Efficacy, immunogenicity, and safety of a next-generation mRNA-1283 COVID-19 vaccine compared with the mRNA-1273 vaccine (NextCOVE): results from a phase 3, randomised, observer-blind, active-controlled trial

Spyros Chalkias, Patrick Dennis, Dena Petersen, Krishnakumar Radhakrishnan, Leroy Vaughan, Reem Handforth, Alexandra Rossi, Rahnuma Wahid, Darin K Edwards, Jing Feng, Weiping Deng, Honghong Zhou, Elizabeth De Windt, Veronica Urdaneta, Yamuna Paila, Bethany Girard, Saul N Faust, Stephen R Walsh, Catherine A Cosgrove, Jacqueline Miller, Rituparna Das

Summary

Background mRNA-1283 is an investigational, next-generation COVID-19 vaccine that encodes only the immunodominant regions of the SARS-CoV-2 spike protein—the receptor-binding domain (RBD) and the N-terminal domain rather than the full-length spike used in currently authorised mRNA vaccines. We evaluated the relative vaccine efficacy (rVE), immunogenicity, and safety of mRNA-1283 compared to the first-generation vaccine (mRNA-1273).

Methods This randomised, observer-masked, active-controlled, phase 3 trial (NextCOVE) was conducted in individuals (aged ≥12 years) with no evidence of SARS-CoV-2 infection within 90 days of screening in the USA, the UK, and Canada. Participants were randomly assigned in a 1:1 ratio to receive one 10 µg dose of the bivalent formulation of mRNA-1283 (original plus omicron BA.4/BA.5) or 50 µg of the bivalent mRNA-1273, encoding the same variants. Randomisation was stratified by age (12–17 years, 18–64 years, and ≥65 years). Primary objectives comparing mRNA-1283 with mRNA-1273 were non-inferior rVE to prevent a first event of COVID-19 from 14 days after study injection to the end of follow-up (assessed in the per-protocol set for efficacy, with non-inferiority declared when the lower bound of the α-adjusted two-sided CI for rVE was greater than –10%), non-inferior immunogenicity at day 29 (assessed in the per-protocol immunogenicity subset, with non-inferiority declared when the lower bounds of the CIs for the geometric mean concentration ratios [GMRs] of neutralising antibodies against SARS-CoV-2 D614G and omicron BA.4/BA.5 were >0·667 and the lower bounds of the 95% CI seroresponse rate differences for the two variants were greater than –10%), and safety (assessed in the safety set, which included all participants who received a vaccination). The trial is registered at ClinicalTrials.gov (NCT05815498) and is complete.

Findings Between March 28 and Aug 23, 2023, we screened 13 054 individuals for eligibility and randomly allocated 11 454 participants (5728 to mRNA-1283 and 5726 to mRNA-1273). 1177 confirmed COVID-19 events occurred up to Jan 31, 2024 (560 [9·9%] of 5679 in mRNA1283.222 and 617 [10·8%] of 5687 in mRNA-1273.222). The median age of participants at enrolment was 56 years (IQR 38–66). Of the 11 417 participants who received a vaccine, 6200 (54·3%) were female and 5217 (45·7%) were male; 9381 (82·2%) were White; and 1510 (13·2%) were Hispanic or Latino. Of the total cohort, 992 (8·7%) participants were aged 12–17 years, 7151 (62·6%) were aged 18–64 years, and 3274 (28·7%) were 65 years and older; in addition, 6857 participants (60·1%) were 50 years and older. The rVE point estimate was 9·3% (99·4% CI –6·6 to 22·8; p=0·0005). The GMR was 1·3 (95% CI 1·2 to 1·5) for BA.4/BA.5 and 1·2 (1·1 to 1·4) for D614G. The day-29 seroresponse rate difference was 14·4% (95% CI 9·3 to 19·4) for BA.4/BA.5 and 10·7% (6·0 to 15·4) for D614G. Local and systemic adverse reactions were similar between mRNA-1283 and mRNA-1273; mRNA-1283 was associated with fewer injection-site pain reactions than mRNA-1273 (3905 [68·5%] of 5701 *vs* 4419 [77·5%] of 5705, respectively). The frequency of unsolicited adverse events, serious adverse events, and medically attended adverse events were similar between groups during the first 28 days after injection. One event of sudden death occurred in a participant with underlying cardiovascular disease in the mRNA-1273 group; it was reported as related to vaccination due to its temporal association.

Interpretation mRNA-1283 was well-tolerated. The rVE and immunogenicity non-inferiority criteria were met, with higher antibody responses for mRNA-1283 versus mRNA-1273. The potential clinical benefit of mRNA-1283 versus mRNA-1273 needs to be confirmed in post-marketing evaluation.

Funding Moderna.

Lancet Infect Dis 2025

Published Online July 7, 2025 https://doi.org/10.1016/S1473-3099(25)00236-1

Moderna, Cambridge, MA, USA (S Chalkias MD, A Rossi BS, R Wahid PhD, D K Edwards PhD, J Feng MS, W Deng PhD, H Zhou PhD, E De Windt MPH, V Urdaneta MD, Y Paila PhD, B Girard PhD, J Miller MD, R Das MD); **DelRicht Research, New Orleans, LA, USA** (P Dennis MD); **Noble Clinical Research, Tucson, AZ, USA** (D Petersen MD); **Panthera Biopartners Rochdale, Rochdale, UK** (K Radhakrishnan MD); **Clinical Research Partners, Richmond, VA, USA** (L Vaughan MD); **Panthera Biopartners Preston, Preston, UK** (R Handforth MD); **NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK** (S N Faust PhD); **Brigham and Women's Hospital, Boston, MA, USA** (S R Walsh); **Vaccine Institute, Centre for Neonatal and Paediatric Infection, Institute of Infection and Immunity, St George's University of London, London, UK** (C A Cosgrove PhD)

Correspondence to: Spyros Chalkias, Moderna, Cambridge, MA 02142, USA **Spyros.Chalkias@Modernatx.com**

Research in context

Evidence before this study

COVID-19 vaccines have helped mitigate the impact of COVID-19 worldwide. However, waning immunity and reduced effectiveness against antigenically divergent variants have reduced the long-term protection provided by existing vaccines. Given the ongoing public health impact of COVID-19, particularly in vulnerable populations, updated vaccination strategies are needed to sustain immune protection and reduce disease burden. A COVID-19 mRNA vaccine that encodes immunodominant neutralising antibody epitopes—the receptor-binding domain (RBD) and N-terminal domain (NTD) of the SARS-CoV-2 spike protein—has the potential to enhance immune responses and improve vaccine effectiveness compared with first-generation mRNA COVID-19 vaccines, which encode the entire spike protein. We searched PubMed for research articles published in English between Aug 14, 2020, to March 10, 2025, using the terms "SARS-CoV-2 vaccines"; "SARS-CoV-2 spike receptor binding domain"; "SARS-CoV-2 spike N-terminal domain"; "animal studies"; and "clinical trials". We identified 40 studies emphasising the immunogenicity of SARS-CoV-2 spike protein subunits, especially the RBD and, to a lesser extent, the NTD. These data support the central role of spike-directed antibodies in mediating protection against COVID-19. A range of vaccine platforms have been shown to elicit robust immune responses targeting these subunits. Recent publications also highlight the induction of neutralising antibodies and cellular immune responses, reinforcing the immunological relevance of these spike protein subunits. The spike regions outside these domains are mainly targeted by non-neutralising antibodies, considered non-protective. Additionally, animal challenge studies have shown protective responses elicited by RBD-based vaccines. We have previously published phase 1 and 2 studies evaluating the RBD and NTD-based vaccine mRNA-1283; however, no randomised, phase 3 study has evaluated the efficacy of an RBD-based and NTD-based COVID-19 vaccine.

Added value of this study

To our knowledge, this is the first randomised, observer-blind, phase 3 study evaluating the relative vaccine efficacy (rVE) of mRNA-1283 versus the original mRNA-1273 vaccine. The 10 µg dose of mRNA-1283 showed non-inferior vaccine efficacy compared with the 50 µg dose of mRNA-1273, with an rVE of 9·3% (99·4% CI −6·6 to 22·8; p=0·0005). mRNA-1283 also met non-inferiority criteria versus mRNA-1273 for the immunogenicity objectives and elicited higher neutralising antibody responses than mRNA-1273 against omicron BA.4/BA.5 and D614G based on geometric mean concentration ratios and seroresponse rate differences. mRNA-1283 was well tolerated, with the frequency of local and systemic adverse reactions similar between groups, except for pain at the injection site, where fewer reactions were reported for mRNA-1283 than mRNA-1273.

Implications of all the available evidence

The introduction of highly efficacious vaccines against SARS-CoV-2 positively affected global public health. Updated vaccine designs and immunisation strategies can further improve prevention of COVID-19. As the length of an mRNA sequence directly correlates to mRNA stability, a shorter sequence encoding for the RBD and NTD instead of the entire spike protein could translate to enhanced refrigerator stability. Enhanced refrigerator stability improves accessibility and ease of handling, as well as maintaining the integrity of the components that underpin a safe and efficacious vaccine. Our rVE and immunogenicity findings suggest that mRNA-1283 might have a clinical efficacy benefit over mRNA-1273, but further studies will be needed to confirm the potential benefit.

