaths have been rarely reported in children, especially in those with comorbidities.[4,5] Infections may also cause a rare complication called multisystem inflammatory syndrome in children (MIS-C), which can be serious and even fatal.[5,6] COVID-19 vaccination is associated with reduced incidence of MIS-C.[7,8] COVID-19 may also increase the risk of diabetes in children.[9] Moreover, children can spread the virus among adults.[10]

In light of these issues, pediatric vaccination has been broadly recommended.[11,12] Two messenger RNA (mRNA) vaccines are approved in the US for children and adolescents aged 6 months to 17 years.[12] In India, an inactivated vaccine and a subunit vaccine are approved for children 5 years and older,[13] although vaccination is only implemented for those aged 12 to 17 years.[14] As of March 31, 2023, around 100 million adolescents in India have received COVID-19 vaccines.[15]

NVX-CoV2373, a SARS-CoV-2 recombinant full-length spike protein nanoparticle vaccine, was originally developed in the US. The vaccine was found safe with 90% efficacy in adults and 79.5% efficacy in adolescents.[16-18] The vaccine is also manufactured in India (as SII-NVX-CoV2373) and was found safe and immunogenic in a phase 2-3 study in adults.[19] The vaccine was granted an emergency use approval by the Indian authorities and the World Health Organization in December 2021.[20,21] The adult study[19] was further expanded to evaluate SII-NVX-CoV2373 in children. Based on this pediatric expansion of the adult phase 2-3 study, the vaccine was further approved for adolescents[22] and children aged 7 to 11 years[23] in India.

The primary objective of this study was to assess the noninferiority of SII-NVX-CoV2373 in adolescents aged 12 to 17 years and children aged 2 to 11 years separately compared to adults in the same study[19] in terms of ratio of geometric mean of enzyme-linked immunosorbent assay (ELISA) units (GMEU) of anti-spike (anti-S) IgG antibodies and geometric mean titers (GMTs) of neutralizing antibodies (NAbs) at 14 days after the second dose. Another primary objective was to assess the seroconversion at 14 days after the second dose and safety of the study vaccine throughout the study in comparison to placebo (eTable 1 in Supplement 3).

Key Points

Question Is SII-NVX-CoV2373, a recombinant full-length spike protein COVID-19 vaccine, noninferior in terms of immune response in children and adolescents compared to adults?

Findings In this phase 2-3 randomized clinical trial, SII-NVX-CoV2373 was noninferior in terms of the geometric mean titer ratio of neutralizing antibodies and anti-spike IgG antibodies in both children and adolescents compared to adults. The vaccine was safe and well tolerated and demonstrated a robust immune response against Delta, Omicron BA.1, and Omicron BA.5 variants.

Meaning The findings suggest that SII-NVX-CoV2373 may be used in pediatric vaccination against COVID-19.

Methods

The full trial protocol can be found in Supplement 1 and the statistical analysis plan in Supplement 2. This study was approved by the Indian regulatory authority and Institutional Ethics Committees. The International Council for Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki were followed. The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline were followed. Written informed consent was provided by parents prior to study enrollment. Verbal assent for individuals aged 7 to 11 years and written assent for those aged 12 to 17 years were also obtained.

This was a phase 2-3 observer-blind, randomized clinical trial. A total of 920 children and adolescents were enrolled across 10 hospitals, 460 each in the child group (ages 2-11 years) and adolescent group (ages 12-17 years). For statistical noninferiority, only 2 age groups were considered in the study design—adolescents aged 12 to 17 years and children aged 2 to 11 years. The regulatory authority requested splitting enrollment of children of 2 to 11 years into 2 subgroups as 7 to 11 years and 2 to 6 years for safety monitoring. Participants were randomized 3:1 to receive 2 doses of either SII-NVX-CoV2373 or placebo on days 1 and 22. After vaccination, participants visited study sites on days 22, 36, 85, and 180 and contacted telephonically on day 120 for safety evaluation.

Initially, 100 participants were enrolled sequentially in each of the following groups: ages 12 to 17 years, ages 7 to 11 years, and ages 2 to 6 years. After a review of the day 8 safety data of the first 100 adolescent participants by an independent data safety monitoring board and the regulatory authority, the rest of the participants of that age group and 100 participants of the next lower age group (7 to 11 years) were enrolled. After a review of the day 8 safety data of the first 100 participants (7 to 11 years) by an independent data safety monitoring board and the regulatory authority, the rest of the participants of that age group and 100 participants of the next lower age group (2 to 6 years) were enrolled. After a review of the day 8 safety data of the first 100 participants (2 to 6 years) by an independent data safety monitoring board and the regulatory authority, the rest of the participants of that age group were enrolled (Supplement 1). The recruitment timeline in adults, adolescents, and children is provided in eFigure 1 in Supplement 3.

