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Immunogenicity, reactogenicity, and safety to assess booster vaccinations with BNT162b2 or double-dose mRNA-1273 in adults ≥75 years (EU-COVAT-1-AGED)–final report

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ABSTRACT

Background: To determine long-term immunogenicity and reactogenicity of different SARS-CoV-2 messenger RNA (mRNA) vaccines in a population ≥75 years of age in a randomized trial.
Methods: Participants were randomized to receive either BNT162b2 30 µg or a double booster dose of mRNA-1273, i.e., 100 µg, as the third and fourth vaccinations (first and second booster). The primary endpoint was the rate of a two-fold geometric mean titer (GMT) antibody increase 14 days after vaccination targeting the receptor binding domain (RBD) region of wild-type SARS-CoV-2. Secondary endpoints included neutralizing capacity against wild-type and 25 variants at 14 days (D14) and 12 months (M12). Safety was assessed by monitoring adverse events (AEs) for 7 days after vaccination.
Findings: Between November 2021 and September 2022, 322 participants received a SARS-CoV-2 vaccine as a first (Part A) or second booster (Part B). Primary endpoint results have been published previously. In Part A, it was reached by 100% of participants in both vaccine arms, with a higher GMT increase in the mRNA-1273 arm (ratio, 1.64). At M12, the GMT of anti-RBD immunoglobulin G (IgG) was slightly higher than at D14 (9319.7 vs 8568.4 IU/mL) in the BNT162b2 arm, while in the mRNA-1273 arm, the GMT was equal (14,163.8 vs 14,266.7 IU/mL at D14). In Part B, the primary endpoint was reached by 78.5% of participants in the BNT162b2 and 87.2% in the mRNA-1273 arm ($P = 0.056$), respectively, with a higher GMT increase of anti-RBD IgG for mRNA-1273 (ratio, 1.38). At M12, GMT of anti-RBD IgG was markedly lower than at D14 (9962 vs 15,248.2 IU/mL) in the BNT162b2 arm as well as in the mRNA-1273 arm (12,024.3 vs 21,325.6 IU/mL). Higher neutralizing capacity in individuals who received a booster with mRNA-1273 was detected against wild-type and 15 of 25 tested variants. Fewer participants in the mRNA-1273 arm had vaccine-related AEs (29.6% vs 38.5%), but severity was more frequently grade 2 (n = 38, 28.1% vs n = 22, 16.3%).
Interpretation: Long-term serological immunogenicity and virus neutralization capacity in participants ≥75 years of age were numerically better with an mRNA-1273 100 µg booster, with a comparable safety profile.

Introduction

After a primary prime-boost vaccination series against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease and/or infection, further booster vaccinations are required to provide protection against severe disease and death due to coronavirus disease 2019 (COVID-19) [1].

Viral escape limits the efficacy of targeted treatments and requires adaptation of existing messenger RNA (mRNA) vaccines. In 2022, due to emerging SARS-CoV-2 variants of concern (VOC), second booster vaccinations, i.e., a fourth dose of a SARS-CoV-2 (variant adapted) vaccine, were recommended for immunosuppressed patients or those of advanced age with comorbidities [2,3]. Immunosenescence, characterized by a decline in both innate and adaptive immune responses with aging, impairs the ability of older adults to mount robust immune reactions to vaccination, making repeated booster doses essential for maintaining protective immunity [4].

Rapid waning of immune response after vaccination has been described for infections with *Omicron* variants; however, recovery of anti-SARS-CoV-2 immunity was observed after booster vaccination [5]. The fold-change of anti-spike immunoglobulin G (IgG) levels between the first and second booster was more pronounced in participants >70 years of age compared with younger participants in a large phase III trial [6]. Concurrently, the risk reduction for death after one or two boosters with different available vaccines was higher than the protection from infection [6].

Among the available mRNA vaccines, both BNT162b2 (BioNTech/Pfizer, Comirnaty®) 30 µg and mRNA-1273 (Moderna, Spikevax®) at the 50 µg dose have proven to be highly effective booster vaccines [7,8]. To date, data on the exact timing of further boosters to induce an optimal and long-lasting immune response from randomized controlled studies in the aged population are scarce [9]. EU-COVAT-1 was a randomized trial of BNT162b2 30 µg vs mRNA-1273 100 µg as a first or second booster against SARS-CoV-2 in participants ≥75 years of age. Although immunogenicity and safety outcomes up to 14 days post-vaccination have been previously reported [10,11], this final report presents final data on the primary endpoint, data on immune responses at 12 months after the first and second booster with both mRNA vaccines, and provides the complete safety analysis.

Methods

Trial design and timelines

EU-COVAT-1 was a multinational, phase II, randomized study to determine immunogenicity, reactogenicity, and safety of booster vaccinations with BNT162b2 30 µg or mRNA-1273 100 µg in adults ≥75 years of age [12]. BNT162b2 30 µg was administered at the standard dose as recommended by the manufacturer. The rationale to use mRNA-1273 at a dose of 100 µg, i.e., double the dose per the approved label, was that the dose for boosting after the primary prime-boost vaccination series had not been defined when the present study was designed [13]. BNT162b2 30 µg or mRNA-1273 100 µg were administered as third dose, i.e., first booster, for participants in Part A, or as a fourth dose, i.e., second booster, for participants in Part B. Ethics approval for this study was first obtained on November 08, 2021 (Ref.: 21-1457-AMG-ff) and granted approval on October 20, 2021 (Ref.: 4647). The study was registered at ClinicalTrials.gov (NCT05160766) and EudraCT (2021-004526-29).

Enrollment of participants for a first booster dose started at a single center in Cologne, Germany, in November 2021. Due to a change in National Immunization Technical Advisory Group (NITAG) recommendations to administer a second booster dose, the trial underwent a major protocol amendment (approved on January 21, 2022). Hence, the trial part in which participants received a first booster was referred to as Part A, and the part in which participants received a second booster referred to as Part B [10,11]. Part B was then conducted in an international, multicenter setting

within the VACCELERATE consortium. Participating trial sites were selected through the VACCELERATE network, and recruitment was supported by the VACCELERATE Volunteer Registry [10,14]. Study sites were located in Cologne, Frankfurt, and Hannover (all Germany), Vilnius (Lithuania), Bergen (Norway), Barcelona, Córdoba, Madrid, and San Sebastián (all Spain).

After approval of variant-adapted vaccines against the VOC *Omicron* and subsequent changes of NITAG recommendations for booster vaccinations in the participating countries, enrollment was prematurely terminated as per sponsor's decision on December 06, 2022.

The study protocols (version 4.0 for Part A and version 6.0 for Part B) are provided in supplementary files 1 and 2 [12].

Participants

Participants ≥75 years of age were eligible if they met the following key inclusion criteria: priming regimen with homologous ChAdOx-1-S, BNT162b2, or mRNA-1273 for Part A, and for Part B the same priming regimen with a first booster with either of the two mRNA vaccines at least 1 month prior to enrollment (Table 1). No SARS-CoV-2 infection within the prior 3 months before enrollment. Participants with major immunosuppression were not eligible. All participants provided written informed consent.

Randomization

To randomize participants, permuted random blocks were utilized. Participants were randomly assigned to either BNT162b2 or mRNA-1273 in a 1:1 ratio. ALEA version 17.1 (ALEA Clinical B.V., Abcoude, The Netherlands) was used as an electronic randomization tool, and the result was registered in the electronic case report form (TrialMaster® 5.0 update 03, Anju Software, Tempe, AZ, USA). No blinding was foreseen in this trial.

