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Immunogenicity, reactogenicity, and safety of a second booster with BNT162b2 or full-dose mRNA-1273: A randomized VACCELERATE trial in adults aged ≥75 years (EU-COVAT-1-AGED Part B)

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ABSTRACT

Objectives: To assess the safety and immunogenicity of a fourth vaccination (second booster) in individuals aged ≥75 years.
Methods: Participants were randomized to BNT162b2 (Comirnaty, 30 µg) or messenger RNA (mRNA)-1273 (Spikevax, 100 µg). The primary end point was the rate of two-fold antibody titer increase 14 days after vaccination, targeting the receptor binding domain (RBD) region of wild-type SARS-CoV-2. The secondary end points included changes in neutralizing activity against wild-type and 25 variants. Safety was assessed by monitoring solicited adverse events (AEs) for 7 days.
Results: A total of 269 participants (mean age 81 years, mRNA-1273 n = 135/BNT162b2 n = 134) were included. Two-fold anti-RBD immunoglobulin (Ig) G titer increase was achieved by 101 of 129 (78%) and 116 of 133 (87%) subjects in the BNT162b2 and the mRNA-1273 group, respectively ($P = 0.054$). A second booster of mRNA-1273 provided higher anti-RBD IgG geometric mean titer: 21.326 IU/mL (95% confidence interval: 18.235-24.940) vs BNT162b2: 15.181 IU/mL (95% confidence interval: 13.172-17.497). A higher neutralizing activity was noted for the mRNA-1273 group. The most frequent AE was pain at the injection site (51% in mRNA-1273 and 48% in BNT162b2). Participants in the mRNA-1273 group had less vaccine-related AEs (30% vs 39%).
Conclusions: A second booster of either BNT162b2 or mRNA-1273 provided substantial IgG increase. Full-dose mRNA-1273 provided higher IgG levels and neutralizing capacity against SARS-CoV-2, with similar safety profile for subjects of advanced age.

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Introduction

Despite successful primary vaccination against SARS-CoV-2, booster vaccinations are required to maintain vaccine-induced protection [1].

Continuous viral escape limits the effect of targeted treatments, in particular, the effect of monoclonal neutralizing antibodies [2].

In light of emerging virus variants and breakthrough infections, the World Health Organization recommended second booster vaccinations, i.e. a fourth dose of a SARS-CoV-2 vaccine, for at-risk populations, in particular, patients of advanced age with comorbidities [3,4].

The COV-BOOST trial showed that the fold change of anti-spike immunoglobulin G (IgG) titers between the first and second booster was more pronounced in individuals aged >70 years compared with younger adults [5]. This implies that there may be potential to further increase the immune response after a booster dose [5], and BNT162b2 (BioNTech/Pfizer, Comirnaty) and messenger RNA (mRNA)-1273 (Moderna, Spikevax) have proved to be highly effective booster vaccines [6].

To date, randomized controlled studies in the aged population are scarce [7]. EU-COVAT-1 – Part B is a randomized head-to-head comparison of BNT162b2 30 µg vs mRNA-1273 100 µg as second booster vaccination in adults ≥75 years of age. We report data on the immune response 14 days after vaccination and on safety until day 90.

Methods

Trial design and timelines

EU-COVAT-1 is a multinational, phase II, randomized clinical trial examining the immunogenicity and reactogenicity of a second booster vaccination with BNT162b2 30 µg or mRNA-1273 100 µg in adults ≥75 years of age (Supplement Table 1, Supplement Figure 1). The rationale to use mRNA-1273 100 µg, i.e., the double of the licensed dose, was based on the fact that the exact dose for boosting was not yet defined when this trial protocol was designed; however, in the studies driven by the manufacturer, the 100 µg dose had shown a higher neutralizing antibody level increase than the 50 µg with a similar safety profile [8].

This trial is conducted within the VACCELERATE network [9]. Participating trial sites were selected through the VACCELERATE Site Network, whereas recruitment of trial participants was supported through the VACCELERATE Volunteer Registry [10]. After approval by the responsible ethics committee on November 8, 2021 (Ref.: 21-1457-AMG-ff) and regulatory approval by the Paul-Ehrlich-Institut on October 20, 2021 (Ref.: 4647); enrollment for the trial started at a single center in Cologne, Germany in November 2021, referred to as Part A (ClinicalTrials.gov Identifier: NCT05160766, EudraCT Number: 2021-004526-29) [11]. The part of the trial we report here on—referred to as Part B—was fully approved on January 21, 2022 and was conducted in a multicenter setting within the VACCELERATE consortium. Enrollment was closed as per sponsor decision on December 6, 2022. Participating sites were located in Cologne, Frankfurt, and Hannover (all in Germany); Vilnius (Lithuania); Bergen (Norway); and Barcelona, Córdoba, Madrid, and San Sebastián (all in Spain). The full clinical trial protocol is provided in the Supplement.

