Safety and immunogenicity of a single-dose omicron-containing COVID-19 vaccination in adolescents: an open-label, single-arm, phase 2/3 trial

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Summary

Background Most individuals show immunity to SARS-CoV-2 from vaccination or infection, or both. We aimed to determine the safety and immunogenicity of an omicron-containing COVID-19 vaccine (mRNA-1273.222) in vaccine-naive adolescents who were SARS-CoV-2 positive.

Methods Part 3 of the phase 2/3 TeenCOVE trial was a phase 3, open-label, single-arm part done in the USA and the Dominican Republic that enrolled healthy, vaccine-naive adolescents (aged 12–17 years) to receive two 50 µg doses of mRNA-1273.222 (ancestral strain Wuhan-Hu-1 and omicron subvariants BA.4 and BA.5), 6 months apart. Primary reactogenicity and safety outcomes included assessment of solicited local or systemic adverse reactions 7 days after vaccination, and unsolicited and prespecified adverse events throughout study participation. Inferred effectiveness (primary immunogenicity outcome) was established by comparing neutralising antibody responses 28 days after dose 1 of mRNA-1273.222 in SARS-CoV-2-positive adolescents with responses 28 days after dose 2 of mRNA-1273 100 µg primary series in SARS-CoV-2-negative young adults (aged 18–25 years) from the COVE trial. This study is registered with ClinicalTrials.gov (NCT04649151).

Findings Between Dec 21, 2022, and June 5, 2023, 379 adolescents (378 of whom were SARS-CoV-2 positive) received at least one mRNA-1273.222 dose and were included in the safety analysis set. The reactogenicity profile was favourable compared with the mRNA-1273 primary series, with no new safety concerns identified. Unsolicited adverse events were reported in 49 (13%) of 379 participants; no deaths or adverse events leading to study discontinuation were reported. The immunogenicity set included 245 adolescents from the per-protocol immunogenicity subset who were SARS-CoV-2 positive at baseline and 296 young adults who were SARS-CoV-2 negative. Compared with the mRNA-1273 primary series in SARS-CoV-2-negative young adults, a single dose of mRNA-1273.222 induced superior (geometric mean ratio [GMR] 95% CI lower bound >1) neutralising antibody responses against omicron BA.4 and BA.5 (GMR 48·95 [95% CI 44·21–54·21]) and non-inferior (GMR 95% CI lower bound >0·667) neutralising antibody responses against ancestral SARS-CoV-2 (GMR 4·25 [95% CI 3·69–4·88]) in SARS-CoV-2-positive adolescents.

Interpretation In vaccine-naive, SARS-CoV-2-positive adolescents, single-dose mRNA-1273.222 was effective against COVID-19 based on successful immunobridging to the two-dose mRNA-1273 primary series in young adults. The findings support a simplified single-dose vaccination schedule with variant-containing mRNA vaccines, regardless of previous vaccination status.

Funding Moderna.

Introduction

Early epidemiological data indicated that the clinical manifestations of COVID-19 were less severe in the paediatric population.[1] However, as the COVID-19 pandemic progressed, the incidence of COVID-19-associated hospitalisations increased rapidly among children and adolescents.[2,3] The paediatric hospitalisation rates peaked during the delta-predominant and omicron-predominant periods, with the omicron peak resulting in rates that were four-times higher than the delta peak period.[2] Of note, more than half of hospitalised children and adolescents aged 17 years or younger had no underlying medical conditions.[4] During the delta-predominant and omicron-predominant periods, the hospitalisation rates were consistently lower among adolescents who were fully vaccinated compared with those who were unvaccinated.[2,3] Vaccination remains a key strategy to reduce the incidence of severe COVID-19 illness among children and adolescents.[2] However, a marked disparity exists in the vaccination rates due to factors such as vaccine hesitancy, socioeconomic conditions,[5,6] and public health infrastructures or policies,[7] with a substantial proportion of the population in some regions or countries remaining unvaccinated. As of November, 2023, only 33% of people

Research in context

Evidence before this study

We searched PubMed on July 24, 2024, for published clinical trials assessing a single dose of variant-containing COVID-19 mRNA vaccines in previously unvaccinated SARS-CoV-2-positive adolescents using the search terms "COVID-19 or SARS-CoV-2" and "mRNA vaccine" and "adolescents" and "single dose" and "clinical trial," with no restrictions on date or language. No articles were found describing a clinical trial of a single dose of variant-containing COVID-19 vaccine in previously unvaccinated baseline SARS-CoV-2-positive adolescents. What is known of the clinical safety and immunogenicity of variant-containing COVID-19 mRNA vaccines is from published phase 2/3 booster studies, which highlights the need for clinical studies on variant-containing vaccines in previously unvaccinated SARS-CoV-2-positive individuals.

Added value of this study

To the best of our knowledge, this study is among the first to show the safety and immunogenicity of a SARS-CoV-2 variant-containing mRNA vaccine administered as a single dose in previously unvaccinated SARS-CoV-2-positive adolescents. A single 50 µg dose of bivalent BA.4 and BA.5 variant-containing mRNA-1273.222 vaccine elicited a robust neutralising antibody response and was well tolerated, with no new safety concerns or vaccine-related serious adverse events in vaccine-naive SARS-CoV-2-positive adolescents. As compared with the two-dose 100 µg mRNA-1273 primary series in SARS-CoV-2-negative young adults (historical comparator group), a single 50 µg mRNA-1273.222 dose induced superior neutralising antibody responses against omicron BA.4 and BA.5 and non-inferior neutralising antibody responses against ancestral SARS-CoV-2 in SARS-CoV-2-positive adolescents, meeting prespecified success criteria for the primary immunogenicity objective.