Procedures

After randomization, intramuscular vaccine injection with either BNT162b2 30 µg or mRNA-1273 100 µg was performed. Antibody assessment was done at baseline (i.e., day 0 prior to vaccination), at day 14, and after 12 months. To determine immunogenicity, anti-SARS-CoV-2 receptor binding domain (RBD) immunoglobulin G (IgG) antibodies (anti-RBD IgG) were determined. Safety and reactogenicity were assessed by the incidence of any adverse events (AEs). Participants filled out a diary for 7 days after on-study vaccination to document solicited AEs. Unsolicited AEs were recorded at any time point as reported by the participants and, if applicable, followed up for another 30 days after the end of trial participation. The same applied to serious AEs (SAEs). All SAEs were independently reviewed by a data monitoring committee, including assessment of relatedness to either of the vaccines.

Antibody titers as plasma levels for anti-RBD IgG and anti-N IgG were measured at the Centre for Experimental Pathogen Host Research (CEPHR) in Dublin, Ireland, via electrochemiluminescence immunoassay by Mesoscale Diagnostics (MSD, Rockville, MD, USA).

SARS-CoV-2 virus neutralization capacity (estimated in % inhibition) in plasma was assessed using V-plex COVID-19 ACE2 neutralization kits (MSD), performed by the Laboratory of Cell Biology & Histology and Vaccine & Infectious Disease Institute in Antwerp, Belgium. Antibodies capable of blocking the binding of ACE2 to spike proteins of the viruses as listed in supplementary methods 1 were measured. All described laboratory investigations were performed in identical fashion for participants of Part A and Part B.

Outcome parameters

The primary endpoint of the study was the rate of 2-fold anti-RBD IgG antibody titer increase at 14 days against wild-type virus after the study vaccination. Secondary endpoints included vaccine-induced antibody titer increases and neutralization antibody titer and change in neutralizing antibody titer capacity against wild-type and variants after 14 days and 12 months, respectively.

Safety endpoints were defined as any unsolicited AEs during the trial, as well as solicited AEs for 7 days after the on-study vaccination, as well as the rate of SAEs (grade ≥3 according to the National Cancer Institute Common Terminology Criteria for Adverse Advents) up to 3 months after on-study vaccination.

The statistical analysis plan can be found in supplementary methods 1.

Role of funding source

This study was conducted within the VACCELERATE consortium (www.vaccelerate.eu). This project received funding from the European Commission – Directorate-General for Research and Innovation under the Framework Programme HORIZON 2020 via the VACCELERATE Grant Agreement (GA) and its annexes No. 101037867. The funders of this trial did not influence the design, data collection, data analysis, data interpretation, or in the writing of this manuscript.

Results

Baseline characteristics

A total of 53 participants were enrolled in Part A between November 8, 2021, and January 4, 2022, and 270 participants in Part B between February 16, 2022, and September 15, 2022 (Supplementary Figures 1a and 1b). Follow-up over 12 months was completed in September 2023.

In the overall trial population, 25 of 52 subjects in Part A received BNT162b2 as the first booster, whereas 27 subjects received mRNA-1273, and 135 participants in Part B received BNT162b2 as second booster, whereas 135 participants received mRNA-1273 (CONSORT diagrams, Supplementary Figures 1a and 1b, Supplementary Table 1). In both Part A and B, the intervention arms were balanced regarding their baseline characteristics, as depicted in Table 1. The mean and median age of the overall trial population was 80.58 and 79 years, respectively (Supplementary Table 2). The most frequent comorbidities were vascular and metabolism disorders (Table 1). Most participants had received priming regimes consisting of two doses of BNT162b2, whereas 70% (n = 95 in each arm) in the two intervention arms of *Part B* also had received a 1st booster dose with BNT162b2 (Table 1, Supplementary Tables 1 and 2).

Immunogenicity

For details regarding the primary endpoint of a 2-fold anti-RBD IgG antibody titer increase at 14 days, we refer to the previously published reports [10,11]. In summary, all 50 vaccinated participants in Part A with available antibody measurements reached the primary endpoint of a two-fold antibody titer increase 14 days after the first booster vaccination. The increase in geometric mean titer (GMT) of anti-RBD IgG was higher in the mRNA-1273 arm (ratio of GMT mRNA-127 vs BNT162b2 was 1.64) (Figure 1a). In Part B, 102 of 130 participants (78.5%) [97.5% confidence interval [CI]: 69.2-86%] in the BNT162b2 arm compared with 116 of 133 (87.2%) [97.5% CI: 79.3-93%] in the mRNA-1273 arm reached a two-fold antibody titer increase 14 days after the second booster vaccination.

Table 1
Baseline characteristics.

	Part A		*Part B*	
	BNT162b2 n = 25	*mRNA-1273[a] n=27*	*BNT162b2 n = 135*	*mRNA-1273 n = 135*
Age (years)				
Mean ± SD	77.7 ± 2.8	78.6 ± 3.2	80.99 ± 5.49	81.09 ± 5.88
Median [Min; Max]	77.0 [75; 87]	78.0 [75; 85]	79 [75; 99]	79 [75; 99]
Age categories				
≥75-<85	24 (96 %)	25 (93 %)	100 (74 %)	106 (79 %)
85+	1 (4 %)	2 (7 %)	35 (26 %)	29 (21 %)
Sex				
Female	9 (36%)	11 (41%)	67 (50%)	68 (50%)
Male	16 (64%)	16 (59%)	68 (50%)[b]	67 (50%)
Body mass index (kg/m²)				
Mean ± SD	25.7 ± 3.1	24.6 ± 4.0	25.55 ± 4.04	25.99 ± 4.0
Median [Min; Max]	25.6 [20.3; 32.8]	24.1 [16.8; 32.6]	25.4 [16.6; 40.2]	25.4 [18; 41.8]
Boosting (comparing third and study vaccination)				
Heterologous boosting			27 (20%)	104 (77%)
Homologous boosting			108 (80%)[b]	31 (23%)
Priming vaccine regimen				
2x BNT162b2	16 (64%)	14 (52%)		
2x ChAdOx-1-Si	6 (24%)	9 (33%)		
2x mRNA-1273	3 (12%)	4 (15%)		
3x BNT162b2			95 (70%)[b]	95 (70%)
2x BNT162b2 + mRNA-1273			20 (15%)	25 (19%)
2x ChAdOx-1-Si + BNT162b2			10 (7%)	8 (6%)
2x ChAdOx-1-Si + mRNA-1273			7 (5%)	5 (4%)
2x mRNA-1273 + BNT162b2			3 (2%)	1 (1%)
3x mRNA-1273			0 (0%)	1 (1%)
Time between first and second vaccination in days				
Mean ± SD	40 ± 19	46 ± 26	35.65 ± 19.95	34.72 ± 19.16
Median [Min; Max]	42 [21; 84]	42 [21; 111]	22 [20; 86]	22 [16; 114]
Time between second and third vaccination in days				
Mean ± SD	202 ± 20	203 ± 24	211.41 ± 38.16	210.79 ± 37.05
Median [Min; Max]	192 [185; 255]	190 [184; 273]	207 [124; 303]	205 [126; 313]
Time between third and fourth vaccination in days				
Mean ± SD			185.85 ± 68.4	191.65 ± 69.67
Median [Min; Max]			176 [52; 308]	195 [74; 324]
Most frequent comorbidities as per system organ class				
Metabolism and nutrition disorders	11 (44 %)	15 (56 %)	58 (43%)	63 (47%)
Hypercholesterolemia	6/25 (24%)	11/27 (40.7%)	23/135 (17%)	26/135 (19.3%)
Dyslipidemia	1/25 (4%)		12/135 (8.9%)	11/135 (8.1%)
Diabetes mellitus			14/135 (10.4%)	7/135 (5.2%)
Type II diabetes mellitus	3/25 (12%)	1/27 (3.7%)	5/135 (3.7%)	3/135 (2.2%)
Hyperuricemia	2/25 (8%)	1/27 (3.7%)	3/135 (2.2%)	3/135 (2.2%)
Surgical procedures	18 (72 %)	18 (66.67 %)	57 (42 %)	60 (44%)
Hysterectomy	5/25 (20%)	2/27 (7.4%)	4/135 (3%)	3/135 (2.2%)
Intraocular lens replacement			9/135 (6.7%)	6/135 (4.4%)
Bilateral cataract	4/25 (16%)	2/27 (7.4%)	6/135 (4.4%)	5/135 (3.7%)
Appendectomy	3/25 (12%)		6/135 (4.4%)	6/135 (4.4%)
Cholecystectomy	3/25 (12%)		5/135 (3.7%)	7/135 (5.2%)
Cataract surgery	2/25 (8%)	4/27 (14.8%)	2/135 (1.5%)	6/135 (4.4%)
Vascular disorders	14 (56%)	19 (70%)	84 (62 %)	79 (58 %)
Arterial hypertension	14/25 (56%)	17/27 (63%)	41/135 (30.4%)	41/135 (30.4%)
Arteriosclerosis	1/25 (4%)	1/27 (3.7%)		1/135 (0.7%)
Hypertension			33/135 (24.4%)	34/135 (25.2%)
Chronic venous insufficiency			4/135 (3%)	1/135 (0.7%)