Safety data were reviewed at periodic intervals by the protocol safety review team and the data safety monitoring board. Blood was collected at baseline and days 22, 36, and 180 for immunogenicity testing. A nasopharyngeal swab was collected for detection of SARS-CoV-2 infection by reverse transcription-polymerase chain reaction at baseline and at any time during the study if any participant had symptoms associated with COVID-19 or contact with an individual with confirmed COVID-19. Parents and participants were sensitized to follow COVID-19-appropriate precautions throughout the study.

Study Population

Children and adolescents aged 2 to 17 years who were healthy or medically stable as per the clinical judgement of the investigator were included. Female adolescents who had attained

menarche were required to have a negative result on a urine pregnancy test before each dose. Children with any acute illness, history of COVID-19 infection, prior receipt of a COVID-19 vaccine, severe allergic reactions, immunocompromised condition, or immunosuppressive medications were excluded.

Randomization and Blinding

The randomization scheme was generated using SAS version 9.4 (SAS Institute) with block size of 4 and 3:1 allocation to SII-NVX-CoV2373 or placebo. Participants, study personnel evaluating study outcomes, and laboratory staff were blinded. Personnel accessing the interactive web response system for randomization and vaccine administration were unblinded. After the vaccines were authorized for use in the specific age group, the blind was broken on or after day 85, and participants in the placebo group were offered SII-NVX-CoV2373 and were continued in the study only for safety follow-up.

Study Products

The study products were administered intramuscularly in the deltoid or anterolateral thigh on days 1 and 22. A single 0.5-mL dose of SII-NVX-CoV2373 (Serum Institute of India) contains 5-µg antigen and 50-µg Matrix-M adjuvant. A solution of 0.9% sodium chloride was used as a placebo.

Safety Assessment

Solicited adverse events (AEs) were collected for 7 days after each injection using diary cards. Unsolicited AEs were collected for 35 days after the first dose (14 days after the second dose). Serious AEs, related medically attended AEs, and AEs of special interest were collected throughout the 179 days.

Immunogenicity Assessment

Immunogenicity was assessed by anti-S IgG antibodies and NAbs on days 1, 22, 36, and 180. Anti-S IgG antibodies against the index strain were measured by validated ELISA assay (Novavax) and expressed as ELISA units (EU)/mL.

NAbs against the ancestral strain were measured using a validated microneutralization assay on days 1 and 36 in all participants and in a 3:1 randomized subset on days 22 and 180 as exploratory objectives. In addition, NAbs against the Omicron BA.1 strain were measured in a 3:1 randomized subset (360biolabs) on days 1, 36, and 180. NAb titers were expressed as 1/dilution (eTable 2 in Supplement 3).

Anti-nucleocapsid IgG antibodies were measured on days 1, 36, and 180 (Abbott; National AIDS Research Institute-Indian Council of Medical Research). Immunogenicity against Delta, Omicron BA.1, and Omicron BA.5 variants was also assessed in a 3:1 randomized subset by anti-S IgG and human ACE2 receptor binding inhibition assays (including the index strain) on days 1, 36, and 180. All details for immunogenicity assessments are provided in eTable 2 in Supplement 3.

Statistical Analysis

Success of the primary immunogenicity objectives required demonstration of noninferiority of geometric means vs adults (anti-S IgG and NAbs for children and adolescents). This noninferiority was statistically evaluated as a family. In each age group (adolescents and children), 345 and 115 participants were to receive the SII-NVX-CoV2373 vaccine or placebo, respectively. Assuming 20% nonevaluable participants, a GMEU/GMT ratio of 1, and a coefficient of variation 1.35, the study had greater than 99% power to achieve the noninferiority objective for children and adolescents separately against adults. The study also provided 82% power to detect at least 1 causally related serious AE among 690 recipients of SII-NVX-CoV2373 if the frequency was 1 in 400. Sample size calculations were performed in PASS version 15.0.7 (NCSS Statistical Software).

Noninferiority was to be concluded if the lower limit of the 2-sided 95% CI for the ratios was greater than 0.67[24] for all 4 end points simultaneously. GMEU/GMT ratio and 95% CI were computed from an analysis of covariance model fitted to the log-transformed anti-S IgG and NAbs with age group (adolescents and children vs adult), log baseline titer, and sex as covariates. A multiple imputation model with classification variables vaccine group, sex, and continuous covariate of log baseline titer of anti-S IgG and NAbs were used to impute 50 values for each missing value when noninferiority was analyzed.[25] No multiplicity adjustment was done, as all primary noninferiority immunogenicity objectives were required to be met to conclude success. Immune responses were also assessed in participants who had negative results on reverse transcription-polymerase chain reaction and anti-nucleocapsid IgG tests at baseline.