Introduction

The burden of COVID-19 remains high globally,[1–3] particularly among people aged 65 years or older, who are at highest risk for admissions to hospital and severe outcomes.[4] mRNA-based COVID-19 vaccines are efficacious, and their use is associated with very rare events of myocarditis and pericarditis.[5–7] Vaccine effectiveness can decrease over time when there is a mismatch between circulating SARS-CoV-2 variants and the vaccine sequence (eg, 56% efficacy in preventing hospitalisations with omicron BA.1 compared with 83% for delta COVID-19 when using the original mRNA-1273 vaccine).[8] There is an unmet need for mRNA COVID-19 vaccines with the potential for enhanced effectiveness.

The mRNA-1283 vaccine encodes the receptor-binding domain (RBD) and the N-terminal domain (NTD) of the SARS-CoV-2 spike protein based on evidence that these domains contain immunodominant epitopes for neutralising antibodies against SARS-CoV-2.[9–11] The spike region outside these domains is primarily a target for non-neutralising antibodies.[12] mRNA-1283 was developed with the potential for enhanced immune responses and vaccine effectiveness compared with first-generation mRNA COVID-19 vaccines that encode the full-length spike protein. Additionally, the length of mRNA sequences directly correlates to mRNA stability,[13] and the shorter sequence of mRNA-1283 compared with mRNA-1273 might translate to enhanced refrigerator stability.[14]

mRNA-1283 was first evaluated in dose-ranging phase 1 and 2 studies,[15,16] where the 10 µg dose was well tolerated and exhibited higher immunogenicity compared with mRNA-1273. In our phase 3 study, NextCOVE, we aimed to evaluate the immunogenicity of mRNA-1283 versus mRNA-1273 and the relative vaccine efficacy (rVE) of mRNA-1283 compared to mRNA-1273 in preventing

COVID-19 of any clinical severity. In addition, the study aimed to evaluate the safety profile of mRNA-1283 when given as a booster dose. Here, we report the prespecified primary analysis of safety, immunogenicity, and rVE, based on COVID-19 events accrued up to Jan 31, 2024.

Methods

Study design and participants

This phase 3, randomised, observer-blind, active-controlled study enrolled participants aged 12 years and older at 196 sites, including hospitals, outpatient clinics, and research centres, in the USA, the UK, and Canada from March 23, 2023, to Aug 23, 2023. The trial was approved by an institutional review board (Advara, Columbia, MD, USA); was conducted according to the principles of the International Council for Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use, the E6(R2) Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki; and followed all national, state, and local laws or regulations. An independent data safety and monitoring board periodically reviewed study data. The trial is registered with ClinicalTrials.gov (NCT05815498) and is complete.

mRNA-1283 is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the membrane-bound NTD and RBD of the spike glycoprotein from SARS-CoV-2 strains, linked by a flexible peptide linker. Bivalent mRNA-1283.222 and mRNA-1273.222 (Spikevax, Moderna) each contain mRNAs that encode the spike glycoprotein of Wuhan-Hu-1 (D614G) and omicron BA.4/BA.5 SARS-CoV-2. mRNA-1283.222 includes two mRNAs (5 µg each in a 1:1 ratio) encoding the NTD and RBD of the spike glycoprotein for both Wuhan-Hu-1 and omicron BA.4/BA.5, while mRNA-1273.222 encodes the full prefusion-stabilised spike glycoprotein (25 µg each for Wuhan-Hu-1 and omicron BA.4/BA.5 in a 1:1 ratio). The study vaccines included the 2022–23 variant formulation recommended by the US Food and Drug Administration[17] and WHO[18] (original and omicron BA.4/BA.5 bivalent) at the time of study enrolment. The predominant circulating SARS-CoV-2 variants between April, 2023, and January, 2024 were XBB.1.5, XBB.1.16, EG.5, and JN.1.[19–21]

Eligible participants were 12 years and older, with no upper age limit. Inclusion criteria required participants to be medically stable and to have received any authorised or otherwise approved COVID-19 vaccination more than 90 days before the screening visit, with the primary series of vaccinations for participants aged 12–17 years and at least one booster dose for participants older than 18 years. Heterologous vaccine regimens were accepted. Exclusion criteria included participants with chronic diseases requiring ongoing medical intervention within the 2 months before enrolment, immunocompromising conditions or medications, or any malignancy within 5 years of screening. A positive SARS-CoV-2 lateral flow or rapid antigen or PCR test in the 90 days before screening was exclusionary; participants with previous SARS-CoV-2 infection outside this window were allowed to participate in the study. Individuals who were acutely ill or febrile 72 h before or at the screening visit were excluded. Demographic data relating to participants' sex, age, race, and ethnicity were self-reported at the time of consent (screening visit). Full inclusion and exclusion criteria are presented in the appendix (pp 8–10). All participants provided written informed consent before enrolment.

See Online for appendix

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive a single dose of mRNA-1283.222 (10 µg) or mRNA-1273.222 (50 µg) with the use of an interactive response technology system. Randomisation was stratified according to participant age (12–17 years, 18–64 years, and ≥65 years), with approximately 1000 adolescents (aged 12–17 years) and approximately 30% of participants 65 years and older. Block randomisation with a block size of six was used in each stratum for treatment assignment.

Dose preparation, administration, and accountability were performed by designated unmasked site personnel who did not participate in clinical study evaluations. The investigators, trial staff, participants, site monitors, and sponsor personnel were unaware of the trial group assignments. Opaque sleeves concealed the syringes during injection. Afterward, only masked study staff conducted assessments and interacted with participants. Randomisation codes were strictly controlled by the pharmacy, and the vaccine identity was disclosed only in emergencies. Laboratory personnel conducting immunogenicity testing remained masked to vaccine assignments throughout the study. In this ongoing trial, participants are being followed up by the trial sponsor until 12 months after injection.

Procedures

A study injection (single 0·2 mL intramuscular injection of mRNA-1283.222 [10 µg] or 0·5 mL intramuscular injection of mRNA-1273.222 [50 µg]) was administered on day 1. Baseline assessments (screening and day 1) included a full physical examination, including vital signs, height, weight, and pregnancy testing. SARS-CoV-2 status at baseline was determined by virological and serological evidence of SARS-CoV-2 infection on or before day 1; positive SARS-CoV-2 status was defined as a positive reverse transcription-PCR (RT-PCR) test for SARS-CoV-2, a positive serology test based on a binding antibody specific to SARS-CoV-2 nucleocapsid, or both; negative SARS-CoV-2 status was defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on a binding antibody specific to SARS-CoV-2 nucleocapsid. Symptom surveillance was conducted every 2 weeks using electronic diary prompts. If the participant had a qualifying

symptom, they were requested to present for an unscheduled visit for clinical evaluation and collection of respiratory samples for SARS-CoV-2 RT-PCR (appendix p 10). Symptom-directed physical examinations were performed on days 29, 91, 181, and 365 and during unscheduled or illness visits. Blood sampling for assessment of humoral immunogenicity was performed at routine clinic visits on day 1 before vaccination, and on days 29, 91, 181, and 365. Safety assessments were performed at routine clinic visits on days 29, 91, 181, and 365; additionally, safety telephone calls were conducted on days 8, 22, and 271 to assess the occurrence of adverse events, medically attended adverse events (MAAEs), serious adverse events (SAEs), adverse events of special interest (AESIs; see appendix p 14 for the full list of AESIs), adverse events leading to study withdrawal, concomitant medications associated with these effects, and any non-study vaccinations. Solicited adverse reactions were recorded using an electronic diary from day 1 through to 7 days post-vaccination. Asymptomatic SARS-CoV-2 infection was defined as absence of clinical symptoms and a positive RT-PCR test on a respiratory sample or a positive serological test for anti-nucleocapsid antibody for those participants with a negative SARS-CoV-2 status at baseline.

Neutralising antibody concentrations (geometric mean concentrations [GMCs]) were assessed with the use of validated SARS-CoV-2 spike-pseudotyped lentivirus neutralisation assays against pseudoviruses containing the SARS-CoV-2 full-length spike proteins of original SARS-CoV-2 D614G and omicron subvariants BA.4 and BA.5. Assay details are described in the appendix (pp 11–12).

Outcomes

rVE refers to a measure that compares the efficacy of one vaccine against a disease to another vaccine for the same disease, demonstrating how much more or less effective one vaccine is compared to the other. Generally, a larger rVE suggests greater efficacy. The prespecified primary efficacy objective was to demonstrate non-inferior rVE of mRNA-1283 compared with mRNA-1273 to prevent the first event of a US Centers for Disease Control and Prevention (CDC)–defined COVID-19 episode starting 14 days after the study vaccination. COVID-19 surveillance supported the primary rVE objective and was based on virological confirmation via RT-PCR of SARS-CoV-2 infection and at least one clinical symptom (CDC definition: fever [≥38°C]; chills; muscle or body aches; headache; sore throat; new or continuous cough; loss or change to sense of smell, taste, or both; shortness of breath or difficulty breathing; fatigue; congestion or runny nose; nausea, vomiting, or both; or diarrhoea). A secondary definition of COVID-19 was used for the sensitivity analysis of rVE: patients who had two or more systemic symptoms (fever, chills, myalgia, headache, sore throat, or new olfactory and taste disorders), or had one or more respiratory signs or symptoms (cough, shortness of breath, difficulty breathing, or clinical or radiographical evidence of pneumonia), and had one or more nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalised) positive for SARS-CoV-2 by RT-PCR. Assessment of the incidence of SARS-CoV-2 infection (symptomatic and asymptomatic), as well as severe COVID-19, were secondary endpoints, details of which are included in the appendix (pp 10–11). The incidence of SARS-CoV-2 infection (symptomatic and asymptomatic) was assessed up to the data cutoff (Feb 23, 2024). Severe COVID-19 was assessed up to Jan 31, 2024, and Feb 23, 2024, the data cutoff date.