mRNA, messenger RNA.
For metric variables mean ± standard deviation, median (minimum [Min]; maximum [Max]) are reported. For categorical variables, absolute frequencies and percentage (%) per vaccine arm are stated.

[a] Please note that in the arm "mRNA-1273 (100µg)" the safety data set consists only of 27 subjects and not 28 as randomized. One subject did not receive study vaccination due to a diagnosed SARS-CoV-2 infection after randomization. This subject was excluded from the entire dataset.

[b] Please note that one subject during the screening visit, concealed the fact to be already vaccinated four times. This only became apparent during the second visit.

The increase in GMT was also higher in the mRNA-1273 arm (ratio of GMT mRNA-127 vs BNT162b2 was 1.38) (Figure 1b).

In Part A, after 12 months of follow-up, the GMT of anti-RBD IgG was higher than at 14 days in the BNT162b2 arm, being 9,319.7 IU/mL (n = 21) (95% CI: 4717.6-18,411.4), compared with 8,568.4 IU/mL (n = 25) (95% CI: 6796.2-10,802.7). In the mRNA-1273 arm, the GMT was similar compared with day 14, being 14,163.8 IU/mL (n = 21) (95% CI: 7820.6-25,651.9), compared with 14,266.7 IU/mL (n = 25) (95% CI: 10,934.5-18,614.4) (Figure 1a).

In Part B, after 12 months of follow-up, the GMT of anti-RBD IgG decreased to 9962 IU/mL (n = 125) (95% CI: 7776.4-12,761.7), compared with 15,248.2 IU/mL (n = 130) (95% CI: 13,241.1-17,559.4) after 14 days in the BNT162b2 arm. This effect was also observed in the mRNA-1273 arm, where the GMT was 12,024.3 IU/mL (n = 121) (95% CI: 9427.7-15,336), compared with 21,325.6 IU/mL (n = 133) (95% CI: 18,235.1-24,939.8) at 14 days (Figure 1b).

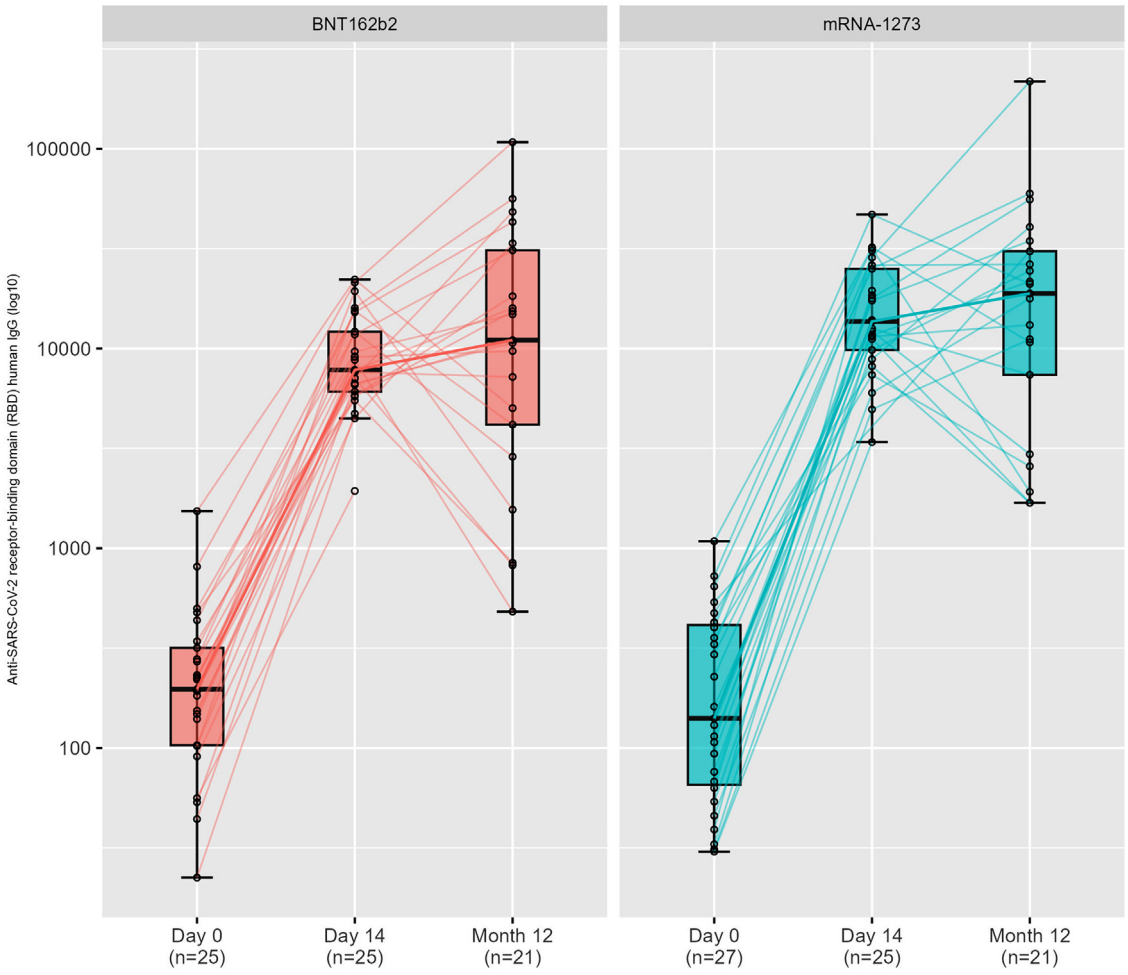

Figure 1a. Anti-RBD IgG between day 0, day 14 and month 12 for Part A.

When separated by priming regimen, in Part A, the study arm with double mRNA-1273 priming followed by an mRNA-1273 booster exhibited the highest sustained anti-RBD levels after 14 days, suggesting the strongest serological response. The cohort with double mRNA-1273 priming and a BNT162b2 booster demonstrated similar results after 1 year, with minimal differences compared with the other study arms (Supplementary Figure 2a, Supplementary Tables 3a and 3b).