Implications of all the available evidence

Our study showed the safety, immunogenicity, and inferred effectiveness of a variant-containing COVID-19 vaccine administered as a single dose in previously unvaccinated SARS-CoV-2-positive adolescents. As most of the global population older than 5 years now have antibodies (from vaccination or infection, or both) against SARS-CoV-2, our findings reinforce the recommendation of the simplified single-dose vaccination schedule in these age groups, regardless of previous vaccination status.

were vaccinated with one or more doses in low-income countries versus 80% of people in high-income countries.[8] Global vaccination data also show that the number of booster vaccines administered in high-income countries is six-times greater than the number of first doses that have been administered in low-income countries.[9] The same factors affecting health inequities have led to variations in COVID-19 mortality across countries, resulting in greater COVID-19 mortality rates in low-income countries compared with high-income countries.[9,10]

As the pandemic and vaccination strategies progressed, an increasing number of people have developed antibodies against SARS-CoV-2 by way of infection or vaccination, or both.[11,12] According to the data collected by the US Centers for Disease Control and Prevention in December, 2022, the SARS-CoV-2 seroprevalence rate was about 99% among adolescents aged 12–17 years and about 95% among children aged 0–11 years.[13] Data from the 2022–23 nationwide blood donor study showed a SARS-CoV-2 seroprevalence rate of 100% among individuals aged 16–29 years during the October–December, 2023, period.[14] Real-world evidence suggests that hybrid immunity (antibodies from infection or vaccination, or from both) provides substantial protection against SARS-CoV-2 infection and severe disease.[15] Given the high SARS-CoV-2 seroprevalence among most age groups, several nations and regions have recommended a simplified COVID-19 vaccination schedule (single dose administered in advance of the SARS-CoV-2 season) for individuals aged 5 years and older.[16,17]

Bivalent mRNA-1273.222 contains sequences for the SARS-CoV-2 ancestral strain Wuhan-Hu-1 and omicron strains BA.4 and BA.5, and induced robust immunogenicity against omicron BA.4 and BA.5 in adults when administered as a booster dose.[18] To date, clinical trial data describing the immunogenicity of a single dose regimen in unvaccinated individuals who were SARS-CoV-2 positive are scarce. Here, we aimed to determine the safety, reactogenicity, and immunogenicity of a single dose of mRNA-1273.222 in adolescents who were SARS-CoV-2 positive with no history of COVID-19 vaccination enrolled in the ongoing TeenCOVE trial.

Methods

Study design

TeenCOVE is an ongoing phase 2/3 study that consists of multiple parts (appendix p 5). Previous evaluations from this trial have included the safety, reactogenicity, and immunogenicity of mRNA-1273 100 µg as a two-dose primary series (parts 1A and 1B)[19] and mRNA-1273 50 µg as a booster dose (part 1C) in healthy adolescents aged 12–17 years.[20] Part 2 was an open-label trial that enrolled healthy adolescents aged 12–17 years to receive mRNA-1273 50 µg as a two-dose primary series given 28 days apart; however, enrolment was discontinued on Aug 19, 2022, when updated variant vaccines were authorised for use as a booster dose. Part 3 of the TeenCOVE study is the phase 3, open-label, single-arm trial done at 16 study sites within the USA and the Dominican Republic. Part 3 was designed to evaluate the

See Online for appendix

safety, reactogenicity, and immunogenicity of a two-dose 50 µg primary series of mRNA-1273.222 administered 6 months apart in healthy, vaccine-naive adolescents.

The study was done according to the study protocol, applicable laws and regulatory requirements, and the ethical principles outlined by the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical guidelines, all Good Clinical Practice guidelines of the International Council for Harmonisation, and all applicable regulatory requirements. The study protocol and any amendments were approved by the institutional review board before study initiation. All participants provided written informed consent. This study is registered with ClinicalTrials.gov (NCT04649151).

Participants

Vaccine-naive adolescents from the Dominican Republic and the USA who were considered in good general health by the study investigators were eligible for enrolment. Participants were excluded if they were pregnant or breastfeeding, had an acute illness or fever 24 h before or at screening, had been previously administered an investigational or approved vaccine against SARS-CoV-2, or were receiving current treatment with investigational agents for prophylaxis against COVID-19. Inclusion and exclusion criteria are described in the appendix (pp 2–3). SARS-CoV-2 status of participants was evaluated by serology and RT-PCR before vaccine administration. Results were considered positive if there was immunological or virological evidence of previous SARS-CoV-2 infection, defined as a positive RT-PCR test or positive Roche Elecsys (Roche Diagnostics, Indianapolis, IN, USA) serology test result, whereas results were considered negative if there was a negative RT-PCR test and negative Elecsys result at day 1.

Randomisation and masking

Randomisation and masking were not applicable, as part 3 of the TeenCOVE trial was a single-arm, open-label study.

Procedure

mRNA-1273.222 contains 25 µg each of two mRNAs encoding the stabilised prefusion spike protein of SARS-CoV-2 (Wuhan-Hu-1 [ancestral strain] and omicron subvariants BA.4 and BA.5). The vaccine was provided as a sterile liquid at a concentration of 0·1 mg/mL and administered as a single intramuscular injection of 0·5 mL (50 µg) into the deltoid muscle. Participants were monitored for 6 months after vaccination, with a planned interim analysis of immunogenicity and safety at day 29 (28 days after mRNA-1273.222 vaccination). Here, we report the day 29 safety, reactogenicity, and immunogenicity interim results from participants who received a single 50 µg dose of mRNA1273.222.

Outcomes

The primary outcomes were safety and reactogenicity of mRNA-1273.222 50 µg and inferred effectiveness of mRNA-1273.222 50 µg achieved by establishing superiority (omicron BA.4 and BA.5) and non-inferiority (ancestral D614G strain) of the antibody responses to SARS-CoV-2 28 days after dose 1 in adolescents with baseline evidence of previous SARS-CoV-2 infection compared with those obtained 28 days after dose 2 of the 100 µg mRNA-1273 primary series in baseline SARS-CoV-2-negative young adults enrolled in the COVE trial (NCT04470427), in which efficacy was previously shown.[21] Inference of mRNA-1273.222 effectiveness was based on an immunobridging approach that compares immune responses elicited by the variant-updated vaccine to those generated by the prototype vaccine with established clinical efficacy.[22] This approach provides an indirect measure of vaccine effectiveness for the prevention of COVID-19 after vaccination.