Participants

Subjects ≥75 years of age were eligible if they met the main inclusion criteria consisting of the following: (i) priming with homologous ChAdOx-1-S, BNT162b2, or mRNA-1273; (ii) first booster with either BNT162b2 or mRNA-1273 at least 1 month before enrollment into study, and (iii) no SARS-CoV-2 infection within the previous 3 months. Participants with current severe immunosuppressive therapy such as high-dose glucocorticosteroids or active cancer treatment were not eligible for this trial. Participants provided written informed consent.

Randomization

Permuted random blocks were used. Participants were randomly assigned to either BNT162b2 30 µg or mRNA-1273 100 µg in 1:1. The software ALEA 17.1. (ALEA Clinical B.V., Abcoude, The Netherlands) was used as electronic randomization tool and results

Table 1
Baseline characteristics and primary end point.

	BNT162b2 *n = 135*	*mRNA-1273* *n = 135*
Age (years)		
Mean ± SD	80.99 ± 5.49	81.09 ± 5.88
Median [min; max]	79 [75; 99]	79 [75; 99]
Vaccine		
BNT162b2	135(100%)[a]	0 (0%)
mRNA-1273	0 (0%)	135 (100%)
Sex		
Female	67 (50%)	68 (50%)
Male	68 (50%)[a]	67 (50%)
Body mass index (kg/m²)		
Mean ± SD	25.55 ± 4.04	25.99 ± 4.0
Median [min; max]	25.4 [16.6; 40.2]	25.4 [18; 41.8]
Priming vaccine regimen		
3x BNT162b2	95 (70%)[a]	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%)
Boosting (comparing third and study vaccination)		
Heterologous boosting	27 (20%)	104 (77%)
Homologous boosting	108 (80%)[a]	31 (23%)
Time between first and second vaccination in days		
Mean ± SD	35.65 ± 19.95	34.72 ± 19.16
Median [min; max]	22 [20; 86]	22 [16; 114]
Time between second and third vaccination in days		
Mean ± SD	211.41 ± 38.16	210.64 ± 37.1
Median [min; max]	207 [124; 303]	203 [126; 313]
Time between third and study vaccination in days		
Mean ± SD	185.85 ± 68.4	191.8 ± 69.9
Median [min; max]	176 [52; 308]	195 [74; 324]
Primary endpoint: overall proportion fold change ≥2 from day 0 to day 14		
	101/129 (78.3%) (97.5% CI: 69-85.9%)	116/133 (87.2%) (97.5% CI: 79.3-93%)

CI, confidence interval; mRNA, messenger RNA
For metric variables Mean ± standard deviation (SD), median (minimum [min]; maximum [max]) are reported. For categorical variables, absolute frequencies and percentage (%) per vaccine group are stated.
[a] 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.

were documented in the electronic case report form (TrialMaster 5.0 update 03, Anju Software, Tempe, AZ, USA). No blinding was used in this trial.

Procedures

After randomization, intramuscular (deltoid) injection of vaccine was performed by trained site staff. For the analysis of immunogenicity, blood was drawn at baseline (day 0 before vaccination) and at day 14. Anti-SARS-CoV-2 receptor binding domain (RBD) IgG antibodies (anti-RBD IgG) and SARS-CoV-2 anti-nucleocapsid (N) IgG (anti-N IgG) were determined at days 0 and 14. Safety and reactogenicity were determined by the occurrence of adverse events (AEs). Solicited AEs were monitored via a participant diary for 7 days. Unsolicited AEs were recorded until the end of trial participation. Per protocol, AEs of grade III or higher were classified as severe adverse events (SAEs), with the seriousness criterion “other medical important event” and were pursued for a further 30 days.

Plasma levels of anti-RBD IgG and anti-N IgG were measured at the Centre for Experimental Pathogen Host Research in Dublin, Ireland, using the Mesoscale Diagnostics (MSD, Rockville, MD, USA) electrochemiluminescence immunoassay. The results were expressed in IU/mL, based on the first World Health Organization International Standard for anti-SARS-CoV-2 human immunoglobulin (NIBSC code: 20/136). Further details are provided online: https://www.euvaccine.eu/covid-immune-monitoring.