In Part B, the study arm with three doses of BNT162b2 followed by an mRNA-1273 booster had the highest GMT increase after 14 days, and the arm with two doses of BNT162b2 or mRNA-1273 followed by a BNT162b2 booster had the highest anti-RBD levels after 1 year (Figure 2a and 2b), while the mean GMT increase was similar in the other arms as well.

Virus neutralization capacity

For Part A, virus neutralization capacity (in %) at 12 months after the first booster vaccination was generally sustained above baseline level in the whole cohort in both arms. In general, neutralization capacity after 14 days increased for all 25 tested variants, while it was lower for *Omicron* variants compared with other variants, an effect that was maintained at 12 months (Figure 3a).

For Part B, mean virus neutralization capacity (in %) at 12 months after the second booster vaccination decreased in both arms for all tested variants, including wild type. This effect was present to the least extent in Omicron variants. Overall, the mRNA-1273 arm presented slightly higher mean neutralization capacity values than the BNT162b2 arm for all tested variants, including wild type (Figure 3b). Compared with *Part A*, virus neutralization capacity was lower in the whole Part B cohort, except for B1.526.1 and P.2 in the BNT126b2 arm, and for B1.351, BA.1, BA2.75.2, BA.4, BF.7, BQ.1, BQ1.1. and XBB.1 (all Omicron) in the mRNA-1273 arm. Overall, both arms showed similar virus neutralization capacities for *Omicron* variants, whereas the mRNA-1273 arm showed markedly higher values for the Wuhan wild-type, B.1.1.7 (Alpha), P.1 and P.2 (both Gamma), B1.617 and B.1.617.1 (Kappa) and AY.3 and AY.4.2 (both Delta), and B.1.526.1 (Iota) (Figures 3a and 3b, Supplementary Tables 4a and 4b). Compared with 14 days after the first booster, mean neutralization capacity against *Omicron* variants improved after 12 months, suggesting another etiology than vaccination only, i.e., antigen exposure during SARS-CoV-2 infection.

In the mixed model for repeated measurements, the between-arm difference (mRNA-1273 minus BNT162b2) at day 14 was statistically significant for the Wuhan wild-type (estimate, 12.61; $P = 0.031$) and for 24 of 25 variants. The difference at month 12 was not statistically significant for the Wuhan wild-type (estimate, 10.29; $P = 0.327$) and for any of the 25 variants (Supplementary Table 5a). In Part B, the difference between arms (mRNA-1273 minus BNT162b2) at day 14 was statistically significant for the Wuhan wild-type (estimate, 4.31; $P = 0.011$) and for 15 of 25 variants. The difference at month 12 was not statistically significant for the Wuhan wild-type (estimate, 5.25; $P = 0.169$) and for any of the 25 variants (Supplementary Table 5b).

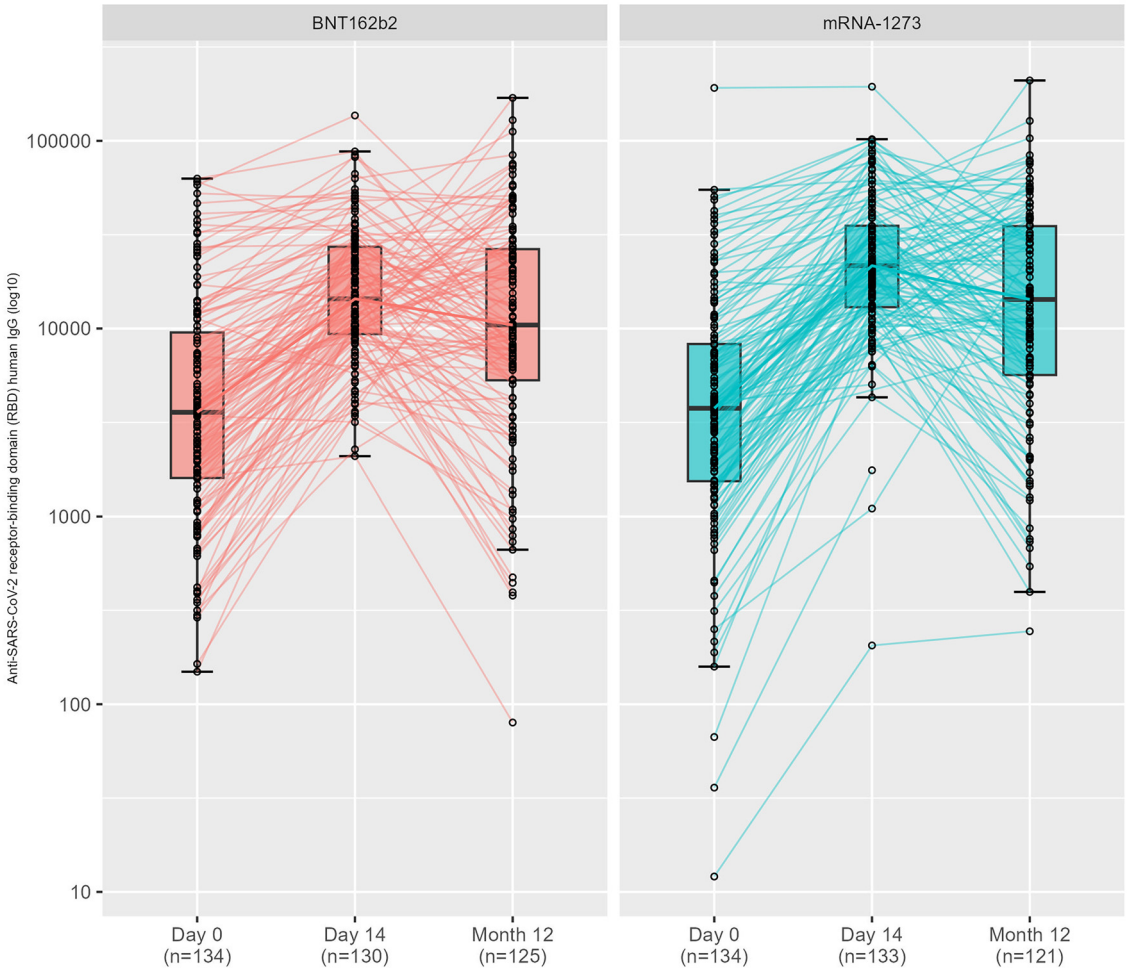

Figure 1b. Anti-RBD IgG between day 0, day 14 and month 12 for Part B.
Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