Seroresponse rates against omicron BA.4 and BA.5 and the ancestral strain 28 days after a single dose of mRNA-1273.222 50 µg were evaluated as a secondary descriptive outcome. Other secondary outcomes prespecified in the protocol included immune response 28 days after dose 2 against omicron BA.4 and BA.5 and the ancestral strain, and immune response against other variants of interest 28 days after dose 1 and dose 2. This study presents interim analysis data for primary and secondary outcomes (immunogenicity against the ancestral strain [D614G] and BA.4 and BA.5 strains) 28 days after a single dose of mRNA-1273.222. Analysis of immune response after dose 2 against the ancestral strain (D614G) and omicron BA.4 and BA.5 strains will be reported in due course. Analysis of immune response against other variants of interest was not done because the pseudovirus neutralisation assays used were specific to the variants contained in mRNA-1273.222 (ancestral and BA.4 and BA.5 strains) and assays specific to emerging variants of interest (such as XBB.1.5) were not available. However, a separate study in adult participants is planned to evaluate the immunogenicity of variant-containing formulations against more recent variants of interest.

Safety assessments included local (ie, pain, erythema, swelling, and axillary swelling or tenderness) and systemic (ie, fever, headache, fatigue, myalgia, arthralgia, nausea or vomiting, and chills) solicited adverse reactions (appendix p 4) up to 7 days after vaccination (ie, the day of injection and 6 subsequent days), unsolicited adverse events up to 28 days after vaccination, as well as serious adverse events, adverse events of special interest, medically attended adverse events, and adverse events leading to study discontinuation from day 1 through the end of the study. Day 29 safety data as of the analysis cutoff date (June 5, 2023) are reported here. An eDiary was used to solicit daily participant reporting

of adverse reactions using a structured checklist on the day of injection and for the 6 days after the day of vaccination. The unsolicited adverse events, serious adverse events, adverse events of special interest, and medically attended adverse events were recorded in the electronic case report form at each study visit or telephone contact.

Immunogenicity was assessed using serum samples from SARS-CoV-2-positive adolescents collected at baseline (day 1) and 28 days after mRNA-1273.222 vaccination; historical serum samples from baseline SARS-CoV-2-negative young adults (from the COVE trial) collected 28 days after dose 2 of the mRNA-1273 100 µg primary series were also evaluated. Contemporaneous evaluations of immunogenicity samples from adolescents and young adults were done at PPD Laboratories (Waltham, MA, USA) using validated pseudovirus neutralisation assays[23] measuring neutralising antibodies (nAbs) against BA.4/BA.5 spike protein or D614G. Primary endpoints were geometric mean concentrations (GMCs) of nAbs at 28 days after dose 1 of mRNA-1273.222 (baseline SARS-CoV-2-positive adolescents) compared with 28 days after dose 2 of mRNA-1273 (baseline SARS-CoV-2-negative young adults) to determine superiority of mRNA-1273.222 against omicron BA.4/BA.5 and non-inferiority against the ancestral (D614G) strain. The seroresponse rates against BA.4/BA.5 and D614G were evaluated as secondary endpoints.

Statistical analysis

With a sample size of at least 300 participants who received mRNA-1273.222 50 µg, the trial had at least a 95% probability of observing at least one participant with an adverse event at a true adverse event rate of 1%. An approximate total of 168 participants in the per-protocol immunogenicity subset who were SARS-CoV-2 positive at baseline and 300 young adults who were SARS-CoV-2 negative at baseline from the COVE trial were needed to provide more than 90% power at a one-sided α of 0·025 to show the superiority of the serum nAb GMC against omicron BA.4 and BA.5 (using a geometric mean ratio [GMR] superiority margin of 1·0 and assuming a true GMR of 1·6) and non-inferiority of the serum nAb GMC against D614G (using a GMR non-inferiority margin of 1·5 [1/1·5=0·667] and assuming a true GMR of 1·1). The standard deviation of the natural log-transformed levels of antibodies was assumed to be 1·5.

Immunogenicity in adolescents was assessed in the per-protocol immunogenicity subset who were SARS-CoV-2 positive at baseline, which included all participants who received the planned dose of study vaccination, had a day 29 antibody assessment, had no major protocol deviations, and had serological or virological evidence of previous SARS-CoV-2 infection at baseline. Immunogenicity in young adults from the COVE trial was assessed in the per-protocol immunogenicity subset, which included young adults aged 18–25 years who received two doses of the mRNA-1273 primary series per schedule, had a day 57 assessment, had no major protocol deviations, and had no serological or virological evidence of previous SARS-CoV-2 infection at baseline.

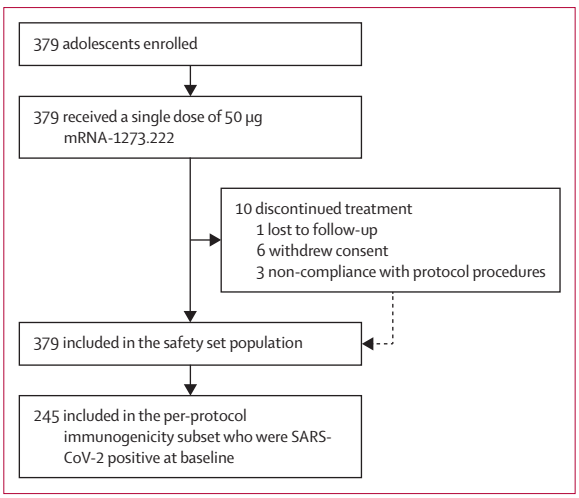

Figure 1: **Trial profile**
The safety analysis set included all participants who received at least one dose of study vaccine. The per-protocol immunogenicity subset included participants who received a planned dose per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that affect key or crucial data, with baseline negative or positive SARS-CoV-2. The per-protocol immunogenicity subset included 247 participants who received dose 1 of mRNA-1273.222, and had baseline (before dose 1) and at least one post-injection antibody assessment at day 29; one participant was excluded from this subset due to a major protocol deviation (did not meet inclusion criteria for BMI). Of the resulting 246 participants in this subset, 245 were SARS-CoV-2 positive at baseline.