Angiotensin-converting enzyme 2 (ACE2) neutralization (% inhibition) of SARS-CoV-2–specific antibodies was estimated from plasma 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 the following spike proteins were measured: wild-type virus and the following variants of concern (VOCs): B.1.1.7, B.1.351, P.1, P.2, B.1.617, B.1.617.1, AY.3, AY.4.2, B.1.617.3, B.1.526.1, BA.1, BA.2, BA.2+L452M, BA.2+L452R, BA.2.12.1, BA.2.75, BA.2.75.2, BA.3, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.1, and XBB.1. Further details on the methodology are provided in Supplement Methods 1.

Outcome parameters

The primary end point of the study was the rate of two-fold anti-RBD IgG antibody titer increase 14 days after the second booster against wild-type virus. Secondary end points included vaccine-induced antibody titer increases and change in neutralization antibody activity against wild-type virus and VOC after 14 days, among others, in subgroups. Safety and reactogenicity were determined by the occurrence of any unsolicited AEs until the end of trial, solicited AEs for 7 days after the second booster dose, and by the rate of SAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Advents up to 3 months.

In this interim report of Part B, the primary and secondary end points until day 14 of this study were included, as well as safety data up to 3 months of follow-up.

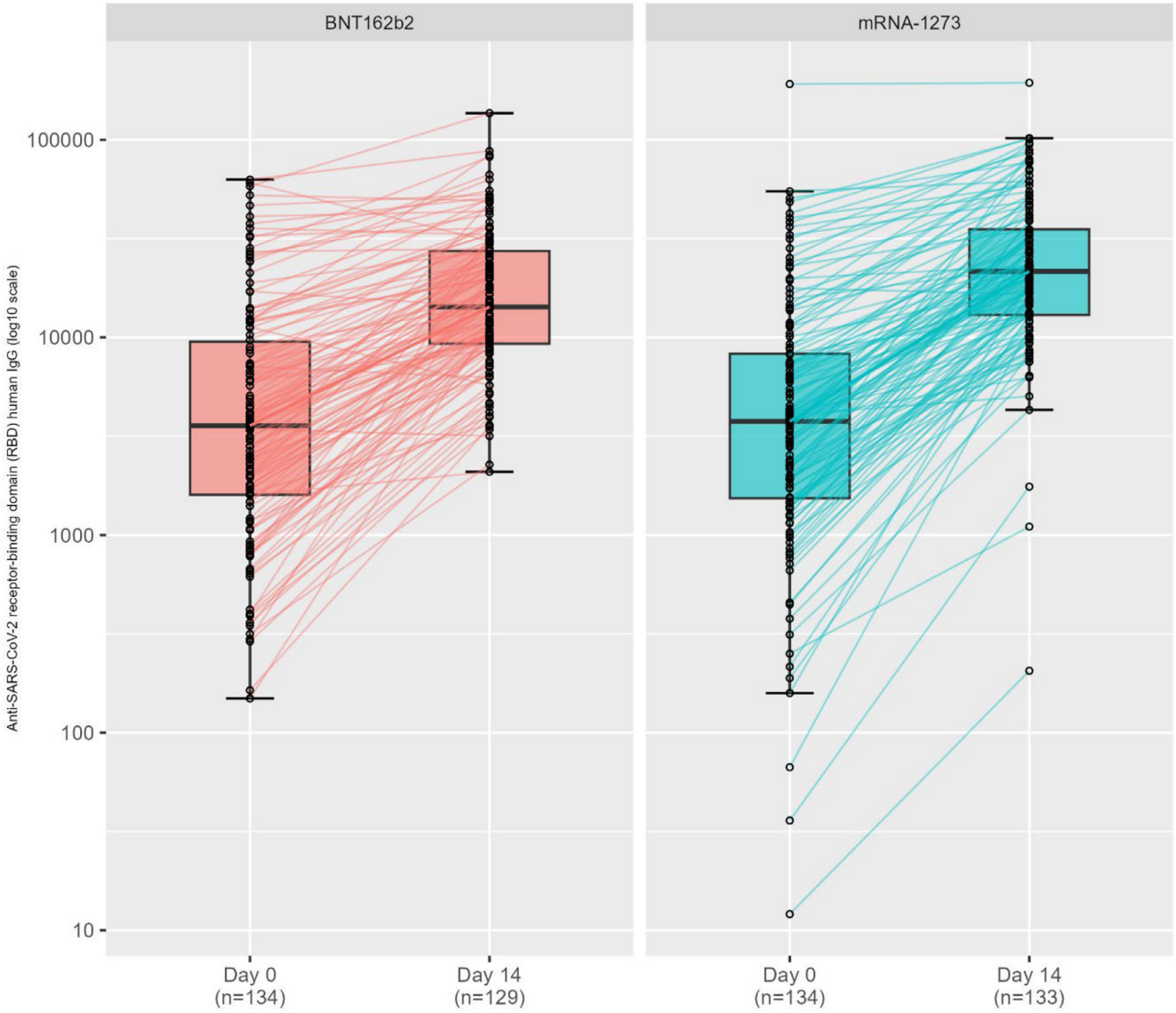

Figure 1. Kinetics of anti-RBD IgG between day 0 (randomization before vaccination) and day 14. Boxplot images represent the median (black line in the middle of each boxplot) of anti-RBD protein IgG titers at baseline (day 0) and 14 days after vaccination with 30 μg BNT162b2 (red, left side) and after vaccination with a full-dose (100 μg) mRNA-1273 in green (right side) (IU/mL), $P = 0.054$ (Cochran–Mantel–Haenszel test). Solid lines connect samples from the same participants at multiple time points.
Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

Statistical design

Sample size calculation was performed for the primary end point for the rate (π) of two-fold antibody titer increase after the second booster vaccination. Because two-sided simultaneous 95% confidence intervals (CI) for this rate were calculated separately for each randomized group in Part B, accordingly, a Bonferroni adjustment was used for the sample size calculation.

With this design, when the sample size is 250 per randomized group, two-sided simultaneous 95% CI (with Bonferroni adjustment for two simultaneous CI in a cohort) for a proportion using the large sample normal approximation will extend no more than ± 7.1% (percentage points) from the observed proportion. For example, if the observed proportion is 50% (where the CI is widest), the CI ranges from about 42.9% to 57.1%. To adjust for potential dropouts in Part B of about 8-10%, the total sample size for Part B (= second booster and cohorts 4-9) was set to 550.

Statistical methods

For the analysis of Part B, day 14 outcome data and safety data up to 3 months of follow-up were exported on June 4, 2023 and April 28, 2023, respectively. For the binary primary end point (participants with a fold change ≥2 for anti-RBD IgG), absolute counts and frequencies in percent were calculated per intervention arm. The corresponding rate together with the simultaneous two-sided 95% CI is reported by implementing a Bonferroni adjusted level of 97.5% for the Clopper-Pearson CI.