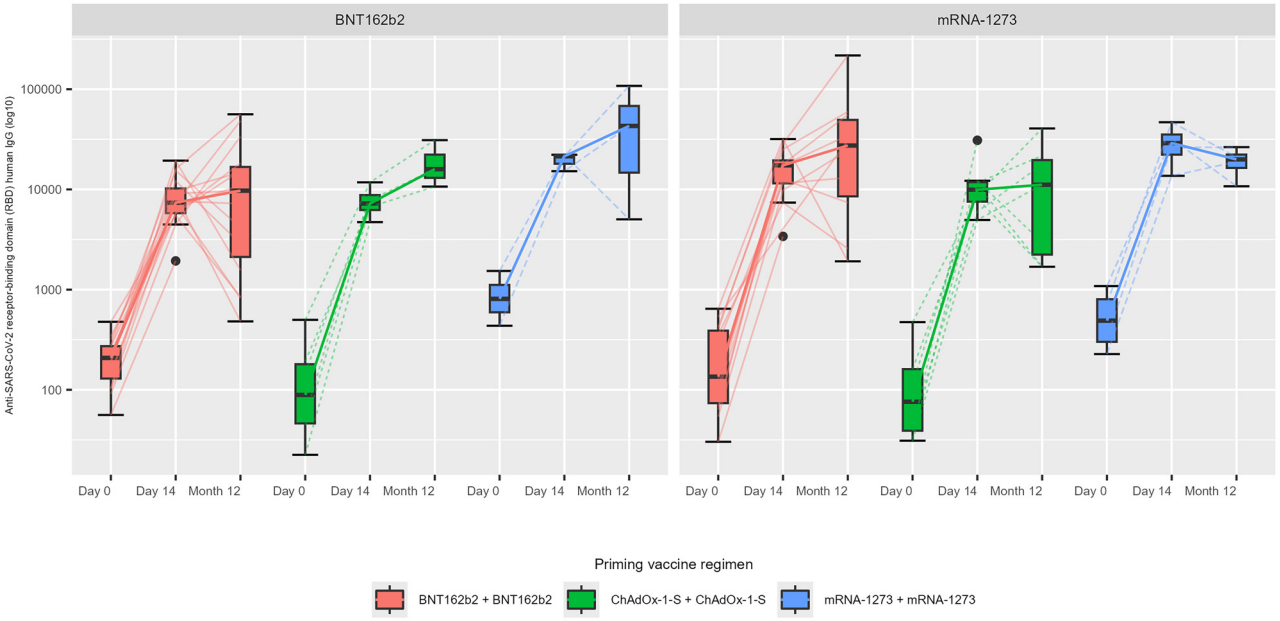

Figure 2a. Anti-RBD IgG between day 0, day 14 and month 12 for Part A by most frequently implemented priming regimen.

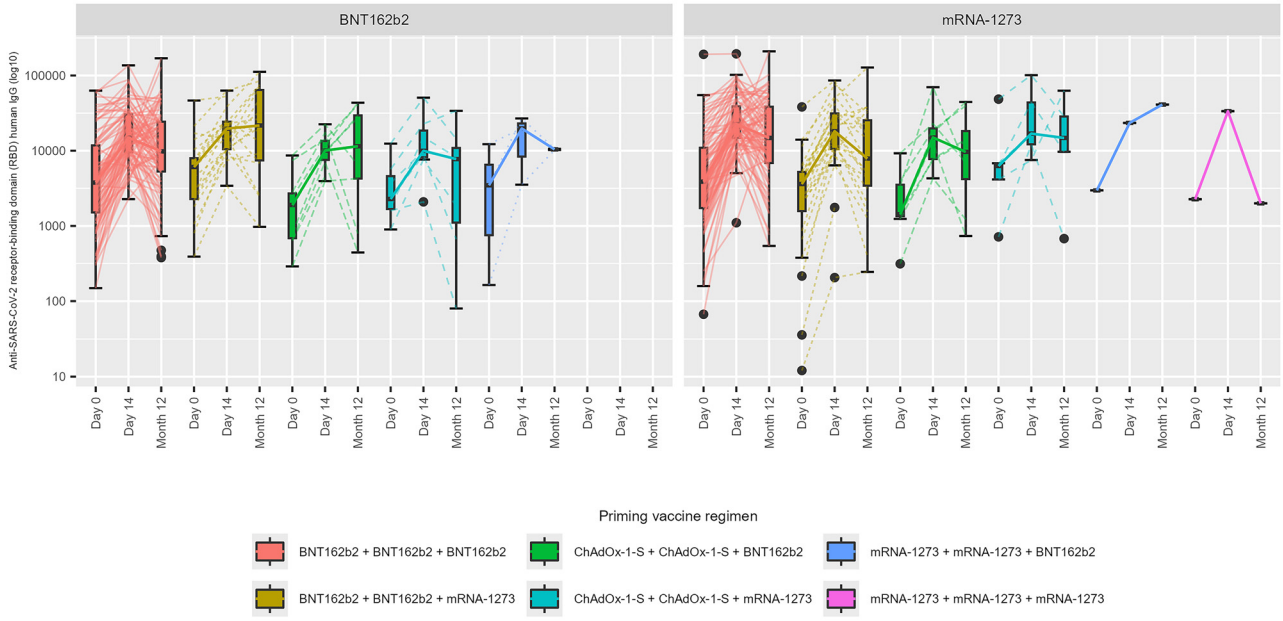

Figure 2b. Anti-RBD IgG between day 0, day 14 and month 12 for Part B by most frequently implemented priming and first booster regimen. Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

Exploratory analysis: participants with SARS-CoV-2 infection

An analysis comparing the arms with vs without prior (i.e., before study entry) SARS-CoV-2 infection with regard to immunogenicity was performed in Part B (in Part A, only one participant had a prior SARS-CoV-2 infection). There were significant differences in anti-RBD IgG at baseline between participants with prior COVID-19 and those without (Mann-Whitney *U*, $P < 0.001$). Accordingly, the increase in anti-RBD IgG after the second booster in participants with prior COVID-19 was lower than in those without prior infection (Supplementary Figures 3a and 3b).

Between day 0 and month 12, in Part A, 11 participants (44%) in the BNT162b2 arm and eight participants (29.6%) in the mRNA-1273 arm reported SARS-CoV-2 infection. In Part B, 34 participants (25.4%) in the BNT162b2 arm and 32 participants (23.9%) in the mRNA-1273 arm reported SARS-CoV-2 infection between day 0 and month 12 (Supplementary Figures 3a and 3b). We detected higher anti-RBD titers in participants who self-reported SARS-CoV-2 infection between day 14 and month 12 in both arms (Supplementary Table 6). No SAE was attributed to SARS-CoV-2 infection.

Safety

The safety analyses of Part A and B have been reported in detail previously [10,11]. The following is a summary of the available safety information from both parts. In Part A, 48 out of 52 participants (92.3%) had at least one AE during the trial (BNT162b2: n = 22 (88%); mRNA-1273: n = 26 (96.3%)). The total number of AEs was 198. The number of AE occurrences was higher (n = 128; 64.65%) in participants who received mRNA-1273 than in participants who received BNT162b2 (n = 70; 35.35%). Most AEs were associated with general disorders and injection site reactions (BNT162b2: n = 41 (20.1%); mRNA-1273: n = 77 (38.9%)) (Supplementary Tables 7a, 8a, 9a). No SAEs, suspected unexpected serious adverse reactions (SUSARs), or deaths were reported in Part A.

In Part B, more participants in the mRNA-1273 arm reported AEs that were judged as vaccine-related (78 out of 135 participants; 57.8%) compared with the BNT161b2 arm (75 out of 135 participants; 55.6%). Of these, 52 (38.52%) grade 1 vaccine-related AEs were associated with the BNT162b2 arm and 40 (29.63%) with the mRNA-1273 arm. Grade 2 vaccine-related AEs were more often reported after vaccination with mRNA-1273 (n = 38; 28.1%) than with BNT161b2 (n = 22; 16.3%). One participant in the BNT161b2 arm reported four vaccine-related AEs of grade 3 (0.74%), which were classified as SAEs. No SAE occurred in the mRNA-1273 arm. The most frequent AEs in Part B were injection site pain (40% for BNT162b2 and 43.7% for mRNA-1273), fatigue (23% for BNT162b2 and 37.8% for mRNA-1273), asthenia (10.4% for BNT162b2 and 11.9% for mRNA-1273), and malaise (8.9% for BNT162b2 and 12.6% for mRNA-1273) (Supplementary Tables 7a, 7b, 8a and 8b, 9a and 9b).