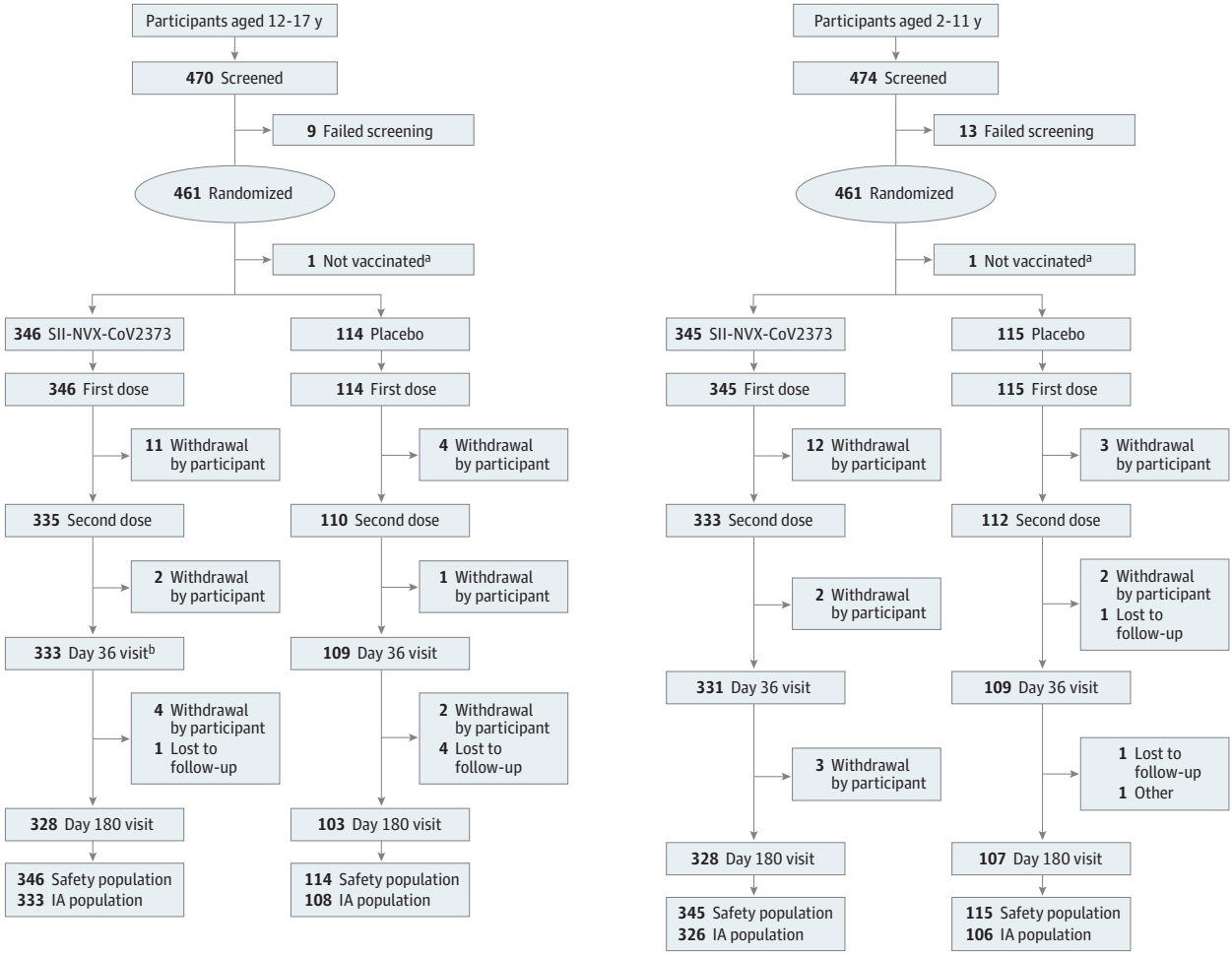
The safety population included all participants who received at least 1 dose of the study vaccine. The immunogenicity analysis population consisted of all participants who received the first dose of the study vaccine and provided an evaluable serum sample for at least 1 assessment and had baseline data available (eTable 3 in Supplement 3). The placebo group participants who were unblinded on or after day 85 and subsequently received the SII-NVX-CoV2373 vaccine were censored from the analysis after unblinding.

Seroconversion was defined as a 4-fold increase in antibody titers with respect to prevaccination titers. The proportion of participants with seroconversion and 95% CIs was calculated by the Clopper-Pearson method. The difference and 95% CI for seroconversion were estimated using Mantel-Haenszel stratum weighted with stratifications of baseline seropositive by age group and overall. Analyses were performed using SAS version 9.4 (SAS Institute).

Results

A total of 470 adolescents were enrolled and 461 (mean [SD] age, 14.3 [1.6] years; 218 [47.4%] female) were randomized. Of these, 460 and 445 received the first and the second dose of the study vaccines, respectively (**Figure 1**). A total of 474 children were enrolled and 461 were randomized (mean [SD] age, 6.7 [2.7] years; 231 [50.2%] female). Of these, 460 and 445 received the first and the second dose of the study vaccines, respectively. Fifteen participants each withdrew before the second dose in both age groups (Figure 1). Demographic and baseline characteristics are provided in **Table 1** for both age groups.

Figure 1. CONSORT Flow Diagram



IA indicates immunogenicity analysis.

[a] Withdrawal by participant before vaccination.

[b] One participant missed day 36 visit, but attended subsequent visits.