Supportive analyses for the primary end point: in addition, the primary end point was determined in the same way for each cohort (according to priming regimen) separately, i.e. further supportive analyses were performed based on different prevaccination regimens. Especially, within each cohort, the multiplicity adjustment was implemented as described previously. To evaluate whether there is a difference between the two randomized intervention groups in the binary primary end point, a Cochrane–

Mantel–Haenszel test was applied stratified by the initial cohort of vaccination regimens. Logistic regression models were performed using the primary end point as dependent variable and intervention group as the main factor. Multiple logistic regression models were used adjusting for factors such as initial vaccination regimens, age, gender, or time lag between the 1st and 2nd, 2nd and 3rd, 3rd and in-study vaccination in further sensitivity analysis. Descriptive tables were provided stratified by taking into consideration the vaccination regimens. The least square mean differences between mRNA-1273 minus BNT162b2 and corresponding 95% CI were calculated using the log10 transformed titer values as the dependent variable in a generalized linear model with the factor booster group (BNT162b2/mRNA-1273), as well as the stratification variables used for randomization. The mean difference (least square mean difference) on the log10 scale was calculated backward to the original scale to yield the ratio for the geometric mean titer (GMT) values at day 14. In addition, the four-fold increase of anti-RBD IgG, geometric mean fold rise, and GMT at day 14 are reported for both vaccination groups. The GMT at day 14 are also reported for the subgroups related to the priming regimen (3 × mRNA-1273 or 3 × BNT162b2 or 2 × BNT162b2 and mRNA-1273 or 2 × mRNA-1273 and BNT162b2 or 2 × ChAdOx-1-S and mRNA-1273 and 2 × ChAdOx-1-S and BNT162b2). Similarly, the impact of previous COVID-19 infection (yes/no) was investigated. The Mann–Whitney U test was used to test whether there was a difference in the anti-RBD antibody titer at baseline (day 0) between the participants with and without previous COVID-19 infection. The values for ACE2 neutralizing capacities of SARS-CoV-2–specific antibodies were analyzed descriptively. To check for the differences in antibody neutralizing capacities at day 14 an analysis of covariance was calculated for wild-type and each variant using the factors vaccine regimen (mRNA-1273 vs BNT162b2) and the corresponding baseline value (day 0), priming vaccination regimens, gender, and age as covariates. The mean differences (plus two-sided 95% CI and *P*-values) between the two vaccine groups was reported. To visualize the data, heatmaps and boxplots are provided. For the safety end points, absolute and percentage numbers per system organ class, preferred term, and severity (for AEs related or also related and unrelated to the investigational medicinal products [IMP]) were reported per intervention group.