nAb GMCs and geometric mean fold rise and the corresponding confidence intervals were calculated with the Student's *t* distribution on log-transformed data and then back-transformed. To determine the superiority against omicron BA.4 and BA.5 and non-inferiority against the ancestral D614G strain of a single dose of mRNA-1273.222 compared with two doses of mRNA-1273, an ANCOVA model was carried out with nAb value at 28 days after dose 1 (present study) and after dose 2 (mRNA-1273 primary series in baseline SARS-CoV-2-negative young adults in COVE) as the dependent variable and study vaccine group (mRNA-1273.222 single dose in baseline SARS-CoV-2-positive adolescents and two doses of mRNA-1273 in baseline SARS-CoV-2-negative young adults) as the fixed variable. A corresponding two-sided 95% CI of GMR estimated from the ANCOVA model was used to assess the difference in immune response in both groups. The superiority of the immune response to mRNA-1273.222 against omicron BA.4 and BA.5 compared with that of mRNA-1273 was declared if the respective GMR 95% CI lower bound was more than 1. The non-inferiority of immune response to mRNA-1273.222 against the ancestral strain compared with that of mRNA-1273 was

	Single dose of mRNA-1273.222 50 µg		Two doses of mRNA-1273 100 µg (per-protocol immunogenicity subset [n=296])
	Safety set (n=379)	Per-protocol immunogenicity subset with baseline SARS-CoV-2 positive status (n=245)	
Age, years	14 (12–15)	14 (12–15)	23 (21–24)
Sex			
Female	179 (47%)	114 (47%)	153 (52%)
Male	200 (53%)	131 (53%)	143 (48%)
Race			
White	39 (10%)	35 (14%)	207 (70%)
Black	122 (32%)	83 (34%)	29 (10%)
Asian	0	0	30 (10%)
American Indian or Alaska Native	0	0	3 (1%)
Native Hawaiian or other Pacific Islander	0	0	2 (1%)
Multiracial	3 (1%)	2 (1%)	14 (5%)
Other*	215 (57%)	125 (51%)	8 (3%)
Not reported	0	0	3 (1%)
Ethnicity			
Hispanic or Latino	358 (94%)	231 (94%)	78 (26%)
Not Hispanic or Latino	21 (6%)	14 (6%)	216 (73%)
Unknown	0	0	2 (1%)
Country			
USA	54 (14%)	44 (18%)	296 (100%)
Dominican Republic	325 (86%)	201 (82%)	0
Baseline RT-PCR results			
Negative	315 (83%)	186 (76%)	296 (100%)
Positive	2 (1%)	0	0
Missing	62 (16%)	59 (24%)	0
Baseline Elecsys anti-SARS-CoV-2 results			
Negative	1 (<1%)	0	296 (100%)
Positive	378 (>99%)	245 (100%)	0
Baseline SARS-CoV-2 status†			
Negative	1 (<1%)	0	296 (100%)
Positive	378 (>99%)	245 (100%)	0

Data are median (IQR) or n (%). Percentages might not add up to 100% due to rounding. Data from the safety set include all participants who received any injection of mRNA-1273.222. *Includes those of mixed or Caribbean ancestry. †Positive if there was immunological or virological evidence of previous COVID-19, defined as positive RT-PCR test or positive Roche Elecsys serology test result at day 1; negative was defined as negative RT-PCR test and negative Elecsys result at day 1.

Table 1: **Participant demographics for the safety set**

declared if the respective GMR 95% CI lower bound was more than 0·667. The seroresponse rate was computed with two-sided 95% CIs using the Clopper–Pearson method, and the seroresponse rate difference with two-sided 95% CI was calculated using the Miettinen–Nurminen method. Seroresponse was defined as antibody measures change from baseline (before dose 1) below the lower limit of quantification (LLOQ) to ≥4×LLOQ or at least a four-fold rise if baseline (before dose 1) was greater than or equal to LLOQ.

Continuous variables were summarised using descriptive summary statistics, and categorical variables were summarised using counts and percentages. Safety was evaluated in the safety set that included all participants who received any dose of mRNA-1273.222 regardless of baseline SARS-CoV-2 status (378 who were SARS-CoV-2 positive, and one who was SARS-CoV-2 negative), and the solicited safety set which included all participants who received any dose of mRNA-1273.222 and contributed any solicited adverse reaction data after injection. Safety was descriptively summarised by the number and percentage of participants with events.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

From enrolment to data cutoff for the interim analysis, between Dec 21, 2022, and June 5, 2023, 379 adolescents were enrolled in part 3 of this study and received a single 50 µg dose of mRNA-1273.222 (figure 1). The median age of participants was 14 years (range 12–17) and most participants (358 [94%] of 379) were Hispanic or Latino (table 1). At the day 29 analysis, participants had been followed up for a median of 35 days (range 4–167) after vaccination. Ten (3%) of 379 participants discontinued the study, due to either withdrawal of consent (n=6), lost to follow-up (n=1), or non-compliance with protocol procedures (n=3). As expected, all enrolled participants except one (378 [>99%] of 379) were SARS-CoV-2 positive at baseline (had immunological or virological evidence of previous COVID-19).