Table 1. Demographic and Baseline Characteristics in the Safety Population

Parameter	Age 2-11 y		Age 12-17 y	
	SII-NVX-CoV2373 (n = 345)	Placebo (n = 115)	SII-NVX-CoV2373 (n = 346)	Placebo (n = 114)
Age, mean (SD), y	6.7 (2.7)	6.5 (2.7)	14.3 (1.6)	14.3 (1.6)
Sex, No. (%)				
Male	176 (51.0)	53 (46.1)	188 (54.3)	54 (47.4)
Female	169 (49.0)	62 (53.9)	158 (45.7)	60 (52.6)
Body mass index,[a] mean (SD)	15.64 (2.93)	15.61 (3.04)	19.47 (4.48)	19.95 (4.83)
Baseline serology or RT-PCR results for SARS-CoV-2, No. (%)[b]				
Positive	37 (10.7)	16 (13.9)	45 (13.0)	14 (12.3)
Negative	306 (88.7)	98 (85.2)	300 (86.7)	100 (87.7)

Abbreviation: RT-PCR, reverse transcription–polymerase chain reaction.

[a] Calculated as weight in kilograms divided by height in meters squared.

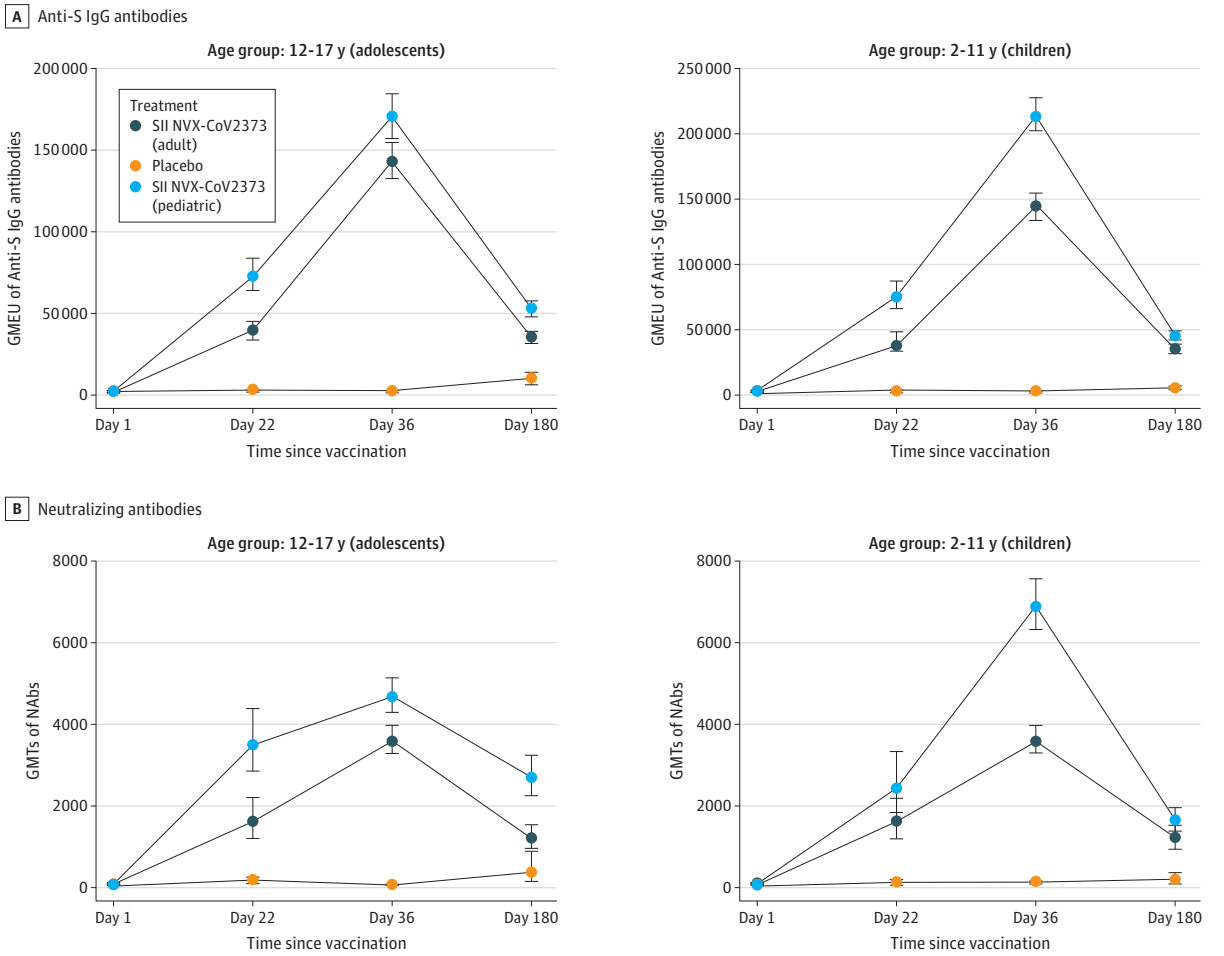
[b] Results missing for 3 participants in the 2- to 11-year-old group and 1 in the 12- to 17-year-old group.