Role of funding source

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 Commission – Directorate General for Research and Innovation under the Framework Program HORIZON 2020 under the VACCELERATE Grant Agreement (GA) and its annexes No. 101037867. The funders of the trial had no role in trial design, data collection, data analysis, data interpretation, or in the writing of the report.

Results

A total of 270 participants were enrolled in Part B from February 16, 2022 to September 15, 2022 at nine trial sites across Europe (Supplement Table 2). In this interim report of Part B, the primary and secondary end points until day 14 of this study were included, as well as safety data up to 3 months of follow-up.

Due to changes of the recommendations for booster vaccinations and licensing of adapted vaccines to circulating SARS-CoV-2 Omicron variants in the respective countries, enrollment of volunteers ceased after September 2022. Therefore, the sponsor formally decided to prematurely terminate enrollment.

A total of 135 of 270 participants received BNT162b2 as second booster, 135 participants received mRNA-1273. Three and one subjects discontinued study participation until month 3 in the BNT162b2 and in the mRNA-1273 group, respectively, but were included in the day 14 immunogenicity analyses. One participant was excluded from any immunogenicity analysis but included in the safety reporting due to an accidentally unreported second booster vaccination before study entry, which only became apparent after vaccination within this study (Supplement Figure 2).

Participants' baseline characteristics are summarized in Table 1 and Supplementary Table 3. The most frequent priming and first booster regimen in 70% of participants in both randomization groups was a course of three-dose BNT162b2. The most frequent comorbidities were vascular disorders (e.g. hypertension), with 61% in the BNT162b2 group and 59% in the mRNA-1273 group (Supplement Table 4). The median time and range (maximum to minimum) to sample collection was 14 (8-21) days for the 14 days of follow-up and 91 (71-146) days for the 3 months of follow-up.

In the BNT162b2 group, 101 of 129 (78.3%) (97.5% CI: 69-85.9%) participants showed a two-fold increase in anti-RBD IgG titers at 14 days compared with 116 of 133 (87.2%) (97.5% CI: 79.3-93%) in the mRNA-1273 group (Table 1, Supplement Table 5). The two rates were compared in a supportive analysis with a Cochran–Mantel–Haenszel test and almost reached statistical significance ($P = 0.054$) despite the small sample size (Supplement Table 6). For the mRNA-1273 group, higher values at day 14 were observed with GMT at day 14 of 21.326 IU/mL (95% CI: 18.235-24.940) and 15.181 IU/mL (95% CI: 13.172-17.497) for BNT162b2 and mRNA-1273, respectively (Supplement Table 5, Figure 1) and a ratio $\frac{GMT_{\text{mRNA-1273}}}{GMT_{\text{BNT162b2}}}$ at day 14 of 1.38 (95% CI: 1.12-1.71). Logistic regression models with ≥ two-fold change as a dependent variable indicate that the odds of having ≥ two-fold change in the mRNA-1273 group is approximately 2.06 times higher than the odds of having ≥ two-fold change in the BNT16b2b group (Supplement Table 6). Similar kinetics were observed when exploring the ≥ four-fold change of anti-RBD IgG with 51.9% and 63.2% for BNT162b2 and mRNA-1273, respectively (Supplement Table 5). There was also a higher geometric mean fold rise in the mRNA-1273 group. Based on the priming regimen, descriptive subgroup analyses for both vaccination groups were performed (Supplement Table 5). Fold changes are shown in Supplement Figure 4.