229 (61%) of 378 participants (95% CI 56–66) reported any solicited adverse reactions within 7 days of the single mRNA-1273.222 vaccination. Solicited adverse reactions were primarily grade 1 or grade 2 in severity, with 25 (7%) of 378 participants reporting grade 3 events and one (<1%) reporting a grade 4 event. Any solicited local adverse reactions were reported by 169 (45%) of 378 mRNA1273.222 recipients (95% CI 40–50), the majority of which were grade 1 (141 [37%]) or grade 2 (18 [5%]); grade 3 events were reported by ten (3%) participants, and no grade 4 events were reported (figure 2A). Pain (161 [43%] of 378) and axillary swelling or tenderness (43 [11%]) were most common. Any solicited systemic adverse reactions were reported by 150 (40%) of 378 participants (95% CI 35–45); the most common were headache (104 [28%]), myalgia (59 [16%]), and fatigue (46 [12%]). 16 (4%) of 378 participants had grade 3 solicited systemic adverse reactions, including ten (3%) who had grade 3 fever events. Most of the grade 3 fever events occurred on day 2 and day 3 after vaccination and lasted for 1 day without other concurrent systemic adverse reactions or unsolicited adverse events. One (<1%) of 378 participants who had grade 4 solicited

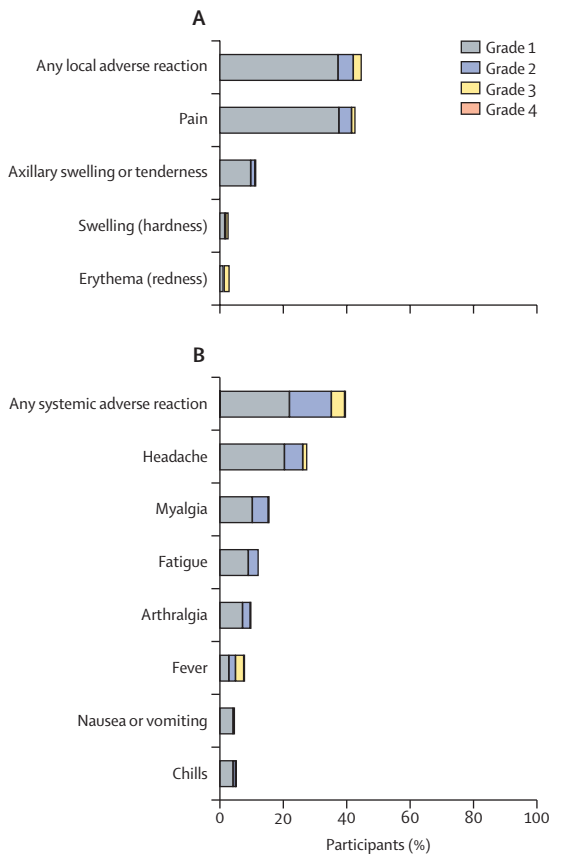

Figure 2: **Summary of solicited adverse reactions within 7 days after mRNA-1273.222 vaccination**

(A) Local solicited adverse reactions. (B) Systemic solicited adverse reactions. Severity grading of adverse reactions is based on the Department of Health and Human Services' 2007 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. Details on reactogenicity severity grading are in the appendix (p 4). Percentages of participants in the solicited safety set (n=378) included all participants who received any injection of mRNA-1273.222 and contributed any solicited adverse reaction data after injection.

	mRNA-1273.222 50 µg (n=379)
Any unsolicited TEAEs	49 (13%)
Severe	3 (1%)
Serious	2 (1%)
Fatal	0
Of special interest*	0
Medically attended	36 (9%)
Leading to study discontinuation	0
Any unsolicited TEAEs related to study vaccination	14 (4%)
Severe	1 (<1%)
Serious	0
Fatal	0
Of special interest*	0
Medically attended	7 (2%)
Leading to study discontinuation	0

Data are n (%). Percentages might not add up to 100% due to rounding. Data from the safety set include all participants who received any injection of mRNA-1273.222. TEAEs=treatment-emergent adverse events. *TEAEs of special interest include anosmia, ageusia, subacute thyroiditis, acute pancreatitis, appendicitis, rhabdomyolysis, acute respiratory distress syndrome, coagulation disorders, acute cardiovascular injury, acute kidney injury, acute liver injury, dermatological findings, multisystem inflammatory disorders, thrombocytopenia, acute aseptic arthritis, new onset of or worsening of neurological disease, and anaphylaxis.

Table 2: **Summary of unsolicited treatment-emergent adverse events up to 28 days after vaccination, safety set**

adverse reactions of fever reported a temperature of 40·5°C on day 5 after vaccination, and at the illness visit, had a concurrent adverse event of lower respiratory tract infection (figure 2B).

Within 28 days after vaccination, unsolicited adverse events were reported by 49 (13%) of 379 participants, including 14 (4%) who's adverse events were considered as related to the study vaccine by the investigator (table 2). The most common unsolicited adverse events by system organ class were infections and infestations (20 [5%] of 379), nervous system disorders (11 [3%]), and general disorders and administration site conditions (11 [3%]). Of the 11 unsolicited adverse events reported under nervous system disorders, six (55%) were considered by the investigator to be related to the vaccine (dizziness occurring within a few hours after vaccination that resolved within 20 min, n=1; and headache with onset within 7 days of vaccination, n=5). Two (1%) of 379 participants reported serious adverse events, neither of which were considered by the investigator as related to the vaccine (hypertension approximately 30 min after vaccination, n=1; and worsening of depression 27 days after vaccination, n=1). Medically attended adverse events were reported by 36 (9%) of 379 participants, including seven (2%) who's adverse events were assessed as vaccine-related by the investigator (all of which occurred within 7 days of injection). Of the three (1%) of 379 participants who reported grade 3 events, one event (pyrexia) was considered related by the investigator, described previously as a grade 4 solicited systemic adverse reaction of fever concurrent with a lower respiratory tract infection. There were no reported deaths, adverse events of special interest (including myocarditis or pericarditis), or adverse events leading to study discontinuation.