The prespecified primary immunogenicity objectives were to show that neutralising antibody responses to mRNA-1283.222 were non-inferior compared with those to mRNA-1273.222 based on evaluation of the coprimary immunogenicity endpoints of geometric mean concentration ratios (GMRs) and differences in the percentages of participants with seroresponses against omicron BA.4/BA.5 and original SARS-CoV-2 D614G at day 29. Seroresponse at the participant level was defined as an antibody value change from below the lower limit of quantification (LLOQ) at baseline to four times the LLOQ or greater; a rise of four-fold or more if baseline was at the LLOQ or greater but less than four times the LLOQ; or a rise of two-fold or more if baseline was more than four times the LLOQ. Secondary immunogenicity endpoints were neutralising antibody GMCs and seroresponse rates against omicron BA.4/BA.5 and the original SARS-CoV-2 D614G at days 91, 181, and 365 after vaccination; these endpoints will be reported in a future analysis.

The primary safety objective was to evaluate the safety and reactogenicity of the 10 µg mRNA-1283.222 vaccine. Participants used an electronic diary to report solicited local and systemic adverse reactions for 7 days after injection. Unsolicited adverse events were assessed until 28 days after injection. Data on MAAEs, AESIs, SAEs, and adverse events leading to study withdrawal were collected throughout the study. Additional information is provided in the appendix (pp 12–15).

Statistical analysis

Statistical analysis methods are detailed in the appendix (pp 17–19). The per-protocol set for efficacy was used for the primary analysis of rVE and consisted of all participants in the full analysis set (all randomly allocated participants regardless of pre-booster [baseline] SARS-CoV-2 infection status who received the planned dose of investigational product) who had no major protocol deviations that affected vaccine efficacy data. rVE in the full analysis set was a sensitivity analysis. The per-protocol immunogenicity subset (PPIS) was the primary analysis population used to characterise immunogenicity. The PPIS consisted of participants from the immunogenicity subset (a random sample of

adult participants, selected in a masked way and stratified by age group; see appendix p 19 for additional details) regardless of pre-booster (baseline) SARS-CoV-2 infection status, who received the planned dose of study vaccination, had baseline and day 29 neutralising antibody data, and had no major protocol deviations that affected immunogenicity data. Safety was assessed in the safety set (all participants who received vaccination) and solicited adverse reactions were assessed in the solicited safety set (participants in the safety set who contributed solicited data).

rVE was defined as the percentage reduction in the risk ratio, and risk ratio was estimated by hazard ratio (HR) of COVID-19 (mRNA-1283 *vs* mRNA-1273; ie, 1 minus the HR) in the setting of time-to-event data and censoring. The study sample size was based on the number of COVID-19 events needed for a non-inferiority analysis of rVE, with the following initial assumptions: a true rVE of 3%, COVID-19 incidence rate of one per 100 person-months for the first 6 months after study vaccination and 1·25 per 100 person-months for the second 6 months of follow-up, and an approximate 10% dropout rate. Target sample size and power calculation are described in detail in the appendix (pp 16–17). The data safety and monitoring board reviewed interim rVE data to support sample size re-estimation. Upon reaching 700 accrued

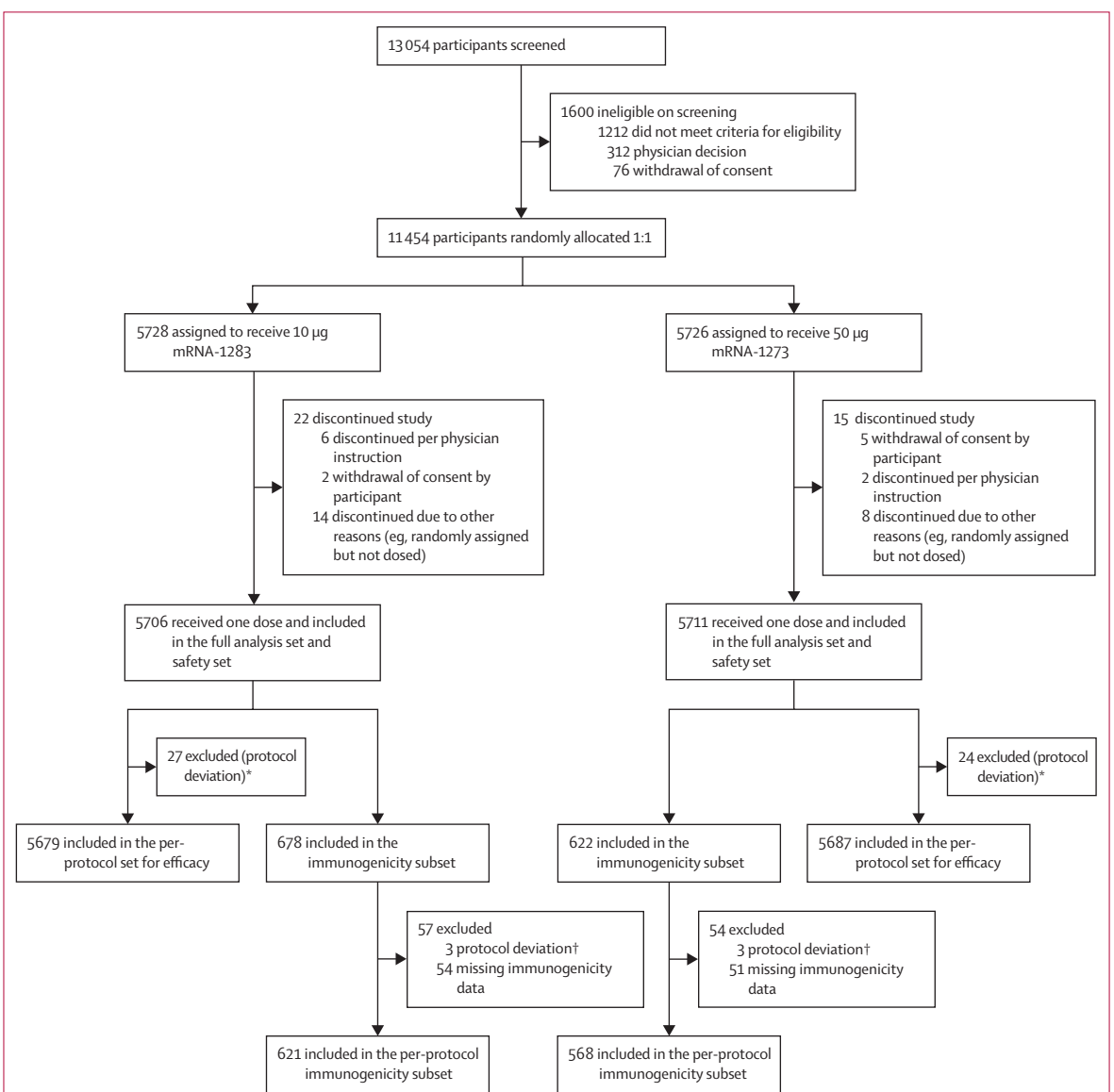

***Figure 1*: Trial profile**

*Reasons for exclusion from the per-protocol efficacy population were participants randomly allocated and dosed twice (n=14), participant received wrong dosage (n=13), and related to exclusion criteria (n=26; participants could have multiple reasons for exclusion). †The most frequent reasons for exclusion from the immunogenicity population for protocol deviations were related to inclusion or exclusion criteria (n=4) and disallowed medications (n=2).

	10 µg mRNA-1283.222 (n=5706)	50 µg mRNA-1273.222 (n=5711)	Total (N=11 417)
Age in years, median (range [IQR])	56 (12–96 [38–66])	55 (12–90 [39–66])	56 (12–96 [38–66])
Age group, years			
≥12 to <18	497 (8·7%)	495 (8·7%)	992 (8·7%)
≥18 to <50	1796 (31·5%)	1772 (31·0%)	3568 (31·3%)
≥50	3413 (59·8%)	3444 (60·3%)	6857 (60·1%)
≥18 to <65	3575 (62·7%)	3576 (62·6%)	7151 (62·6%)
≥65	1634 (28·6%)	1640 (28·7%)	3274 (28·7%)
Sex			
Male	2586 (45·3%)	2631 (46·1%)	5217 (45·7%)
Female	3120 (54·7%)	3080 (53·9%)	6200 (54·3%)
Race			
White	4670 (81·8%)	4711 (82·5%)	9381 (82·2%)
Black	640 (11·2%)	635 (11·1%)	1275 (11·2%)
Other*	355 (6·2%)	329 (5·8%)	684 (6·0%)
Unknown or not reported	41 (0·7%)	36 (0·6%)	77 (0·7%)
Ethnicity			
Hispanic or Latino	769 (13·5%)	741 (13·0%)	1510 (13·2%)
Not Hispanic or Latino	4860 (85·2%)	4864 (85·2%)	9724 (85·2%)
Not reported	59 (1·0%)	87 (1·5%)	146 (1·3%)
Unknown	18 (0·3%)	19 (0·3%)	37 (0·3%)
Infection status†			
Negative	1402 (24·6%)	1372 (24·0%)	2774 (24·3%)
Positive	4211 (73·8%)	4270 (74·8%)	8481 (74·3%)
Missing	93 (1·6%)	69 (1·2%)	162 (1·4%)
Type of last COVID-19 vaccine			
mRNA original monovalent	2605 (45·7%)	2618 (45·8%)	5223 (45·7%)
mRNA omicron bivalent‡	2882 (50·5%)	2900 (50·8%)	5782 (50·6%)
Non-mRNA vaccine	204 (3·6%)	181 (3·2%)	385 (3·4%)
No previous COVID-19 vaccine	1 (<0·1%)	0	1 (<0·1%)
Unknown	13 (0·2%)	12 (0·2%)	25 (0·2%)
Missing	1 (<0·1%)	0	1 (<0·1%)
Dosing interval from last previous dose of COVID-19 vaccine to investigational product, months	9·8 (7·6–16·9)	9·8 (7·7–16·7)	9·8 (7·7–16·8)
(Table 1 continues in next column)			
(Continued from previous column)			
Participants with at least one CDC-defined higher-risk condition at baseline§			
Yes	2683 (47·0%)	2731 (47·8%)	5414 (47·4%)
No	3023 (53·0%)	2980 (52·2%)	6003 (52·6%)
Participants with at least two CDC-defined higher-risk conditions at baseline§			
Yes	962 (16·9%)	1032 (18·1%)	1994 (17·5%)
No	4744 (83·1%)	4679 (81·9%)	9423 (82·5%)