Immunogenicity Results

Anti-S IgG (Index Strain)

Baseline anti-S IgG titers were comparable between the 2 groups in both adolescents and children. After the second dose, geometric mean anti-S IgG titers were 170 193.6 (95% CI, 157 429.7-183 992.4) and 214 029.6 (95% CI, 201 610.9-227 213.1) in the SII-NVX-CoV2373 group in adolescents and children, respectively. On day 180, titers declined but were still higher than baseline in both adolescents (geometric mean, 51 961.6; 95% CI, 47 560.1-56 770.5) and children (geometric

Figure 2. Summary of Anti-Spike (Anti-S) IgG Antibodies and Neutralizing Antibodies (NAbs) Against SARS-CoV-2 in the Immunogenicity Analysis Population



The geometric mean of enzyme-linked immunosorbent assay (ELISA) units (GMEUs) of anti-S IgG and geometric mean titers (GMTs) of NAbs and corresponding 95% CIs were calculated by exponentiating the log-transformed mean and its 2-sided 95% CI at each visit.

mean, 44 882.1; 95% CI, 41 578.6-48 448.0) (**Figure 2**; eTable 4 in Supplement 3). Noninferiority for SII-NVX-CoV2373 for adolescents and children in comparison to the adult cohort was met, with a GMEU ratio of 1.20 (95% CI, 1.08-1.34) in adolescents and 1.52 (95% CI, 1.38-1.67) in children (**Table 2**).

On day 36, seroconversion was 98.8% (95% CI, 96.9-99.7) in adolescents and 99.1% (95% CI, 97.3-99.8) in children in the SII-NVX-CoV2373 group and 7.8% or lower in the placebo groups (eTable 5 in Supplement 3). On day 180, seroconversion in the SII-NVX-CoV2373 group was 91.7% (95% CI, 88.1-94.5) in adolescents and 94.2% (95% CI, 91.1-96.6) in children (eTable 6 and eFigure 2 in Supplement 3).

NAbs (Ancestral Strain)

Baseline NAb titers were comparable between the SII-NVX-CoV2373 and placebo groups in both age groups. After the second dose, geometric mean NAb titers were 4686.4 (95% CI, 4282.0-5129.0) and 6916.2 (95% CI, 6322.8-7565.5) in the SII-NVX-CoV2373 group in adolescents and children, respectively. On day 180, titers declined in adolescents (geometric mean, 2683.2; 95% CI, 2227.8-3231.7) and children (geometric mean, 1604.6; 95% CI, 1341.0-1920.0). (Figure 2; eTable 4 in Supplement 3). Noninferiority for each pediatric cohort in comparison to the adult cohort was met, with a GMT ratio of 1.33 (95% CI, 1.17-1.50) in adolescents and 1.93 (95% CI, 1.70-2.18) in children (Table 2).

On day 36, seroconversion was 97.9% (95% CI, 95.7-99.1) and 97.8% (95% CI, 95.6-99.1) in the SII-NVX-CoV2373 group among adolescents and children, respectively, and less than 11.0% in the placebo group (eTable 5 in Supplement 3). Seroconversion was 94.1% (95% CI, 88.2-97.6) in adolescents and 92.4% (95% CI, 84.9-96.9) in children on day 180 (eTable 6 and eFigure 2 in Supplement 3).

The titers and seroconversion in participants with negative test results at baseline showed similar trends for both anti-S IgG and NAbs. Details are shown in eTables 7 and 8 in Supplement 3.

Immunogenicity Against Specific Variants

Among SII-NVX-CoV2373 recipients, geometric mean anti-S IgG titers against the Delta variant on day 36 were 157 379.2 (95%

Table 2. Noninferiority of SII-NVX-CoV2373 (Pediatric) Compared to SII-NVX-CoV2373 (Adult) in Terms of Anti-Spike IgG and Neutralizing Antibodies 14 Days After the Second Dose in the Immunogenicity Analysis Population

Multiple imputation results[a]	Pediatric group, age 2-11 y (n = 326)	Adult group (n = 340)	Pediatric group, age 12-17 y (n = 333)	Adult group (n = 340)
Anti-spike IgG				
GMEUs (95% CI)[b]	216 369.87 (202 056.83-231 696.80)	142 586.82 (133 280.59-152 542.85)	171 204.19 (158 598.33-184 812.00)	142 122.16 (131 793.34-153 260.47)
GMEU ratio (95% CI)[b]	1.52 (1.38-1.67)		1.20 (1.08-1.34)	
Neutralizing antibodies				
GMTs (95% CI)[b]	6940.82 (6349.74-7586.93)	3602.39 (3300.10-3932.37)	4732.36 (4323.63-5179.73)	3568.04 (3264.78-3899.48)
GMT ratio (95% CI)[b]	1.93 (1.70-2.18)		1.33 (1.17-1.50)	

Abbreviations: GMEUs, geometric mean of enzyme-linked immunosorbent assay units; GMTs, geometric mean titers.