There were significant differences in anti-RBD IgG at baseline between participants with previous COVID-19 and those without (Mann–Whitney U, $P < 0.001$), which is expected since individuals who were previously infected with the virus may have a different baseline immune response (Figure 2). Accordingly, increase of anti-RBD IgG after the second booster in participants with previous COVID-19 was lower than in those without previous infection (Supplement Table 7).

In the safety analyses, for IMP-related AEs within 7 days after vaccination, in the mRNA-1273 group, more participants reported solicited AEs and more AEs were reported in total (Figures 3a/b, Supplement Tables 8, 9, and 10). There was no statistically significant difference between the groups in terms of the number of subjects with IMP-related AEs (75 of 135 [55.6%] in BNT 162b2 vs 77 of 135 [57%]) in mRNA-1273, *P* of chi-square test = 0.9), but the groups differed in the occurrence of IMP-related AEs (*t* test for the subgroup of subjects with at least one AE: mean ± SD 3.6 ± 2.96 in BNT162b2 vs 5.39 ± 4.33 in mRNA-1273, $P = 0.0034$). The most frequent AEs related to IMP in both groups were injection site pain (48.1% in BNT162b2 and 51.1% in mRNA-1273), fatigue (23% in BNT162b2 and 37.8% in mRNA-1273), and asthenia (10.4% in BNT162b2 and 11.9% in mRNA-1273) (Figure 3a and Supplement Tables 8 to 11). Other frequently reported AEs were headache and

Table 2
AEs and AE grading within 7 days of vaccination related to IMP for BNT162b2 vs mRNA-1273.

	BNT162b2 *n = 135*	*mRNA-1273* *n =135*
Participants with no AE related to IMP	60 (44.4%)	58 (43%)
Participants with at least one AE of worst grade I related to IMP	53 (39.3%)	39 (28.9%)
Participants with at least one AE of worst grade II related to IMP	21 (15.6%)	34 (25.2%)
Participants with at least one AE of worst grade III[a] or higher related to IMP	6 (4.4 %)	4 (3%)
Participants with at least one SAE related to IMP	1 (0.7 %)	0 (0%)

AE, adverse event; IMP, investigational medicinal product; mRNA, messenger RNA; n, number of participants; SAE, serious AE.
[a] AE of grade III or higher were classified as SAE with the seriousness criterion "other medical important event."

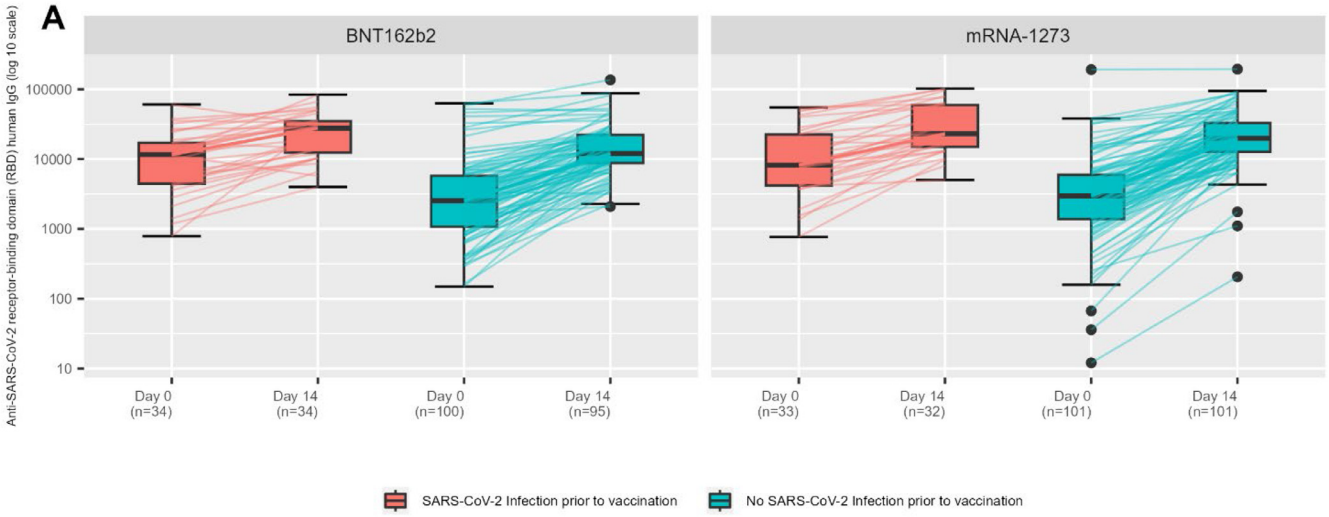

Figure 2. Boxplot images represent the median (black line in the middle of each boxplot) of anti-RBD protein IgG titers at baseline (day 0) and 14 days after vaccination with 30 µg BNT162b2 and previous SARS-CoV-2 infection (left box panel a) and after vaccination with a full-dose (100 µg) mRNA-1273 and no previous SARS-CoV-2 infection (right side panel a).
Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