Data are n (%), or median (IQR) unless otherwise stated. Participants were included in the treatment group depending on the treatment received. Percentages were based on the number of participants in the safety set. CDC=US Centers for Disease Control and Prevention. RT-PCR=reverse transcriptase PCR. *Other included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or multiple. †Positive SARS-CoV-2 status was defined as either a positive RT-PCR test for SARS-CoV-2, a positive serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before day 1, or both; negative SARS-CoV-2 status was defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before day 1. Participants with a previous SARS-CoV-2 infection were allowed to participate in the study unless an infection or vaccination had occurred within 90 days of screening. ‡Participants who received the last mRNA COVID-19 vaccine dose on or after Sept 1, 2022. §The CDC has defined a set of medical conditions and COVID-19 risk factors.

Table 1: **Demographics and baseline characteristics (safety set)**

For more on **CDC list** see https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html

COVID-19 events, an early rVE review was triggered. Based on prespecified decision rules, the data safety and monitoring board advised the sponsor that the rVE objective had been met, no further enrolment was needed, and the primary analysis would proceed with 11 454 participants (additional details are shown in the appendix, pp 16–17). The primary rVE analysis was based on COVID-19 events (CDC definition) accrued through to Jan 31, 2024.

The hypothesis for the rVE endpoint was tested based on confirmed COVID-19 when all coprimary immunogenicity endpoints were met, as testing for rVE could only proceed once all immunogenicity endpoints had been met. A Cox proportional hazards model was used, including the study vaccination group as a fixed effect, to estimate the HR (as a measure of the risk ratio), stratified by age group at random allocation. The proportional hazards assumption was tested using an interaction term between the treatment group and the log of time. Non-inferiority was considered to be met if the lower bound of the α-adjusted two-sided CI for rVE was greater than –10% (the upper bound of the α-adjusted two-sided CI for HR was <1·1). The α-adjusted confidence level was derived using the O'Brien–Fleming alpha spending function to preserve the overall one-sided α of 0·025 type 1 error rate (appendix p 17). For the primary rVE analysis, a 99·4% CI was used for hypothesis testing, and an α-adjusted two-sided 99·4% confidence level was calculated using Lan–DeMets–O'Brien–Fleming spending function (nominal one-sided α=0·0028). It was based on 1177 CDC-defined COVID-19 events, representing 56·4% information fraction of target total number of events (N=2087, target rVE of 3% [mRNA-1283 *vs* mRNA-1273]). Descriptive rVE subgroup analyses were also performed based on age and other prespecified subgroups (sex, race, ethnicity, pre-booster SARS-CoV-2

status, geographical region, and type of previous COVID-19 vaccine). Two different analyses were conducted for older age groups at increased risk for severe COVID-19 disease[22] compared with younger individuals: a subgroup aged 50 years and older and one aged 65 years and older. A negative binomial regression model was used in a post hoc sensitivity analysis of rVE based on risk ratio. The model included treatment group and was adjusted for age strata at random allocation. The log of time to event or censoring was used as an offset term to adjust for different observation periods among participants.

Non-inferiority in neutralising antibody titres at day 29 was demonstrated if the lower bound of the two-sided 95% CI for the GMR was greater than 0·667 for both variants. Non-inferiority in seroresponse rates at day 29 was shown if the lower bound of the two-sided 95% CI for the seroresponse rate difference was greater than –10% for both variants. GMRs were estimated based on the ratio of the ANCOVA-based geometric means of the two treatment groups. For the primary immunogenicity analysis, the ANCOVA model included a group variable (mRNA-1283.222 *vs* mRNA-1273.222) as the fixed effect, adjusted by SARS-CoV-2 infection status at baseline, age group at random allocation, number of previous booster doses, and type of last COVID-19 vaccine received. Additionally, a sensitivity analysis was conducted using an ANCOVA model that included log-transformed baseline serum antibody values as an additional covariate, along with the explanatory variables from the primary analysis. All analyses were conducted using SAS version 9.4 or higher.

Role of the funding source

The study sponsor, Moderna, was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between March 28 and Aug 23, 2023, 13 054 participants were screened. 1600 were ineligible on screening, and a total of 11 454 participants were randomly allocated (5728 to mRNA-1283.222 and 5726 to mRNA-1273.222; figure 1). 5706 participants received mRNA-1283.222 (99·6% of 5728) and 5711 received mRNA-1273.222 (99·7% of 5726), forming the safety population. The per-protocol population set for efficacy included 5679 and 5687 participants in the mRNA-1283.222 and mRNA-1283 groups, respectively. The PPIS population, a randomly selected subset in whom neutralising antibody data were assessed, included 621 participants in the mRNA-1283 group and 568 participants in the mRNA-1273 group. Major protocol deviations for the overall population are summarised in the appendix (p 23); a total of 4893 participants (42·7%) had one or more major protocol deviations. The median follow-up was 8·8 months (IQR 7·7–9·5). Of the 11 417 participants who received a vaccine, 475 (4·16%) discontinued the study (261 [4·6%] of 5706 for mRNA-1283.222 and 214 [3·7%] of 5711 for mRNA-1273.222). Discontinuation from the study was most often due to withdrawal of consent (263 [2·3%]); full details are provided in the appendix (p 24).

Demographics and baseline characteristics of the safety population are shown in table 1 (further detail is provided in the appendix, pp 25–29). The median age of participants at enrolment was 56 years (range 12–96 [IQR 38–66]). Of the 11 417 participants who received a vaccine, 6200 (54·3%) were female and 5217 (45·7%) were male; 9381 (82·2%) were White; and 1510 (13·2%) were Hispanic or Latino. 992 (8·7%) participants were aged

	10 µg mRNA-1283.222 (n=5679)	50 µg mRNA-1273.222 (n=5687)
Overall participants with COVID-19, n/N (%)	560/5679 (9·9%)	617/5687 (10·8%)
Person-months*	40 778·0	40 781·7
Incidence rate per 100 person-months (95% CI)†	1·4 (1·3 to 1·5)	1·5 (1·4 to 1·6)
rVE based on hazard ratio, % (99·4% CI)‡	9·3% (–6·6 to 22·8)	..
p value¶	0·0005	..
Adolescent aged 12–17 years	491/5679	490/5687
Participants with COVID-19, n/N (%)	29/491 (5·9%)	23/490 (4·7%)
Person-months*	2852·9	2906·2
Incidence rate per 100 person-months (95% CI)†	1·0 (0·7 to 1·5)	0·8 (0·5 to 1·2)
rVE based on hazard ratio, % (95% CI)‡§	–29·2% (–123·3 to 25·3)	..
Adults aged 18–64 years	3558/5679	3562/5687
Participants with COVID-19, n/N (%)	382/3558 (10·7%)	422/3562 (11·8%)
Person-months*	26 393·2	26 343·4
Incidence rate per 100 person-months (95% CI)†	1·4 (1·3 to 1·6)	1·6 (1·5 to 1·8)
rVE based on hazard ratio, % (95% CI) ‡§	9·7% (–3·8 to 21·3)	..
Adults aged ≥50 years	3399/5679	3431/5687
Participants with COVID-19, n/N (%)	330/3399 (9·7%)	392/3431 (11·4%)
Person-months*	24 553·9	24 799·0
Incidence rate per 100 person-months (95% CI)†	1·3 (1·2 to 1·5)	1·6 (1·4 to 1·7)
rVE based on hazard ratio, % (95% CI)‡§	15·0% (1·6 to 26·6)	..
Adults aged ≥65 years	1630/5679	1635/5687
Number of participants with COVID-19, n/N (%)	149/1630 (9·1%)	172/1635 (10·5%)
Person-months*	11 531·9	11 532·1
Incidence rate per 100 person-months (95% CI)†	1·3 (1·1 to 1·5)	1·5 (1·3 to 1·7)
rVE based on hazard ratio, % (95% CI)‡§	13·5% (–7·7 to 30·6)	..