[a] Multiple imputation model with classification variables of vaccine group, sex, and continuous covariate of log baseline titer were used to impute 50 values for each missing value. There were 2 adults (18 years and older), 4 adolescents (aged 12-17 years), and 1 child (aged 2-11 years) with missing values that were imputed for both anti-spike IgG and neutralizing antibodies. The Rubin method in PROC MIANALYZE was used to pool estimates and standard errors across the 50 multiply imputed data sets.

[b] Pooled analysis of covariance results, least squares means, and 95% CIs by treatment were used to generate the GMEUs and GMTs and 95% CIs, and the differences in least squares means and corresponding 95% CI limits were used to obtain the GMEU and GMT ratios and 95% CIs using back-transforming to the original scale.

CI, 122 688.8-201 878.3) in adolescents and 251 510.2 (95% CI, 204 159.5-309 843.0) in children. Among SII-NVX-CoV2373 recipients, geometric mean anti-S IgG titers against the Omicron BA.1 variant on day 36 were 74 971.0 (95% CI, 57 583.6-97 608.5) in adolescents and 105 031.3 (95% CI, 83 738.1-131 739.0) in children, while the same against the Omicron BA.5 variant were 71 869.4 (95% CI, 56 343.4-91 673.9) in adolescents and 97 840.4 (95% CI, 80 494.6-118 923.9) in children. The titers were still higher than baseline on day 180 in both age groups (eTable 9 in Supplement 3). A similar trend was observed for hACE2 receptor-binding inhibition antibody titers against the Delta, Omicron BA.1, and Omicron BA.5 variants among SII-NVX-CoV2373 recipients in both age groups (eTable 10 in Supplement 3). Increases in NAbs against the Omicron BA.1 variant were seen with GMTs 140.3 (95% CI, 106.7-184.5) and 138.6 (95% CI, 97.6-196.9) at day 36 in the SII-NVX-CoV2373 group in adolescents and children, respectively. Titers were still higher than baseline on day 180 in both age groups (eTable 11 in Supplement 3).

SARS-CoV-2 Infections (Symptomatic and Asymptomatic)

There were 10 (7 symptomatic COVID-19 and 3 asymptomatic) cases from 14 days after the first dose through end of study (eTable 12 in Supplement 3). No case was severe, and all participants recovered completely.

Safety Results

Serious AEs and AEs of Special Interest

There were no AEs of special interest reported. Two serious AEs (viral infection and gastroenteritis) were reported in adolescents, but these were deemed unrelated to the study treatments.

Unsolicited AEs

Among adolescents, 30 unsolicited AEs were reported in 28 participants (8.1%) in the SII-NVX-CoV2373 group and 12 unsolicited AEs in 6 participants (5.3%) in the placebo group. None of the reported AEs were considered related except for 1 event of diarrhea in the placebo group.

Among children, 49 unsolicited AEs were reported in 39 participants (11.3%) in the SII-NVX-CoV2373 group and 14 unsolicited AEs in 13 participants (11.3%) in the placebo group. None were considered related to the study vaccines except 3 events in the SII-NVX-CoV2373 group (1 each of pyrexia, allergic dermatitis, and diarrhea) and 1 in the placebo group (diarrhea).

Solicited AEs

Among adolescents, after the first dose, there were 271 solicited AEs in 138 participants (39.9%) in the SII-NVX-CoV2373 group and 54 solicited AEs in 26 participants (22.8%) in the placebo group. After the second dose, there were 322 solicited AEs in 126 participants (37.6%) in the SII-NVX-CoV2373 group and 41 solicited AEs in 19 participants (17.3%) in the placebo group (**Table 3**).

Among children, after the first dose, there were 248 solicited AEs in 122 participants (35.4%) in the SII-NVX-CoV2373 group and 29 solicited AEs in 15 participants (13.0%) in the placebo group. After the second dose, there were 367 solicited AEs in 163 participants (48.9%) in the SII-NVX-CoV2373 group and 27 solicited AEs in 13 participants (11.6%) in the placebo group. Common AEs in both age groups included injection site pain, tenderness, headache, fatigue, and fever (Table 3).

Almost all solicited and unsolicited AEs were mild and all resolved without sequelae. Most solicited AEs started within 1 day and lasted for 2 days or less.

Discussion

This phase 2-3 randomized clinical trial evaluated the safety and immunogenicity of SII-NVX-CoV2373 in children and adolescents compared with adults. The vaccine was highly immunogenic, with more than 98% seroconversion. There was a marked increase in both anti-S IgG and NAb titers 14 days after the second dose compared to baseline. No AEs of special interest or causally related serious AEs were reported. SII-NVX-CoV2373 was also safe and well tolerated.