hyperhidrosis after vaccination with mRNA-1273 (Figure 3b). The number of participants with no AEs related to IMP was similar with 60 reported AEs in the BNT162b2 group vs 58 AEs in the mRNA-1273 group (Table 2). The number of participants with IMP-related AEs (grade I) was lower in the mRNA-1273 group (29.6% vs 39.3%), but there were more participants (n = 34) with at least one grade II AE-related to IMP in the mRNA-1273 group. A total of 10 participants in the BNT162b2 group (7.4 %) and 12 participants in the mRNA-1273 group (8.9%) reported SARS-CoV-2 infection between day 0 and month 3.

A total of 14 SAE occurred in nine subjects, four in three subjects in the mRNA-1273 group, and 10 in six subjects in the BNT162b2 group. Four grade III AEs (thus classified as SAEs) were reported by the same participant in the BNT162b2 group 5 days after vaccination (joint pain, malaise, muscle pain, and chills), all of which resolved within 1 day. All remaining SAEs were hospitalizations or medical consultations due to other medically important events and were not IMP-related. No deaths occurred. The full safety data will be included in the final report of this study.

ACE2 neutralizing capacity of SARS-CoV-2 specific antibodies (in %) 14 days after the second booster was lower for Omicron variants than other variants (Figure 4). The mRNA-1273 group showed a consistent pattern of a higher SARS-CoV-2 antibody neutralization capacity than the BNT162b2 group (Figure 4), markedly so against Wuhan wild-type, B.1.1.7 (Alpha variant), and AY.4.2 (Delta variant) (Figure 4, Supplement Figure 5). In the exploratory analysis of covariance analyses, the mean differences between the two groups yielded statistical significance for Wuhan wild-type and 15 of 25 variants. The estimated mean differences between mRNA-1273 minus BNT162b2 varied between 2.2 and 7.8 percentage points (Supplement Table 12).

Discussion

With the participants' mean age of 81 years, this study included the oldest population so far in a randomized comparison of two mRNA-based SARS-CoV-2 vaccines. We demonstrated a two-fold anti-RBD IgG antibody titer increase in 83% of trial participants 14 days after vaccination. A 100-µg dose of mRNA-1273 elicits higher anti-RBD IgG levels than a 30-µg dose of BNT162b2 and a higher neutralizing activity against circulating SARS-CoV-2 variants at the short term without a significantly higher rate of AEs.

Vaccine response in the age group ≥75 years has been assessed rarely in randomized trials. In a smaller cohort of subjects with a median age of 71 years, a significant and sustained increase of neutralizing anti-RBD antibodies 15 and 28 days after booster vaccinations with both mRNA-1273 and BNT162b2 in all participants was observed. This study did not detect an influence of age on the immune response; however, this study was not randomized and did only include 65 subjects [12]. Age-related immunosenescence is a relevant factor for vaccine efficacy and duration of antibody-mediated immunity, partly caused by reduced B- and T-cell responses [13,14]. Subsequently, the immune response to vaccines is expected to be impaired in the elderly [15]. Age ≥80 years, five comorbidities, male sex, immunosuppression, and stage V chronic kidney disease were detected as risk factors for developing severe COVID-19 in a large analysis of 30 million individuals after primary and booster vaccination [16]. Further boosters or even sea-