CDC=US Centers for Disease Control and Prevention. RT-PCR=reverse transcription PCR. rVE=relative vaccine efficacy. COVID-19 outcome was defined as the presence of at least one CDC listed symptom and a positive RT-PCR test on a respiratory sample. *Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date, or efficacy data cutoff date, whichever is the earliest; 1 month=30·4375 days. †Incidence rate is defined as the number of participants with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months, presented as number of events per 100 person-months. ‡rVE=1 minus risk ratio, where risk ratio was estimated by hazard ratio (mRNA-1283.222 *vs* mRNA-1273.222); hazard ratio and CI are estimated using a stratified Cox proportional hazard model (stratified by age group per random allocation) with Efron's method of tie handling and with the treatment group as a fixed effect. Age stratification was removed from model for age subgroup analysis. §α-adjusted two-sided (99·4%) confidence level is calculated using Lan–DeMets O'Brien–Fleming spending function (nominal one-sided α 0·0028). It is based on 1177 CDC-defined COVID-19 events, representing 56·4% information fraction of target total number of events (2087, target rVE of 3% [mRNA-1283.222 *vs* mRNA-1273.222]). ¶Based on stratified Cox proportional hazard model to test the null hypothesis log (hazard ratio) ≥log (1·1).

Table 2: **rVE of mRNA-1283.222 versus mRNA-1273.222 for efficacy by age group**

12–17 years, 7151 (62·6%) were aged 18–64 years, and 3274 (28·7%) were 65 years and older; in addition, 6857 participants (60·1%) were 50 years and older. Baseline SARS-CoV-2 infection, COVID-19 vaccination history, and dosing intervals were balanced between groups (table 1, appendix pp 25–29). Demographics of the PPIS population were similar to those of the overall study (data not shown).

Across both groups, 1177 confirmed COVID-19 events occurred up to Jan 31, 2024 (560 [9·9%] of 5679 in mRNA1283.222 and 617 [10·8%] of 5687 in mRNA-1273.222). The proportional hazards assumption was met for the stratified Cox proportional hazards model. The HR–based rVE with the α-adjusted CI was 9·3% (99·4% CI –6·6 to 22·8; p=0·0005; table 2). The prespecified non-inferiority success criterion was met, given that the lower bound of the rVE CI was greater than –10%. In the subgroup analyses by age group, the rVE was –29·2% (95% CI –123·3 to 25·3), 9·7% (–3·8 to 21·3), 15·0% (1·6 to 26·6), and 13·5% (–7·7 to 30·6) for age subgroups 12–17 years, 18–64 years, 50 years and older, and 65 years and older, respectively (table 2, appendix pp 30–32). rVE analysis across other demographic characteristics is shown in the appendix (pp 33–38). The rVE was also calculated against severe COVID-19 (appendix pp 39–40). A total of 55 severe events occurred from 14 days post-vaccination up to Jan 31, 2024. The rVE based on these severe events was 38·1% (95% CI –6·7 to 64·1); from 14 days post-vaccination up until the Feb 23, 2024, data cutoff, 59 severe events occurred (rVE 35·9% [–8·2 to 62·0]; appendix pp 39–40). The estimated rVE for SARS-CoV-2 symptomatic or asymptomatic infections was consistent with the primary rVE outcome (5·1% [–4·0 to 13·4]; appendix p 41). The rVE in the full analysis set (appendix p 42), the rVE based on the sensitivity analysis (appendix p 43), and the rVE based on the Kaplan–Meier approach (appendix p 56) were also consistent with the primary analysis.

mRNA-1283.222 increased neutralising antibody titres between baseline and day 29 in the PPIS (figure 2). The omicron BA.4/BA.5 GMC was 355·9 (95% CI 324·8–389·9) and 2346·2 (2158·0–2550·9) at baseline and day 29, respectively, in the mRNA-1283.222 group and 346·1 (312·2–383·7) and 1753·8 (1607·0–1914·0) at baseline and day 29, respectively, in the mRNA-1273.222 group (table 3). The omicron BA.4/BA.5 geometric mean fold rise (GMFR) was 6·6 (95% CI 6·0–7·2) in the mRNA-1283.222 group and 5·1 (4·6–5·6) in the mRNA-1273.222 group (table 3). The original SARS-CoV-2 D614G (henceforth D614G) GMC was 2140·2 (95% CI 1954·7–2342·8) and 10 657·6 (9960·2–11 403·9) at baseline and day 29, respectively, in the mRNA-1283.222 group and 2151·9 (1950·5–2374·2) and 8576·5

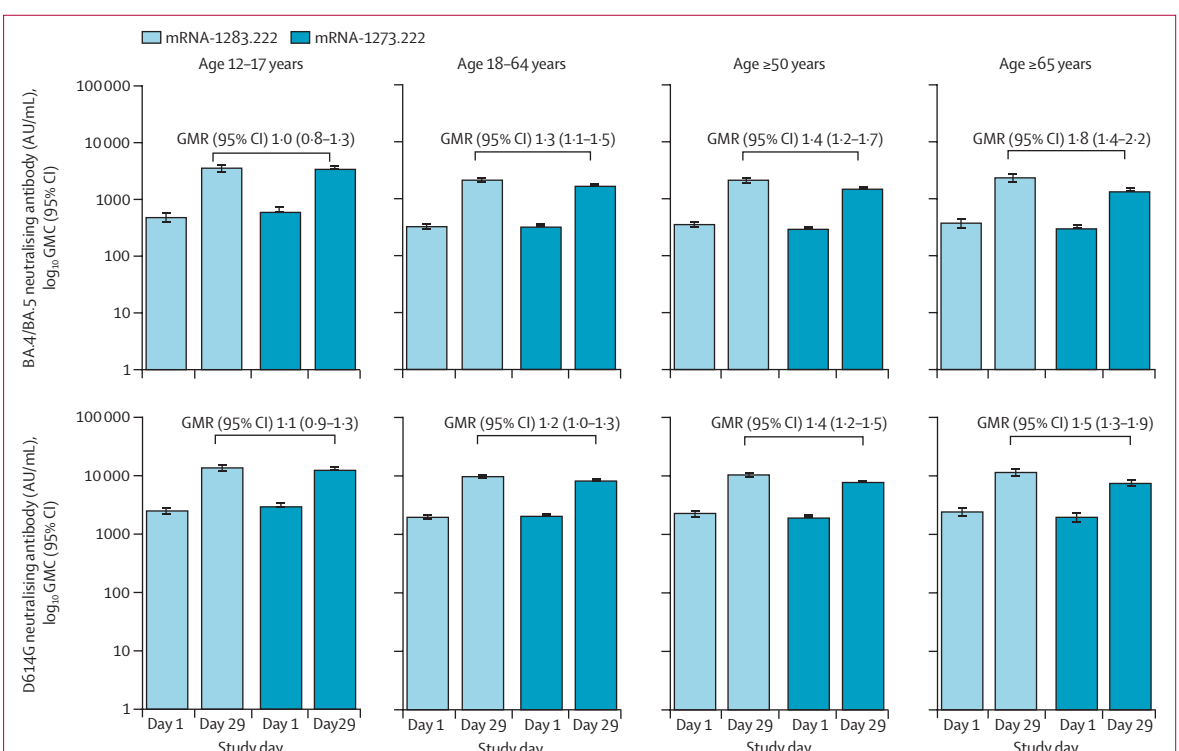

Figure 2: **Neutralising antibody levels against omicron BA.4/BA.5 and original SARS-CoV-2 D614G, by age group**
Immunogenicity analyses were based on the per-protocol immunogenicity subset, which consisted of a randomly sampled subset of participants who received the planned study vaccination and had no major protocol deviations that affected immunogenicity data. Error bars indicate 95% CI. GMC=geometric mean concentration. GMR=geometric mean ratio.