Table 3. Summary of Solicited Adverse Events (AEs) in the Safety Population

	Participants with ≥1 AE, No. (%; total No. of events)							
	Age 2-11 y				Age 12-17 y			
	First dose		Second dose		First dose		Second dose	
	SII-NVX-CoV2373 (n = 345)	Placebo (n = 115)	SII-NVX-CoV2373 (n = 333)	Placebo (n = 112)	SII-NVX-CoV2373 (n = 346)	Placebo (n = 114)	SII-NVX-CoV2373 (n = 335)	Placebo (n = 110)
Participants with ≥1 solicited AE	122 (35.4; 248)	15 (13.0; 29)	163 (48.9; 367)	13 (11.6; 27)	139 (40.2; 272)	26 (22.8; 54)	129 (38.5; 329)	20 (18.2; 42)
Participants with ≥1 local solicited AE	84 (24.3; 118)	10 (8.7; 15)	87 (26.1; 136)	9 (8.0; 17)	90 (26.0; 123)	12 (10.5; 16)	86 (25.7; 140)	10 (9.1; 13)
Injection site pain	81 (23.5; 81)	9 (7.8; 9)	83 (24.9; 83)	9 (8.0; 9)	85 (24.6; 85)	11 (9.6; 11)	82 (24.5; 82)	9 (8.2; 9)
Injection site tenderness	27 (7.8; 27)	3 (2.6; 3)	20 (6.0; 20)	1 (0.9; 1)	23 (6.6; 23)	1 (0.9; 1)	29 (8.7; 29)	3 (2.7; 3)
Injection site swelling	6 (1.7; 6)	2 (1.7; 2)	14 (4.2; 14)	2 (1.8; 2)	8 (2.3; 8)	2 (1.8; 2)	13 (3.9; 13)	0
Injection site induration	2 (0.6; 2)	1 (0.9; 1)	5 (1.5; 5)	2 (1.8; 2)	7 (2.0; 7)	1 (0.9; 1)	10 (3.0; 10)	1 (0.9; 1)
Injection site erythema	2 (0.6; 2)	0	14 (4.2; 14)	3 (2.7; 3)	0	1 (0.9; 1)	6 (1.8; 6)	0
Participants with ≥1 systemic solicited AE	80 (23.2; 130)	10 (8.7; 14)	133 (39.9; 231)	8 (7.1; 10)	87 (25.1; 149)	19 (16.7; 38)	99 (29.6; 189)	17 (15.5; 29)
Fever	50 (14.5; 50)	6 (5.2; 6)	99 (29.7; 99)	1 (0.9; 1)	27 (7.8; 27)	7 (6.1; 7)	58 (17.3; 58)	3 (2.7; 3)
Headache	19 (5.5; 19)	2 (1.7; 2)	37 (11.1; 37)	4 (3.6; 4)	39 (11.3; 39)	11 (9.6; 11)	42 (12.5; 42)	9 (8.2; 9)
Malaise	17 (4.9; 17)	2 (1.7; 2)	19 (5.7; 19)	1 (0.9; 1)	14 (4.0; 14)	2 (1.8; 2)	23 (6.9; 23)	2 (1.8; 2)
Fatigue	15 (4.3; 15)	1 (0.9; 1)	18 (5.4; 18)	2 (1.8; 2)	30 (8.7; 30)	5 (4.4; 5)	30 (9.0; 30)	4 (3.6; 4)
Myalgia	12 (3.5; 12)	2 (1.7; 2)	14 (4.2; 14)	1 (0.9; 1)	16 (4.6; 16)	5 (4.4; 5)	14 (4.2; 14)	4 (3.6; 4)
Arthralgia	4 (1.2; 4)	0	11 (3.3; 11)	0	15 (4.3; 15)	3 (2.6; 3)	10 (3.0; 10)	4 (3.6; 4)
Nausea	5 (1.4; 5)	0	20 (6.0; 20)	0	7 (2.0; 7)	2 (1.8; 2)	8 (2.4; 8)	2 (1.8; 2)
Vomiting	8 (2.3; 8)	1 (0.9; 1)	13 (3.9; 13)	1 (0.9; 1)	1 (0.3; 1)	3 (2.6; 3)	4 (1.2; 4)	1 (0.9; 1)

An age effect was seen in the immune responses. The titers in both adolescents and children were higher than in adults.[19] Moreover, the titers in the children were higher than in the adolescents.

We set out to demonstrate noninferiority of SII-NVX-CoV2373 in children compared with adults because no vaccine was approved in India for children at the time of study. The vaccine efficacy had already been demonstrated in adults.[16,17] As a result, although we used a placebo as a control, adult results were used to immuno-bridge the vaccine in children. This approach has been used in other COVID-19 vaccine studies.[26-29]

There was a decline in antibody titers in the vaccine group on day 180, although antibody titers were still much higher than baseline and the placebo group. Seroconversion was still 90% or greater. Similar results were seen with SII-NVX-CoV2373 in adults.[19]

The GMTs in the placebo groups on day 180 were higher than the baseline and day 36. This was probably due to the effect of the Omicron wave in India from December 2021 to March 2022. Titers were also higher in adolescents than in children, possibly due to higher infection rates among adolescents compared to children. None of the children in the study had received a COVID-19 vaccine or reported prior infection. Globally, rates of infection among children aged 5 to 14 years and those younger than 5 years were 10.82% and 2.7%, respectively.[30]