Overall, seven participants—all enrolled in Part B—died during the conduct of this study; five had received mRNA-1273 and two had received BNT162B2. In all reported cases, investigators and the data monitoring committee (DMC) did not establish a causal relationship between the participants' deaths and the study vaccines. Reasons for death are reported in Supplementary Table 10.

Discussion

The primary endpoint, defined as a two-fold increase in anti-RBD IgG antibody titers 14 days after the first or second booster dose, was achieved by 100% of participants in both arms of Part A, and by 78.5% and 87.2% of participants in the BNT162b2 and mRNA-1273 arms, respectively, in Part B. Importantly, this antibody response persisted over 12 months, although titers and neutralization capacity declined over time, particularly against emerging variants. Both anti-RBD IgG titers and neutralization capacity were higher with a 1st or 2nd booster of a double dose (i.e., 100 µg) of mRNA-1273 compared with BNT162b2 in persons ≥ 75 years. This effect was generally sustained after a follow-up of 12 months; however, a decrease in antibody titers and neutralization capacity was observed for either vaccine in Part B. The rationale for using a 100 µg dose of mRNA-1273 instead of the later approved 50 µg dose was based on a comparable safety profile of both doses, considering that the trial population may be subject to immunosenescence while, at the same time,

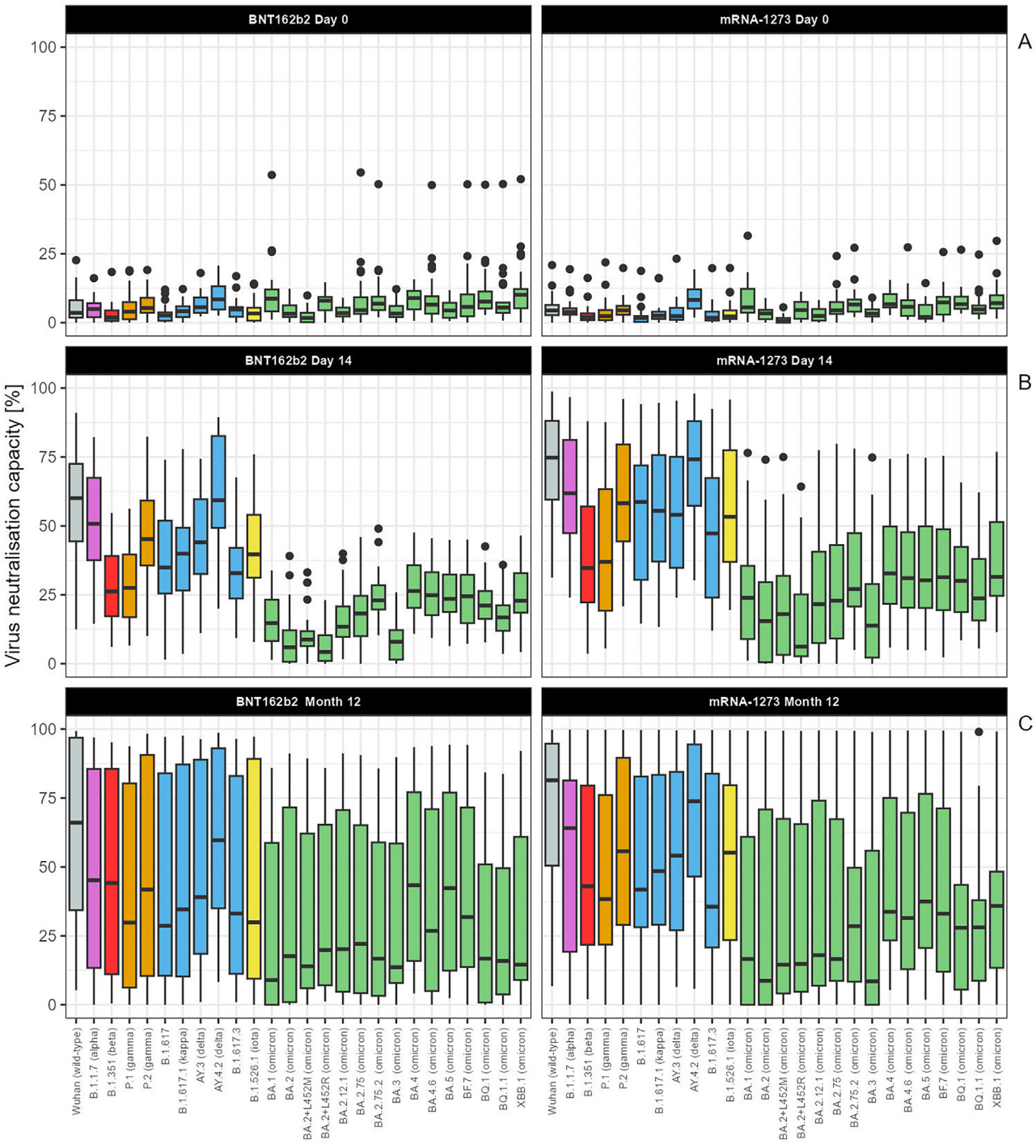

Figure 3a. Part A virus neutralization capacity at baseline, after 14 days and 12 months.

correlates of protection were lacking [8]. Other randomized studies in immunocompromised populations, including a meta-analysis, confirmed a higher serological response in terms of antibody titer increase with a double-dose mRNA-1273 booster [15–17].

Immune response to booster vaccinations against SARS-CoV-2 has rarely been studied in randomized trials involving participants ≥75 years, despite this group being at higher risk for severe disease [18]. A non-randomized trial with a lower number of participants showed a significant and sustained increase in neutralizing anti-RBD antibodies 15 and 28 days after a booster dose with mRNA-1273 or BNT162b2 in participants with a median age of 71 years [19]. With a mean age of 80.6 years, EU-COVAT-1 AGED recruited the oldest population to date in a comparative, randomized trial with SARS-CoV-2 vaccines, while previous studies were single-arm or post hoc analyses of longitudinal vaccine cohorts [20,21].

A decline in neutralizing antibody titers 3 to 6 months after vaccination has been described, though memory B cells targeting variants expand upon exposure to wild-type spike protein [22]. This recall response with cross-reactivity to multiple SARS-CoV-2 variants indicates that the antibodies encoded by these memory B cells are of higher quality and able to overcome epitope changes associated with mutations in variants [22]. Importantly, T