	Omicron BA.4/BA.5		Original SARS-CoV-2 D614G	
	10 µg mRNA-1283.222 (N=621)	50 µg mRNA-1273.222 (N=568)	10 µg mRNA-1283.222 (N=621)	50 µg mRNA-1273.222 (N=568)
Overall				
Baseline GMC (95% CI)	355·9 (324·8 to 389·9)	346·1 (312·2 to 383·7)	2140·2 (1954·7 to 2342·8)	2151·9 (1950·5 to 2374·2)
Day 29				
GMC (95% CI)	2346·2 (2158·0 to 2550·9)	1753·8 (1607·0 to 1914·0)	10 657·6 (9960·2 to 11 403·9)	8576·5 (7990·4 to 9205·6)
GMFR (95% CI)	6·6 (6·0 to 7·2)	5·1 (4·6 to 5·6)	5·0 (4·6 to 5·4)	4·0 (3·7 to 4·3)
Estimated GMC (95% CI)†	2340·9 (2167·0 to 2528·8)	1753·8 (1618·2 to 1900·7)	10 631·9 (9960·2 to 11 348·9)	8576·5 (8012·5 to 9180·1)
GMR (95% CI)‡	1·3 (1·2 to 1·5)	Ref	1·2 (1·1 to 1·4)	Ref
SRR, n (% [95% CI])§	496 (79·9% [76·5 to 83·0])	372 (65·5% [61·4 to 69·4])	519 (83·6% [80·4 to 86·4])	414 (72·9% [69·0 to 76·5])
SRR difference (95% CI)¶	14·4% (9·3 to 19·4)	Ref	10·7% (6·0 to 15·4)	Ref
Adolescents aged 12–17 years				
n/N	91/621	93/568	91/621	93/568
Baseline GMC (95% CI)	479·2 (388·4 to 591·2)	593·0 (468·9 to 749·9)	2492·7 (2061·2 to 3014·5)	2946·4 (2367·6 to 3666·6)
Day 29				
Estimated GMC (95% CI)†	3561·4 (3037·5 to 4175·7)	3398·9 (2908·9 to 3971·4)	13 617·7 (12 006·3 to 15 445·3)	12 404·3 (10 966·5 to 14 030·6)
GMR (95% CI)	1·0 (0·8 to 1·3)	Ref	1·1 (0·9 to 1·3)	Ref
SRR, n/N (% [95% CI])	80/91 (87·9% [79·4 to 93·8])	75/93 (80·6% [71·1 to 88·1])	78/91 (85·7% [76·8 to 92·2])	69/93 (74·2% [64·1 to 82·7])
SRR difference, % (95% CI)	7·3 (–3·4 to 18·0)	Ref	11·5 (–0·1 to 23·1)	Ref
Adults aged 18–64 years				
n/N	378/621	316/568	378/621	316/568
Baseline GMC (95% CI)	325·0 (290·2 to 363·9)	319·2 (278·9 to 365·2)	1961·4 (1744·9 to 2204·8)	2051·6 (1802·7 to 2334·8)
Day 29				
Estimated GMC (95% CI)†	2120·6 (1917·3 to 2345·6)	1661·0 (1487·8 to 1854·4)	9734·8 (8938·8 to 10 601·7)	8251·3 (7517·2 to 9057·1)
GMR (95% CI)	1·3 (1·1 to 1·5)	Ref	1·2 (1·0 to 1·3)	Ref
SRR, n/N (% [95% CI])	301/378 (79·6% [75·2 to 83·6])	201/316 (63·6% [58·0 to 68·9])	314/378 (83·1% [78·9 to 86·7])	240/316 (75·9% [70·8 to 80·6])
SRR difference, % (95% CI)	16·0% (9·3 to 22·7)	Ref	7·1% (1·1 to 13·2)	Ref
Adults aged ≥50 years				
n/N	337/621	329/568	337/621	329/568
Baseline GMC (95% CI)	354·7 (311·5 to 404·0)	291·6 (253·9 to 334·9)	2284·2 (2016·3 to 2587·7)	1906·5 (1665·3 to 2182·7)
Day 29				
Estimated GMC (95% CI)†	2114·7 (1896·1 to 2358·6)	1469·9 (1316·4 to 1641·3)	10 462·7 (9541·9 to 11 472·4)	7729·8 (7042·7 to 8484·0)
GMR (95% CI)	1·4 (1·2 to 1·7)	Ref	1·4 (1·2 to 1·5)	Ref
SRR, n/N (% [95% CI])	257/337 (76·3% [71·4 to 80·7])	214/329 (65·0% [59·6 to 70·2])	276/337 (81·9% [77·4 to 85·9])	235/329 (71·4% [66·2 to 76·2])
SRR difference, % (95% CI)	11·2 (4·3 to 18·1)	Ref	10·5 (4·1 to 16·9)	Ref
Adults aged ≥65 years				
n/N (%)	152/621	159/568	152/621	159/568
Baseline GMC (95% CI)	373·3 (302·5 to 460·6)	296·8 (242·1 to 363·8)	2425·8 (1988·9 to 2958·6)	1968·9 (1609·5 to 2408·5)
Day 29				
Estimated GMC (95% CI)†	2339·5 (1984·3 to 2758·3)	1326·8 (1130·0 to 1557·7)	11 451·1 (9936·3 to 13 196·9)	7463·3 (6499·4 to 8570·1)
GMR (95% CI)	1·8 (1·4 to 2·2)	Ref	1·5 (1·3 to 1·9)	Ref
SRR, n/N (% [95% CI])	115/152 (75·7% [68·0 to 82·2])	96/159 (60·4% [52·3 to 68·0])	127/152 (83·6% [76·7 to 89·1])	105/159 (66·0% [58·1 to 73·4])
SRR difference, % (95% CI)	15·3 (4·9 to 25·3)	Ref	17·5 (8·0 to 26·9)	Ref

GMC=geometric mean concentration. GMFR=geometric mean fold rise. GMR=geometric mean ratio. LLOQ=lower limit of quantification. SRR=seroresponse rate. *Immunogenicity analyses were based on the per-protocol immunogenicity set, which consisted of a randomly sampled subset of participants who received the planned study vaccination and had no major protocol deviations that affected immunogenicity data. †Estimated with an ANCOVA model, with serum antibody value at day 29 (on the log scale) as the dependent variable and the treatment group (mRNA-1283.222 *vs* mRNA-1273.222) as a fixed effect, adjusted by SARS-CoV-2 status at baseline, age group, number of previous boosters, and type of last COVID-19 vaccine before study entry. Coefficients for least-square means used margins by level. The resultant least-square means, and difference in least-square means (95% CIs), were back-transformed to the original scale for presentation. Age group was removed from the model for age subgroup analyses. ‡The ANCOVA-based GMR (mRNA-1283.222 *vs* mRNA-1273.222) met the prespecified non-inferiority criterion, with the lower bound of the 95% CI of the GMR >0·667. ¶The SRR difference (mRNA-1283.222 *vs* mRNA-1273.222) met the prespecified non-inferiority criterion, with the lower bound of the 95% CI of the SRR greater than –10%. SRR was calculated at the participant level as an antibody value change from baseline below the LLOQ to ≥4 × LLOQ; or ≥4-fold rise if baseline is ≥LLOQ and <4 × LLOQ; or ≥2-fold rise if baseline is ≥4 × LLOQ. The SRR two-sided 95% CIs were calculated using the Clopper–Pearson method.

Table 3: **Neutralising antibody levels and seroresponse rates against omicron BA.4/BA.5 and original SARS-CoV-2 D614G, overall and by age group***

(7990·4–9205·6) at baseline and day 29, respectively, in the mRNA-1273.222 group. The D614G GMFR was 5·0 (95% CI 4·6–5·4) in the mRNA-1283.222 group and 4·0 (95% CI 3·7–4·3) in the mRNA-1273.222 group.

At day 29, the omicron BA.4/BA.5 GMR was 1·3 (95% C 1·2–1·5) and the D614G GMR was 1·2 (1·1–1·4), meeting the prespecified non-inferiority criterion (lower bound of the 95% CI >0·667; table 3). The omicron BA.4/BA.5 day 29 seroresponse rate was 79·9% (95% CI 76·5–83·0) in the mRNA-1283.222 group and 65·5% (61·4–69·4) in the mRNA-1273.222 group, while for D614G it was 83·6% (80·4–86·4) and 72·9% (69·0–76·5), respectively. The day 29 difference in the percentage of participants with a seroresponse rate against BA.4/BA.5 was 14·4% (95% CI 9·3–19·4), and for D614G it was 10·7% (6·0–15·4), meeting the prespecified non-inferiority criterion (lower bound of 95% CI greater than –10%). The immunogenicity results based on the