SII-NVX-CoV2373 showed high GMTs for Delta, Omicron BA.1, and Omicron BA.5 variants, albeit lower than those for the index strain. This is similar to results observed with other COVID-19 vaccines.[31,32] Still, such high titers indicate that vaccines based on the index strain may give protection from Delta, Omicron BA.1, and Omicron BA.5 variants, especially against severe disease and death.[33]

Baseline serology and reverse transcription–polymerase chain reaction positivity for SARS-CoV-2 ranged from 10.7% to 13.9% in both the pediatric age groups. The corresponding value in the phase 3 study in adults was 32%.[19] This probably means that the first wave in 2020 as well as the second wave in 2021 and the third wave in 2021 to 2022 in India did not affect children significantly. However, another study[34] conducted from March to June 2021 showed a seroprevalence of 55.7% in individuals younger than 18 years and 63.5% in those 18 years and older in India. While this study measured total antibodies against the spike protein receptor-binding domain,[34] our study measured anti-nucleocapsid IgG antibodies. Disparities in prevalence estimates obtained using different assays are known.[35]

Among both age groups, GMTs were markedly higher in the SII-NVX-CoV2373 group than in the placebo group on both day 36 and day 180. Although participants with documented previous SARS-CoV-2 infection were not included in the immune response assessments, any undetected infections beyond day 36 could have affected the vaccine immune response to some extent.

NVX-CoV2373 has shown around 90% efficacy in adults and subsequently 79.5% efficacy in adolescents.[16-18] The immune responses in children were much higher than what have been

observed in adults.[19] Higher levels of all immune markers are known to be associated with a reduced risk of symptomatic infection.[36] Human challenge studies of seasonal coronaviruses reported high levels of baseline neutralizing antibodies in uninfected or asymptomatic people,[37] thus indicating that high antibody titers provide protection from disease. Considering these factors, SII-NVX-CoV2373 is expected to give a high degree of protection in children, at least as much as in adults.

To our knowledge, this is the first study in India in which any recombinant protein COVID-19 vaccine has been tested in individuals aged 2 to 5 years. mRNA vaccines have been tested elsewhere in the population aged 6 months to 5 years.[12] There has been a concern about myocarditis with mRNA vaccines in younger populations.[38-41] So far, SII-NVX-CoV2373 has not been shown to cause any related serious AE or AEs of special interest in any study in India, although the size of the studies has been small.

Cases of myocarditis or pericarditis were rarely detected during clinical trials and postauthorization use of NVX-CoV2373.[42] However, causal association has not been proven. Continued surveillance for any such rare events should be maintained.

Pediatric COVID-19 vaccination has faced some degree of hesitancy among parents.[43-45] One study in Canada found that despite parents' high COVID-19 vaccination uptake for themselves (88.8%), the intention for vaccinating children aged 5 to 11 years was relatively low (56.9%).[46] As a result, vaccine coverage has not been optimal.[47] Reasons cited for this hesitancy include vaccine safety and effectiveness.[48] There is also a perception that the risk for serious illness is low in children.[48] In light of this, the safety profile in children can be an advantage of the SII-NVX-CoV2373 vaccine.

Limitations

This study has limitations. We excluded individuals with previous SARS-CoV-2 infection from the study. However, we could assess the actual vaccine effect, and no response was seen in the placebo group on day 36. We did not assess the efficacy of the vaccine. However, NVX-CoV2373 efficacy has already been demonstrated in adults and adolescents,[16-18] and therefore, SII-NVX-CoV2373—with its identical composition as NVX-CoV2373—could be immunologically bridged. Severe COVID-19 has been reported in children with some underlying medical conditions,[5] but we excluded such children from our study. Immunogenicity of COVID-19 vaccines among such children and adolescents has been lower than among healthy individuals,[49-52] which is expected. However, it was still an acceptable immune response.[52] Recruitment in the study was conducted sequentially, which probably meant that the adults and the adolescents and children were exposed to different strains, including Delta, Omicron BA.1, and Omicron BA.5 variants during the follow-up period. This may have affected the immunogenicity results.

Conclusions

To our knowledge, there are only a few published phase 2-3 studies of authorized COVID-19 vaccines in the pediatric population for primary immunization—2 mRNA vaccines,[26-29] a subunit vaccine,[53] NVX-CoV2373[18] (adolescents only), and a nonrandomized study of an inactivated vaccine.[54] Our study is the first, to our knowledge, publishing data for the spike protein vaccine among children and adds to the existing evidence that COVID-19 vaccines work well in the pediatric population.

SII-NVX-COV2373 was safe and well tolerated in children and adolescents aged 2 to 17 years in this study. The vaccine was highly immunogenic, with these age groups showing a higher immune response than in adults, and showed robust responses against Delta, Omicron BA.1, and Omicron BA.5 variants. The findings suggest that this vaccine may be used in pediatric vaccination for COVID-19.

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