At 28 days after vaccination (day 29), a single dose of mRNA-1273.222 in adolescents who were SARS-CoV-2 positive at baseline induced an 18-fold increase from baseline in nAb GMC levels against omicron BA.4 and BA.5 (figure 3; table 3). The nAb GMC against BA.4 and BA.5 was 2771·0 (95% CI 2500·8–3070·3) after a single dose of mRNA-1273.222 in adolescents who were SARS-CoV-2 positive at baseline, which was higher than levels induced 28 days after the two-dose mRNA-1273 primary series (day 57) in young adults who were SARS-CoV-2 negative at baseline in the COVE trial (GMC 56·6 [95% CI 54·5–58·8]). Of note, the nAb levels against

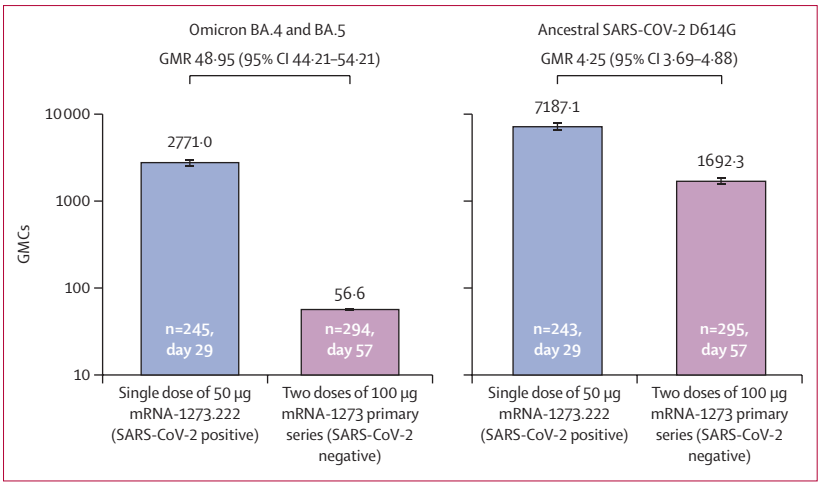

***Figure 3*: Serum neutralising antibody levels against omicron BA.4 and BA.5 and ancestral SARS-CoV-2 strain D614G after vaccination in previously unvaccinated adolescents who were baseline SARS-CoV-2 positive and in young adults who were baseline SARS-CoV-2 negative**

Pseudovirus neutralising antibody GMCs against BA.4 and BA.5 or ancestral D614G are shown at day 29 in SARS-CoV-2-positive adolescents and at day 57 in SARS-CoV-2-negative young adults. GMC data from participants with non-missing data at baseline and the corresponding post-vaccination timepoints are shown. GMRs of ANCOVA-modelled GMCs ($GMC_{mRNA\text{-}1273.222}/GMC_{mRNA\text{-}1273}$) are shown above the respective bar plot. Antibody values reported as below the LLOQ were replaced by 0·5 × LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available. VAC137 neutralising antibody assay (LLOQ: 103, ULOQ: 110592) was used for omicron BA.4 and BA.5 and VAC62 neutralising antibody assay (LLOQ: 10, ULOQ: 111433) was used for ancestral SARS-CoV-2. GMC=geometric mean concentration. GMR=geometric mean ratio. LLOQ=lower limit of quantification. ULOQ=upper limit of quantification.

BA.4 and BA.5 were below the LLOQ at baseline for all young adult participants in the COVE trial and for most young adults at day 57. Values reported below the LLOQ were imputed to a value of 51·5 (prespecified in the statistical analysis plan to be imputed to 0·5×LLOQ). In a comparison of the nAb GMCs against BA.4 and BA.5 in adolescents (day 29) with those in young adults in the COVE trial (day 57), the estimated GMR was 48·95 (95% CI 44·21–54·21), meeting the prespecified superiority criterion for the immunogenicity against BA.4 and BA.5. The seroresponse rate against BA.4 and BA.5 was 94·7% (95% CI 91·1–97·1) at day 29 after mRNA-1273.222 vaccination in adolescents who were SARS-CoV-2 positive at baseline; comparatively, none of the young adult participants who were SARS-CoV-2 negative at baseline in the COVE trial had seroresponse against BA.4 and BA.5 28 days after dose 2 of mRNA-1273, resulting in a seroresponse rate difference of 94·7% (95% CI 91·1–96·9).

At 28 days after vaccination, a single dose of mRNA-1273.222 in adolescents who were SARS-CoV-2 positive at baseline induced a 13·6-fold increase in the nAb levels against the ancestral strain compared with baseline levels (table 3). The nAb GMC against the ancestral strain was 7187·0 (95% CI 6495·3–7952·7) 28 days after dose 1 of mRNA-1273.222 in adolescents who were SARS-CoV-2 positive at baseline, compared with 1692·3 (1537·4–1862·7) 28 days after dose 2 of mRNA-1273 in young adults who were SARS-CoV-2 negative at baseline. The estimated GMR of the day 29 GMC in the current trial compared with the day 57 GMC in young adults in the COVE trial was 4·25 (95% CI 3·69–4·88), meeting the prespecified non-inferiority criterion for immunogenicity against the ancestral strain (figure 3; table 3). Day 29 seroresponse rate against the ancestral strain was 94·6% (95% CI 91·0–97·1) after mRNA-1273.222 in adolescents who were SARS-CoV-2 positive at baseline, compared with 99·3% (97·6–99·9) at 28 days after dose 2 of the mRNA-1273 primary series in young adults who were SARS-CoV-2 negative at baseline; the difference in seroresponse rate was –4·7% (95% CI –8·4 to –2·1).

The nAb levels against both the omicron BA.4 and BA.5 variants and the ancestral strain following a single dose of mRNA-1273.222 were similar across various subgroups including sex, race, ethnicity, BMI, and country, even though the sample sizes were small in some subgroups.