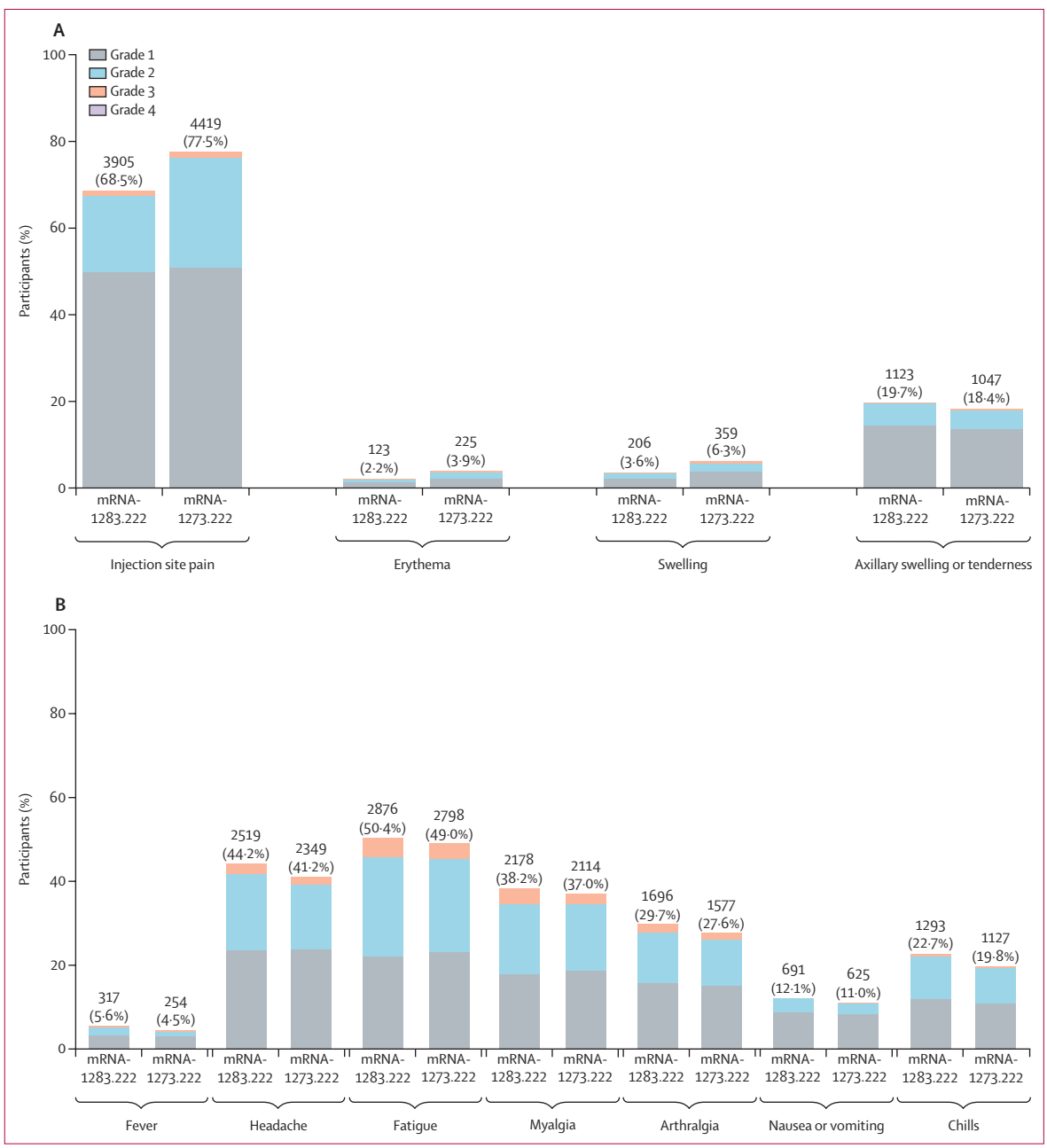

Figure 3: **Solicited local and systemic reactions**
Percentage of participants who had local (A) or systemic (B) adverse reactions within 7 days after injection. No grade 4 solicited local adverse reactions were reported. One grade 4 fever was reported in the mRNA-1273.222 group. Data are from the solicited safety set (mRNA-1283.222 n=5702; mRNA-1273.222 n=5706).

sensitivity analysis, incorporating baseline antibody value, were consistent with the primary analysis and are shown in the appendix (pp 44–47). The age subgroup analysis GMRs for the omicron BA.4/BA.5 and D614G strains are shown in figure 2 and table 3.

The frequency of local adverse reactions in the solicited safety set was similar between mRNA-1283.222 (4007 [70·3%] of 5701) and mRNA-1273.222 (4473 [78·4%] of 5705), with a lower frequency of injection-site pain in the mRNA-1283.222 group compared with the mRNA-1273.222 group (3905 [68·5%] of 5701 *vs* 4419 [77·5%] of 5705). The frequency of systemic adverse reactions was similar between both groups (3672 [64·4%] of 5702 and 3664 [64·2%] of 5706, respectively). The most common local adverse reaction was injection-site pain, and the most common systemic adverse reactions were fatigue, headache, and myalgia (figure 3). Most adverse reactions were mild to moderate, began 1–2 days after injection, and resolved within a median of 3 days (appendix pp 48–52); local grade 3 events were reported by 92 (1·6%) of 5701 and 122 (2·1%) of 5705 participants given mRNA-1283.222 and mRNA-1273.222, respectively (appendix pp 50–52). Systemic grade 3 events were reported in 408 (7·2%) of 5702 and 329 (5·8%) of 5706 participants in each group, respectively (appendix pp 50–52). Fatigue was the most common systemic grade 3 event, occurring in 263 (4·6%) of 5702 and 219 (3·8%) of 5706 participants, respectively.

The frequency of unsolicited adverse events, SAEs, and MAAEs were similar between groups during the first 28 days after injection (appendix p 53). Throughout the follow-up period, up to data cutoff on Feb 23, 2024, SAEs were reported by 156 (2·7%) of 5706 participants in the mRNA-1283.222 group and 151 (2·6%) of 5711 in the mRNA-1273.222 group (appendix p 54). The incidence of AESIs was similar between groups (60 [1·1%] of 5706 *vs* 60 [1·1%] of 5711, respectively). One AESI of possible vaccine-associated delayed anaphylaxis in the mRNA-1283.222 group was considered related by the investigator. There were no confirmed events of myocarditis or pericarditis in either group. Study discontinuation due to adverse events occurred in eight (0·1%) of 5706 and 12 (0·2%) of 5711 participants in the mRNA-1283.222 and mRNA-1273.222 groups, respectively. Fatal events were reported in five (0·1%) of 5706 and ten (0·2%) of 5711 participants in the mRNA-1283.222 and mRNA-1273.222 groups, respectively. No fatal events were reported by the investigator as being related to mRNA-1283.222. One death (<0·1%) on day 7 of a 77-year-old female recipient of mRNA-1273.222 with underlying cardiovascular disease was assessed by the investigator as being vaccine-related related due to the temporal relationship.

Discussion

In this phase 3 study in participants aged 12 years and older, a single dose of the next-generation COVID-19 vaccine mRNA-1283 demonstrated non-inferior vaccine efficacy compared to mRNA-1273 (rVE 9·3% [99·4% CI –6·6 to 22·8]; p=0·0005). The rVE met the prespecified non-inferiority criterion, as the lower bound of the rVE confidence interval (–6·6%) was above the prespecified –10% threshold. mRNA-1283 was designed to elicit a more focused neutralising antibody response compared with mRNA-1273, and the antibody response with mRNA-1283 was higher than with mRNA-1273 given the lower bound of the GMR's CI was greater than one for both omicron BA.4/BA.5 and D614G. The magnitude of the increase in antibody titres was similar to the increase observed between the original COVID-19 vaccines and the first variant-containing booster vaccines.[23] The higher immune response of mRNA-1283 over mRNA-1273 is expected to translate into a clinical benefit in vaccine efficacy, although post-approval studies are needed to confirm this benefit. To our knowledge, this is the first pivotal randomised controlled trial evaluating a modified COVID-19 vaccine designed to target immunodominant epitopes of the spike protein. Notably, mRNA-1283 was developed using the same mRNA-based platform as mRNA-1273, and the study was conducted during a period when global health authorities recommended a bivalent COVID-19 formulation.[18] As of writing, COVID-19 vaccine recommendations have transitioned to monovalent formulations. In previous studies, mRNA-1283 elicited similar or higher immune responses than mRNA-1273 regardless of valency or the variant sequence evaluated.[15,16] Therefore, mRNA-1283 is expected to be updated similarly to mRNA-1273. Additionally, mRNA-1283 is administered at a lower dose (10 µg) than mRNA-1273 (50 µg), while simultaneously eliciting higher immune responses; this could facilitate the development of combination vaccines for respiratory pathogens.[24]

The increase in the antibody response (mRNA-1283 *vs* mRNA-1273) and rVE point estimates were most pronounced in adults aged 50 years and older or 65 years and older, suggesting a correlation between immune response and vaccine efficacy, which has also been observed with mRNA-1273.[25] The adolescent group in the study was the smallest age group (992 of 11 417) and had the lowest number of COVID-19 events, leading to the most imprecise rVE point estimate in this subgroup. However, the similar immunogenicity in adolescents between mRNA-1283 and mRNA-1273 in our study, paired with effectiveness data from mRNA-1273 clinical studies,[26,27] is reassuring for the mRNA-1283 vaccine performance in adolescents.

No new safety concerns were identified with mRNA-1283. The frequency of local and systemic adverse reactions for mRNA-1283 was similar to that of mRNA-1273, except for pain at the injection site, which was lower with mRNA-1283 than mRNA-1273. The frequency of adverse reactions was lower in participants 65 years and older than in younger adults and adolescents.

The mRNA-1283 design was hypothesised to potentially lower the risk of myocarditis and pericarditis, which in

the post-authorisation setting of COVID-19 mRNA vaccines have been shown to occur at very low frequencies (<1 in 10 000), mostly in young men.[7,31] The full-length spike protein has a furin cleavage site between the S1 and S2 domains. Cleavage of the S1 domain permits entry of the spike protein into systemic circulation, which may be associated with rare events of myocarditis and pericarditis.[28–30] mRNA-1283 does not include the furin cleavage site and, therefore, could limit or prevent systemic circulation of antigen.

No events of pericarditis were reported in the mRNA-1283.222 group. One event of suspected pericarditis was reported in the mRNA-1273.222 group on day 136 that was assessed by the investigator as not related to study vaccine; the cardiac event adjudication committee adjudicated the case as not meeting the criteria for a Charter-defined event. Although no events of myocarditis were observed in this study, the study was not designed to evaluate very rare adverse events and additional clinical and post-licensure studies, including real-world surveillance, are needed.

The study has several limitations. It was not powered for a superiority analysis of rVE (mRNA-1283 *vs* mRNA-1273). The rVE subgroup analyses did not test a statistical hypothesis, but the subgroup results were consistent with the overall rVE outcome. Although representation of race and ethnicities was balanced across the two vaccine groups, the study population was predominantly White and not fully representative of the racial demographics of the general US population. Additionally, immunocompromised and very old individuals were not enrolled, and further studies to characterise the immune responses in these populations will be needed. The adolescent population was only around 10% of the study population. During the follow-up period, XBB.1.5, XBB.1.16, EG.5, and JN.1 were the predominant circulating SARS-CoV-2 variants,[21] and these were distinct from the bivalent study vaccine composition (original SARS-CoV-2 and omicron BA.4/BA.5). Although a selection bias cannot be excluded when using the per-protocol efficacy set, the rVE in the full analysis set was consistent with the rVE in the per-protocol set. Another potential limitation of this study is that some asymptomatic infections could have been undetected; however, random allocation is expected to have equally distributed any undetected symptomatic asymptomatic cases and, therefore, they would be balanced between the two groups. Additionally, very rare adverse events, such as myocarditis and pericarditis, could not be evaluated in this study. Finally, this study is limited by the lack of assessments of cell-mediated immunity, which is less susceptible to immune evasion, thus supporting protection in the setting of emerging SARS-CoV-2 variants and potentially offering durable protection against severe COVID-19 disease.[32,33]

In conclusion, the next-generation COVID-19 vaccine, mRNA-1283, was well tolerated and had non-inferior efficacy and superior immunogenicity to mRNA-1273. These data suggest that mRNA-1283 has the potential for a clinical efficacy benefit compared with mRNA-1273, although this would need to be confirmed in post-marketing evaluation.