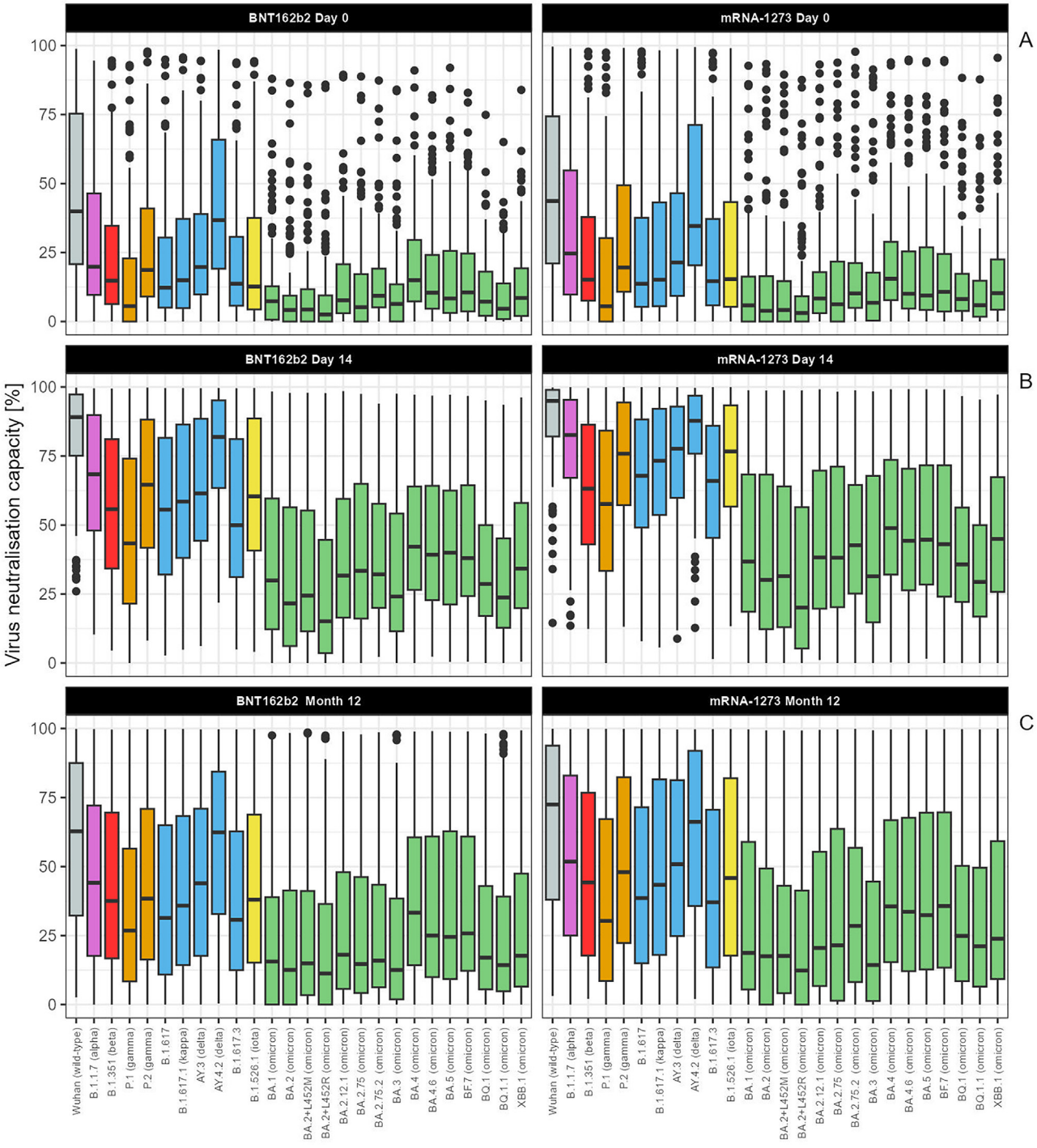

Figure 3b. Part B virus neutralization capacity at baseline, after 14 days and 12 months.
mRNA, messenger RNA.

cell-mediated immunity has been shown to exhibit strong cross-reactivity to SARS-CoV-2 variants, including *Omicron* [23,24]. This cellular component is more strongly conserved than the humoral response and may provide lasting protection against severe disease despite waning antibody levels. Therefore, detailed investigation of vaccine-induced and infection-induced T cell responses is essential in older adults and should be a priority in defining future correlates of protection and optimizing next-generation vaccines.

Furthermore, we observed lower seroneutralization activity against emerging SARS-CoV-2 *Omicron* variants in both parts A and B and across both vaccine groups. As new variants continue to emerge, variant-adapted vaccines have expanded the landscape of SARS-CoV-2 vaccination studies, with novel booster vaccines demonstrating a significant increase in GMT in participants who had heterologous priming. The rapid evolution of SARS-CoV-2 as an endemic, highly mutational virus raises ongoing challenges for immunity, as circulating variants continuously escape immune detection. This phenomenon is further complicated by the fact that some studies have found no effect of vaccination on disease severity, viral load, or duration of infection, particularly among people of advanced age [25]. In the EU-COVAT-1 AGED, there was no signal indicative of more severe disease in older adults; however,

this study only evaluated serological and self-reported parameters and may be limited in its interpretation. Conversely, other studies have reported strong effects of age on disease course and severity [26].

We detected higher anti-RBD titers in participants who self-reported SARS-CoV-2 infection between day 14 and month 12. Whereas this finding is not unexpected, the non-structured evaluation of SARS-CoV-2 infection during an ongoing pandemic is a limitation of this study, affecting the prediction of booster efficacy and generalizability of the month 12 serological data. Structured and time-specific documentation of SARS-CoV-2 infection would have allowed for additional cellular immunity analyses and prediction of the durability of antibodies in those with booster vaccination and infection. In a meta-analysis, individuals with hybrid immunity had the highest magnitude and durability of protection. However, this effect generally waned rapidly within 6 months, underlining the limited effectiveness of SARS-CoV-2 immunity as well as the limited validity of antibody titers as correlates of protection [27].

Immunosenescence limits vaccine responsiveness in older adults. In the context of SARS-CoV-2 vaccination, immunosenescence may lead to lower peak antibody titers, reduced neutralization capacity, and faster waning of humoral responses, as observed in this study. Despite these limitations, booster vaccinations, particularly at higher doses such as mRNA-1273, can transiently overcome some of these age-related immune impairments and elicit a robust antibody response [28,29]. However, the durability of this response remains suboptimal compared with that of younger individuals, underscoring the need for tailored vaccine strategies in older populations.

In our study, vaccine-related SAEs were reported in only one participant. Notably, despite deaths and a higher number of SAEs during the trial, these were not attributed to the vaccine but were explained by pre-existing medical conditions and the advanced age of the participants.

Our study faced multiple challenges as the pandemic evolved. This included the decision to maintain the mRNA-1273 booster dose at 100 µg even after the European Medicines Agency (EMA) approved 50 µg as a booster dose [30]. In a future pandemic, adaptive platform trials may enhance recruitment and facilitate the rapid evaluation of new vaccine regimens and doses, as demonstrated in exemplary fashion with the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial on treatment of COVID-19 [31,32].

The findings of this study need to be interpreted in the context of several limitations. The trial protocol did not foresee systematic assessment of SARS-CoV-2 infection, thus limiting interpretation of individual antibody titers, as intercurrent infection may have boosted antibody response at any time between baseline and the immunogenicity readings (day 14 and month 12). No clinical endpoints, i.e., protection against clinical disease and related severity, were assessed. Changes in vaccination policy of NITAGs in Europe and the approval of variant-adapted vaccines prompted a modification of the study design, resulting in Part A and Part B, and, eventually, premature termination of the trial [10,12]. In addition, it cannot be excluded that participants concealed subsequent vaccinations in line with national recommendations without reporting these to the study teams.

Both the first and second booster vaccinations with either BNT162b2 or mRNA-1273 resulted in a substantial increase in antibody anti-RBD-titers 14 days after vaccination in participants of advanced age. This response was sustained over 12 months, while virus neutralization capacity was lower against SARS-CoV-2 variants emerging later. Double-dose mRNA-1273 (100 µg) provided higher antibody titers compared with BNT162b2 (30 µg), with an overall similar safety profile in participants ≥75 years of age.