Discussion

Previous reports from the TeenCOVE study have shown the safety, efficacy, and durable (up to 1 year) immunogenicity of a two-dose primary mRNA-1273 vaccination series in adolescents aged 12–17 years who had no serological or virological evidence of SARS-CoV-2 infection throughout the study.[19,24] Additionally, a two-dose primary series elicited robust immune responses in adolescent participants who had serological or virological evidence of a previous SARS-CoV-2 infection at baseline.[24] Part 3 of the TeenCOVE study is among the first clinical trials to evaluate the safety and immunogenicity of a single-dose regimen of a variant-containing mRNA COVID-19 vaccine in previously unvaccinated individuals. A single 50 µg dose of the mRNA-1273.222 vaccine in previously unvaccinated, SARS-CoV-2-positive adolescents (immunological or virological evidence of previous COVID-19) was well tolerated, with a favourable safety and tolerability profile, and elicited strong nAb responses that were superior (omicron BA.4 and BA.5 variants) or non-inferior (ancestral D614G strain) to the original mRNA-1273 vaccine series administered to young adults in the COVE trial, in which vaccine efficacy was established.[21] The current study provides evidence for the inferred effectiveness of a single 50 µg injection in populations with high SARS-CoV-2 seroprevalence, thereby supporting the recent recommendations for a simplified single-dose vaccination schedule in the USA and other countries.[16,17] In this recent (2023–24) recommendation, a monovalent omicron XBB.1.5 variant vaccine was recommended as a single dose in people aged 5 years and older regardless of previous vaccination.[16,17]

In the current study, most of the vaccine-naive population enrolled were seropositive at baseline (before dose 1), which is in line with current seroepidemiology data for the general population.[13,14] In the USA, the majority of

	Omicron BA.4 and BA.5		Ancestral SARS-CoV-2 D614G	
	Adolescents given mRNA-1273.222, single dose (n=245)	Young adults given mRNA-1273, primary series (n=296)	Adolescents given mRNA-1273.222, single dose (n=245)	Young adults given mRNA-1273, primary series (n=296)
Predose baseline, day 1‡	245	296	243	296
GMC (95% CI)§	153·5 (137·2–171·9)	51·5 (not evaluable)	534·9 (461·4–620·2)	8·5 (8·0–9·0)
Day 29 after mRNA-1273.222 or day 57 after primary series‡	245	294	243	295
GMC (95% CI)§	2771·0 (2500·8–3070·3)	56·6 (54·5–58·8)	7187·1 (6495·3–7952·7)	1692·3 (1537·4–1862·7)
GMFR (95% CI)§	18·0 (15·8–20·6)	1·1 (1·1–1·1)	13·6 (12·1–15·3)	199·9 (178·5–223·8)
Seroresponse rate‡¶	232/245	0/294	228/241	293/295
Seroresponse rate, % (95% CI)‖	94·7 (91·1–97·1)	0 (0–1·2)	94·6 (91·0–97·1)	99·3 (97·6–99·9)

Data are n, unless otherwise specified. Adolescents are aged 12–17 years and young adults are aged 18–25 years. GMC=geometric mean concentration. GMFR=geometric mean fold rise. LLOQ=lower limit of quantification. ULOQ=upper limit of quantification. *Data are from the per-protocol immunogenicity subset baseline SARS-CoV-2 positive, which includes all participants who received the planned dose of study vaccination per schedule, had a day 29 antibody assessment, had no major protocol deviations, and had serological or virological evidence of SARS-CoV-2 infection at baseline. †Data are from the per-protocol immunogenicity subset, which included baseline SARS-CoV-2-negative participants. ‡Number of participants with non-missing data at baseline and at the corresponding datapoint. §95% CIs were calculated based on the *t* distribution of the log-transformed values of the difference in the log-transformed values for GMC and GMFR, respectively, then back-transformed to the original scale for presentation. ¶Antibody values reported as below the LLOQ were replaced by 0·5 × LLOQ; values greater than the ULOQ were replaced by the ULOQ if actual values were not available; VAC137 neutralising antibody assay (LLOQ: n=103; ULOQ: n=110 592) was used for omicron BA.4/BA.5 and VAC62 neutralising antibody assay (LLOQ: n=10; ULOQ: n=111433) for ancestral SARS-CoV-2. ‖95% CIs were calculated using the Clopper–Pearson method.

Table 3: **Summary of neutralising antibody responses and seroresponse rates against omicron BA.4 and BA.5 and ancestral strain D614G 28 days after a single mRNA-1273.222 dose in previously unvaccinated adolescents* positive for SARS-CoV-2 or after the two-dose mRNA-1273 primary series in adults† negative for SARS-CoV-2**

adults, children, and adolescents have evidence of immunity to SARS-CoV-2 from infection or vaccination. Data from a nationwide blood donor seroprevalence survey in the USA, based on about 143 000 blood donors (aged 16 years or older), estimated that the overall SARS-CoV-2 seroprevalence rate due to vaccination or infection was 98·9% between October and December, 2023;[14] the corresponding SARS-CoV-2 seroprevalence rates were about 98·9% in adolescents aged 12–17 years and about 94·6% among children aged 0–11 years in December, 2022.[13] Globally, the seroprevalence of SARS-CoV-2 was estimated to be 59·2% (95% CI 56·1–62·2%) by September, 2021, and 13·5% (10·6–16·6) in children aged 5–9 years by the end of 2021; during the sixth wave, SARS-CoV-2 seroprevalence in young people aged 0–19 years was 56·7% (52·8–60·5).[11,12] Real-world studies have shown that hybrid immunity (induced by a combination of vaccination and infection) confers substantial protection against reinfection, hospitalisation, and severe illness.[15] Overall, although natural infection invokes a diverse immune response to multiple antigenic sites on the virus,[25] vaccination confers immunity by eliciting antibodies specifically targeting the SARS-CoV-2 spike antigens,[21] which are important for effectively preventing infection and are associated with better patient survival.[25,26] The original COVID-19 vaccine, mRNA-1273, was designed to provide protective immunity against the ancestral strain of SARS-CoV-2 and was highly effective in reducing COVID-19 morbidity and mortality.[27] However, the emergence of omicron subvariants containing more than 30 mutations in the SARS-CoV-2 spike protein[28] has led to the need for variant-updated vaccines.[29] In light of the continued genetic evolution of the SARS-CoV-2 virus, as well as the risks and complications associated with COVID-19 infection, our data highlight the ability of a variant-containing vaccine to provide potent, updated immune responses with a single dose in participants regardless of previous COVID-19 vaccination status, including those not previously vaccinated. Vaccine efficacy has previously been shown[19,21,30] or inferred by immunobridging across mRNA-1273 vaccine studies, including previous variant-containing vaccines.[18,31,32] In addition, immunogenicity was shown for variant-updated vaccine formulations containing a strain more closely matched to the circulating variant.[18,31,32] Thus, the benefits observed for the mRNA-123.222 in the present study are likely to extend to future variant-containing vaccines. Continued monitoring of neutralisation and vaccine effectiveness of mRNA variant-containing vaccines against future emerging variants is essential as it will guide the development of future vaccination strategies against COVID-19.