Contributors

The sponsor was responsible for the overall trial design, site selection, monitoring, and data analysis, which was facilitated by Parexel International. SC, AR, RW, DKE, JF, WD, HZ, EDW, VU, BG, JM, and RD contributed to the design of the study. SC, JF, WD, HZ, JM, and RD contributed to study oversight. SC, BG, AR, PD, DP, KR, LV, RH, SNF, SRW, and CAC contributed to data collection. JF, WD, and HZ conducted statistical analyses. BG and YP were responsible for immunogenicity assays. SC, EDW, and VU were responsible for safety data and oversight. SC, JF, WD, HZ, JM, and RD interpreted the data, results, or both. SC drafted the manuscript. SC, JF, and SRW directly accessed and verified the underlying data reported in the manuscript. All authors contributed to the review and editing of the manuscript and approved the final version for submission to the journal. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. SC verifies that all authors had full access to the study data and accepts responsibility to submit for publication.

Declaration of interests

SC, AR, RW, DKE, JF, WD, HZ, EDW, VU, YP, BG, JM, and RD are employees and shareholders of Moderna. PD, DP, KM, LV, RH, SNF, SRW, and CAC declare all support for this manuscript from Moderna. SNF declares consulting fees from Moderna, Sanofi, Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Medimmune, Merck, and Valneva Vaccines and Antimicrobials. SRW declares grants or research support from NIH/NIAID, Sanofi Pasteur, Janssen Vaccines, Moderna, AbbVie, F2G, Pfizer, Vir Biotechnology, and Worcester HIV Vaccine; consulting fees from Janssen Vaccines and BioNTech; and spouse's stock or stock options from Regeneron. CAC declares grants from GSK, Novavax, and Moderna.

Data sharing

As the trial is ongoing, access to patient-level data and supporting clinical documents with qualified external researchers will be made available upon request and subject to review after the trial completion date. A materials transferor data access agreement with the sponsor will be required to access shared data. Such requests can be made to Moderna, 325 Binney Street, Cambridge, MA 02142, USA, or at data_sharing@modernatx.com. All other relevant data are presented in the paper. The protocol is available online at ClinicalTrials.gov (NCT05815498).

Acknowledgments

We thank the participants in the trial and their families, and the members of NextCOVE Study Trial team (listed in the appendix pp 4–7) for their dedication and the contributions to the study, as well as the members of the data safety and monitoring board for their hard work, support, and guidance of the trial. Medical writing and editorial assistance were provided by Mary Bausch-Jurken, Barbara Kuter, Denise McGinnis, and Alana Simorellis (all from Moderna); and Anja Varjacic, Renee Gordon, and Jessica Nepomuceno (all of MEDiSTRAVA), in accordance with Good Publication Practice 2022 guidelines, funded by Moderna, and under the direction of the authors. This study was funded by Moderna.

References

1 Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. *J Infect Dis* 2022; **226:** 1593–607.

2 Panagiotakopoulos L, Godfrey M, Moulia DL, et al. Use of an additional updated 2023–2024 COVID-19 vaccine dose for adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices—United States, 2024. *MMWR Morb Mortal Wkly Rep* 2024; **73:** 377–81.

3 WHO. COVID-19 epidemiological update—15 July 2024. World Health Organization. https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-169 (accessed Aug 26, 2024).

4 Taylor CA, Patel K, Patton ME, et al. COVID-19-associated hospitalizations among US adults aged ≥65 years—COVID-NET, 13 states, January–August 2023. *MMWR Morb Mortal Wkly Rep* 2023; **72:** 1089–94.

5 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384:** 403–16.

6 El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 2021; **385:** 1774–85.

7 Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices—United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 977–82.

8 Follmann D, Wang X, Baden LR, et al. Who to boost when: the effect of age and dosing interval on delta and omicron COVID-19 incidence in the open-label phase of the COVE trial. *Open Forum Infect Dis* 2024; **11:** ofae689.

9 Cerutti G, Guo Y, Zhou T, et al. Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite. *Cell Host Microbe* 2021; **29:** 819–833.e7.

10 Dejnirattisai W, Zhou D, Ginn HM, et al. The antigenic anatomy of SARS-CoV-2 receptor binding domain. *Cell* 2021; **184:** 2183–200.e22.

11 Piccoli L, Park YJ, Tortorici MA, et al. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. *Cell* 2020; **183:** 1024–42.e21.

12 Crowley AR, Natarajan H, Hederman AP, et al. Boosting of cross-reactive antibodies to endemic coronaviruses by SARS-CoV-2 infection but not vaccination with stabilized spike. *eLife* 2022; **11:** e75228.

13 Chheda U, Pradeepan S, Esposito E, Strezsak S, Fernandez-Delgado O, Kranz J. Factors affecting stability of RNA—temperature, length, concentration, pH, and buffering species. *J Pharm Sci* 2024; **113:** 377–85.

14 Stewart-Jones GBE, Elbashir SM, Wu K, et al. Domain-based mRNA vaccines encoding spike protein N-terminal and receptor binding domains confer protection against SARS-CoV-2. *Sci Transl Med* 2023; **15:** eadf4100.

15 Yassini P, Hutchens M, Paila YD, et al. Interim analysis of a phase 1 randomized clinical trial on the safety and immunogenicity of the mRNA-1283 SARS-CoV-2 vaccine in adults. *Hum Vaccin Immunother* 2023; **19:** 2190690.

16 Chalkias S, Pragalos A, Akinsola A, et al. Safety and immunogenicity of SARS-CoV-2 spike receptor-binding domain and N-terminal domain mRNA vaccine. *J Infect Dis* 2025; **231:** e754–63.

17 US Food & Drug Administration. Update: COVID-19 vaccine booster composition. June 30, 2022. https://www.fda.gov/vaccines-blood-biologics/update-covid-19-vaccine-booster-composition (accessed Dec 17, 2024).

18 WHO. WHO SAGE roadmap on uses of COVID-19 vaccines in the context of omicron and substantial population immunity. World Health Organization. March 30, 2023. https://iris.who.int/handle/10665/366671 (accessed Dec 18, 2024).

19 WHO. JN.1 Initial risk evaluation. Dec 19, 2023. https://www.who.int/docs/default-source/coronaviruse/18122023_jn.1_ire_clean.pdf (accessed Dec 18, 2024).

20 WHO. JN.1 updated risk evaluation. World Health Organization. Feb 9, 2024. https://www.who.int/docs/default-source/coronaviruse/09022024_jn.1_ure.pdf?sfvrsn=a153518c_3 (accessed Dec 18, 2024).

21 Ma KC, Castro J, Lambrou AS, et al. Genomic surveillance for SARS-CoV-2 variants: circulation of omicron XBB and JN.1 lineages—United States, May 2023 to September 2024. *MMWR Morb Mortal Wkly Rep* 2024; **73:** 938–45.

22 CDC. Underlying conditions and the higher risk for severe COVID-19. US Centers for Disease Control and Prevention. Feb 6, 2025. https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html (accessed Feb 26, 2025).

23 Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against Covid-19. *N Engl J Med* 2022; **387:** 1279–91.

24 Rudman Spergel AK, Wu I, Deng W, et al. Immunogenicity and safety of influenza and COVID-19 multicomponent vaccine in adults ≥50 years: a randomized clinical trial. *JAMA*. 2025; **333:** 1977–87.

25 Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science* 2022; **375:** 43–50.

26 Figueroa AL, Ali K, Berman G, et al. Safety and durability of mRNA-1273-induced SARS-CoV-2 immune responses in adolescents: results from the phase 2/3 TeenCOVE trial. *EClinicalMedicine* 2024; **74:** 102720.

27 Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 2021; **385:** 2241–51.

28 Ogata AF, Cheng CA, Desjardins M, et al. Circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients. *Clin Infect Dis* 2022; **74:** 715–18.

29 Yonker LM, Swank Z, Bartsch YC, et al. Circulating spike protein detected in post-COVID-19 mRNA vaccine myocarditis. *Circulation* 2023; **147:** 867–76.

30 Forte E. Circulating spike protein may contribute to myocarditis after COVID-19 vaccination. *Nat Cardiovasc Res* 2023; **2:** 100.

31 Buoninfante A, Andeweg A, Genov G, Cavaleri M. Myocarditis associated with COVID-19 vaccination. *NPJ Vaccines* 2024; **9:** 122.

32 Rostad CA, Campbell JD, Paulsen GC, et al. Evaluation of cellular immune responses after mRNA-1273 vaccination in children 6 months to 11 years of age. *J Infect Dis*. 2025; **231:** e945–55.

33 Vardhana S, Baldo L, Morice WG 2nd, Wherry EJ. Understanding T cell responses to COVID-19 is essential for informing public health strategies. *Sci Immunol* 2022; **7:** eabo1303.