Declaration of competing interest

JS has received research grants by the German Federal Ministry of Education and Research (BMBF), the Medical Faculty of the University of Cologne, Basilea Pharmaceutica, Noscendo and Scynexis; has received speaker honoraria by AbbVie, Akademie für Infektionsmedizin e.V., Forum für medizinische Fortbildung GmbH, Hikma, Lilly, Mundipharma, Pfizer, VITIS GmbH; has been a consultant to or participated on advisory boards of AiCuris, Alvea, Basilea, Kite-Gilead, Micron Research, Mundipharma, Shionogi all outside the submitted work. He received travel support from Page Medical, German Society for Infectious Diseases and Meta-Alexander Foundation. LY no conflicts declared. CS no conflicts declared. KGIM has received honoraria for lectures from Takeda, IQVIA and BioNTech, has received a Research Grant from Norwegian Regional Health authorities, West, grant nr F12626 and is a member of an advisory board on committee for National vaccination programs, Norwegian Public Health Institute. AJCS no conflicts declared. ERR no conflicts declared. JMM no conflicts declared. IVM no conflicts declared. IP no conflicts declared. TW no conflicts declared. BZ no conflicts declared. MA has received research grants from Pfizer and Gilead; contributed to educational activities organized/supported by Pfizer, Roche, Gilead, GSK, Moderna and Sanofi. All honoraria from these activities are paid to the Institution. UB no conflicts declared. SH no conflicts declared. JSG has received speaker honoraria from AstraZeneca, Gilead, Pfizer, and Menarini, and has been a member of an advisory board for Pfizer, outside of the submitted work. JJ no conflicts declared. LT no conflicts declared. MZ received honoraria for lecturing courses by Pfizer Malaysia; was an employee with AiCuris AG and is now an employee with DEBRA Research gGmbH. AC no conflicts declared. LMB no conflicts declared. JG no conflicts declared. SCM reports grants from the German Center for Infection Research, from the Else-Kröner-Fresenius Stiftung, lecture and speaker honoraria from Akademie für Infektionsmedizin e.V., AstraZeneca, GSK, Octapharma, and Pfizer; all outside of the submitted work. JAN no conflicts declared. JN no conflicts declared. RS reports grants from the German Center for Infection Research and the Ministry of Culture and Science of the State of North Rhine-Westphalia, lecture and speaker honoraria from Akademie für Infektionsmedizin e.V., Ärztliche Akademie für medizinische Fort- und Weiterbildung in Nordrhein, Forum für medizinische Fortbildung GmbH, Infektio Saar Netz, Hikma, Mundipharma and Pfizer and travel support from the European Confederation of Medical Mycology (ECMM), International Society for Human and Animal Mycology (ISHAM), Page Medical and Pfizer; all outside of the submitted work. JFI has received research grants by the Instituto de Salud Carlos III, Ministry of Science. Spain; has received grants or research contracts from Laboratorios Faes, Normon, Pfizer, Italfarmaco, GSK, Prestige; has been a consultant or has received speaker honoraria from Faes, Normon, Cinfa, Mundipharma, Abbott, Novartis and docency colaborations from AbbVie. RN no conflicts declared. CG no conflicts declared. GS no conflicts declared. AGL no conflicts declared. PWGM has received honoraria and/or grant funding from Gilead, Janssen, MSD, ViiV Healthcare, GSK and AstraZeneca, outside of the submitted work. CL no conflicts declared. AH no conflicts declared. KL no conflicts declared. SMK has received grants from Pfizer, MSD, Huvepharma, AiCuris, Astra Zeneca, Mylan, Janssen pharma. HG no conflicts declared. SKS no conflicts declared. FK no conflicts declared. MP no conflicts declared. PK reports grants or contracts from German Federal Ministry of Research and Education (BMBF) B-FAST (Bundesweites Forschungsnetz Angewandte Surveillance und Testung) and NAPKON (Nationales Pandemie Kohorten Netz, German National Pandemic Cohort Network) of the Network University Medicine (NUM), the State of North Rhine-Westphalia and the Dr. Heinz Lux-Stiftung; consulting fees Ambu GmbH, Gilead

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Ethics approval and consent to participate

The trial was approved by the Ethics Committee of the Faculty of Medicine, University of Cologne, Germany (Identifier: 21-1457-AMG-ff) and all ethics committees of the participating trial sites (details can be given on demand by the corresponding author). All participants provided written informed consent before start of trial participation following all principles of ICH-GCP guidelines.

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The research leading to these results was conducted as part of the VACCELERATE consortium. For further information please refer to www.vaccelerate.eu. This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 101037867. Global trial coordination, correspondence with ECs and Competent Authority in Germany, data management, safety management and monitoring were performed by the CTCC, University of Cologne. Trial coordination and correspondence with ECs and Competent Authority in all other countries (Ireland, Lithuania, Norway and Spain) were performed by ECRIN. Randomization was implemented by a 24/7-Internet service (ALEA 17.1) and prepared centrally by the Institute of Medical Statistics and Computational Biology (IMSB) at the University of Cologne. Statistical design and data analysis were performed by the Center for Medical Data Science (CeDAS), Medical University of Vienna. Medical University of Vienna procedures are implemented according to the standard operating procedures of CTCC and CeDAS. Anti-receptor binding domain and anti-N laboratory analysis were performed and results provided by UCD Centre for Experimental Pathogen Host Research (CEPHR) at University College Dublin in Ireland; neutralizing antibody laboratory analysis was performed and results provided by Faculty of Medical & Health Sciences Molecular Pathology Group, Laboratory of Cell Biology & Histology University of Antwerp. Samples for biobanking are stored at the Biobank Antwerp with legal entity part of University Hospital Antwerp. We thank all study team members for their effort and cooperation within this study. We would like to extend special thanks to Katharina Köbe for technical assistance.

Author contributions

OAC obtained funding. The study was conceived by OAC and decided on by the VACCELERATE Coordination Board. OAC, MZ, SH, UB, LT, JF, AJC, PK, FK, MP, AC, and JN participated in the design of the study and OAC, MA, UB, MZ, AC, SH, LT, JS, LMB, JG, JJ, RS, and PK supervised and coordinated the trial. JS, PK, FK, LY and OAC contributed to drafting the manuscript. FK, LY, and MP participated in the design of the study, are responsible for the sample size calculation and the statistical analysis and contributed to drafting the manuscript. JS, CS, KGIM, AJCS, ERR, JMM, IVM, IP, TW, BZ, LMB, JG, JAN, SCM, JMN, RS, PK, and OAC enrolled participants. JFI, RN, CG, GS, AGL, PM, SKS, AH, SMK, HG, KL, and CL were responsible for laboratory analyses. KL and CL were responsible for sample kit preparation, developing the sample collection and management manual, shipping sample collection materials and samples and biobank. All authors read and approved the final manuscript.

Consent for publication

Written informed consent obtained from every participant included **permission to publish research findings.**

Availability of data and materials

On reasonable and approved requests made to the corresponding author, data can be shared through secure online platforms.

Authorship eligibility guidelines

Authorship for trial publications follow the recommendations on authorship published by the International Committee of Medical Journal Editors and the VACCELERATE Publication Policy V01.0 from 20 December 2021.

Roles and responsibilities

The trial sponsor University of Cologne is represented by Professor Oliver A. Cornely. Overall project coordination, randomization, data management, safety management and central monitoring for the entire trial and correspondence with ethics committees and the competent authorities in Germany were assigned to CTCC. Project coordination and correspondence with ethics committees and competent authorities for countries other than Germany were performed by ECRIN. Statistical design and data analysis were performed by MUW and CeDAS. The services of the Biobank Antwerp, Antwerp, Belgium (ID: BE 71030031000" Biobank Antwerp [BB190007], BBMR-ERIC, Belgian [BIORESOURCE]) are used for storage of the generated samples and aliquots.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2026.108466.

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