In addition, our data underscore the importance of continued and uninterrupted access to COVID-19 vaccines in children and adolescents, as vaccination remains a key strategy to reduce severe illness in this age group.[2] The current study enrolled unvaccinated participants, most of whom had a recent SARS-CoV-2 infection at baseline (before dose 1). Data from national immunisation surveys done in the USA have shown that a substantial proportion of children and adolescents have either not received any COVID-19 vaccination (48% from the US National Immunization Survey–Child COVID Module, December 2023 data) or have not been up to

date with the updated 2023–24 COVID-19 vaccine (86% from the same US survey, May 2024 data).[33] Thus, a substantial proportion of adolescents remain at high risk for COVID-19 and its associated complications.

Overall, a single dose of the variant-containing vaccine was well tolerated, with overall lower reactogenicity (any solicited reaction: 60·6%) than the original mRNA-1273 primary series (97·1%).[19] Overall, the rates of grade 3 and grade 4 solicited systemic adverse reactions of fever in this analysis (2·6% and 0·3%) were comparable to those previously reported in adolescents after the second dose of the mRNA-1273 primary series (1·9% and <0·1%).[19] Rates of nervous system disorders in this analysis (2·9%) were generally similar to those previously reported in adults after any dose of the mRNA-1273 primary series (4·5%).[21] No new safety concerns were identified, with no vaccine-related serious treatment-emergent adverse events or trial discontinuations due to an adverse event.

Limitations of this study include the open-label study design, lack of live virus neutralising antibody and cellular immune response data, and the short follow-up time of participants. In addition, the comparator group consisted mostly of White non-Hispanic or Latino, seronegative young adult participants compared with the mostly Hispanic or Latino, seropositive adolescents in the current study. However, these differences in the race and ethnicity background between the two groups had no effect on mRNA-1273.222 immunogenicity in the current trial, consistent with previous reports for mRNA-1273.[34] In addition, in previous studies of the Moderna COVID-19 vaccine, no effect on the efficacy and safety of mRNA-1273 has been observed based on race and ethnicity.[34,35] The comparator group was also enrolled at a different time period[21] when the original SARS-CoV-2 strain was still circulating, thus, they might have had a different immunity profile. However, the young adult cohort was selected as a comparator for immune responses in adolescents for immunobridging, as they were enrolled in the pivotal COVE study in which vaccine efficacy was shown. Blood samples were also tested simultaneously for immunogenicity assessments, reducing the limitation of potential assay variability. Furthermore, the effect of breakthrough infections on day 29 immunogenicity was not assessed. However, participants included in the immunogenicity analysis had to have evidence of recent infection before vaccination on day 1 as determined by the Roche Elecsys test (anti SARS-CoV-2 nucleocapsid protein antibody test) or RT-PCR test, or by both; as such, the likelihood of reinfection 28 days after vaccination is likely to be low. The current report also does not include data on immunogenicity against more recent SARS-CoV-2 variants; however, this will be evaluated in a separate study. The antibody persistence following single-dose variant-containing mRNA vaccination, which will be crucial for characterising long-term protection with this vaccination strategy, was also not assessed in the current report; these data are being evaluated and will be reported in due course.

In conclusion, a single dose of mRNA-1273.222 in vaccine-naive SARS-CoV-2-positive adolescents aged 12–17 years had a similar safety profile to the original version of mRNA-1273 vaccine and was immunogenic against omicron BA.4 and BA.5 and ancestral D614G. Vaccine effectiveness against COVID-19 was further shown by the successful immunobridging to the two-dose mRNA-1273 primary series in young adults. Considering the high SARS-CoV-2 seroprevalence rates among most populations older than 5 years, these findings reinforce the recommendation of a single-dose variant mRNA vaccine in these age groups regardless of previous vaccination status.

Contributors

ALF, WD, JMM, and RD made substantial contributions to the concept design. ALF, DT, WD, YS, GC, BG, CR-A, PM, and RD collected the data. ALF, AY, WD, WX, GC, JMM, RD, CR-A, and FP analysed and interpreted the data. MO was involved in the writing and critical review of the manuscript. WD and WX directly accessed and verified the underlying data reported in the Article. All authors critically reviewed the paper for important intellectual content and approved the final draft of the manuscript. ALF verifies that all authors had full access to the data in the study and accept responsibility to submit for publication.

Declaration of interests

ALF, WD, WX, YS, GC, MO, BG, JMM, RD, and FP are employees of Moderna, and hold stock or stock options in the company. FP served on the scientific advisory board of CEPI from June, 2021, to June, 2023. AY is a consultant for Moderna. DT, CR-A, and PM declare no competing interests.

Data sharing

As the trial is ongoing, access to patient-level data presented in the Article and supporting clinical documents by qualified external researchers who provide methodologically sound scientific proposals might be available upon reasonable request for products or indications that have been approved by regulators in the relevant markets and are subject to review from 24 months after study completion. Such requests can be made to Moderna at data_sharing@modernatx.com. A materials transfer or data access agreement with the sponsor will be required for accessing shared data. All other relevant data are presented in the paper. The protocol is available online at ClinicalTrials.gov (NCT04649151).

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