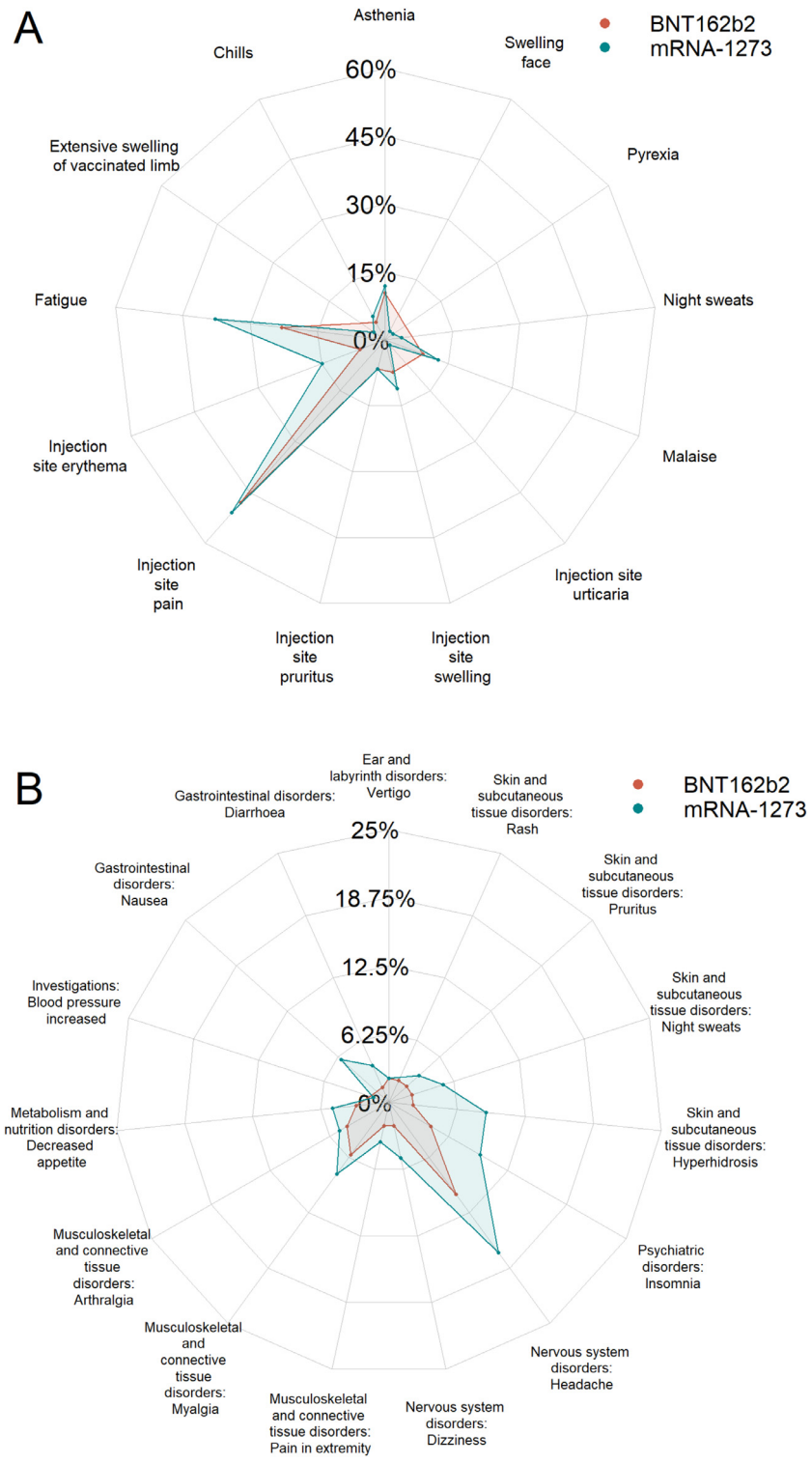

Figure 3. a/b. Spider chart of frequent AEs 7 days after on-study vaccination (BNT162b2 = red, mRNA-1273 = turquois) based on safety data set including all participants who received study intervention (BNT162b2 n = 135, mRNA-1273 n = 135). Plot a shows AEs (with frequencies over 1%) reported for the system organ class "general disorders and administration site conditions." Plot b shows AEs for other system organ classes.
AE, adverse event; Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

sonal vaccinations for improved immunity against SARS-CoV-2 and prevention of severe COVID-19 may provide better immunogenicity in individuals of advanced age [17]. This hypothesis has often been phrased and was proven for vaccines against other viruses but has not yet been established in a randomized trial for SARS-CoV-2 [18,19].

Neutralization activity and anti-RBD IgG titers were higher with a second booster of a full-dose mRNA-1273 (100 µg) vs BNT162b2 (30 µg), resulting in an improved antibody-mediated protection for individuals ≥75 years of age. This is in line with findings in populations of advanced age who had received heterologous booster doses, and with the 100-µg dose of mRNA-1273 inducing the high-

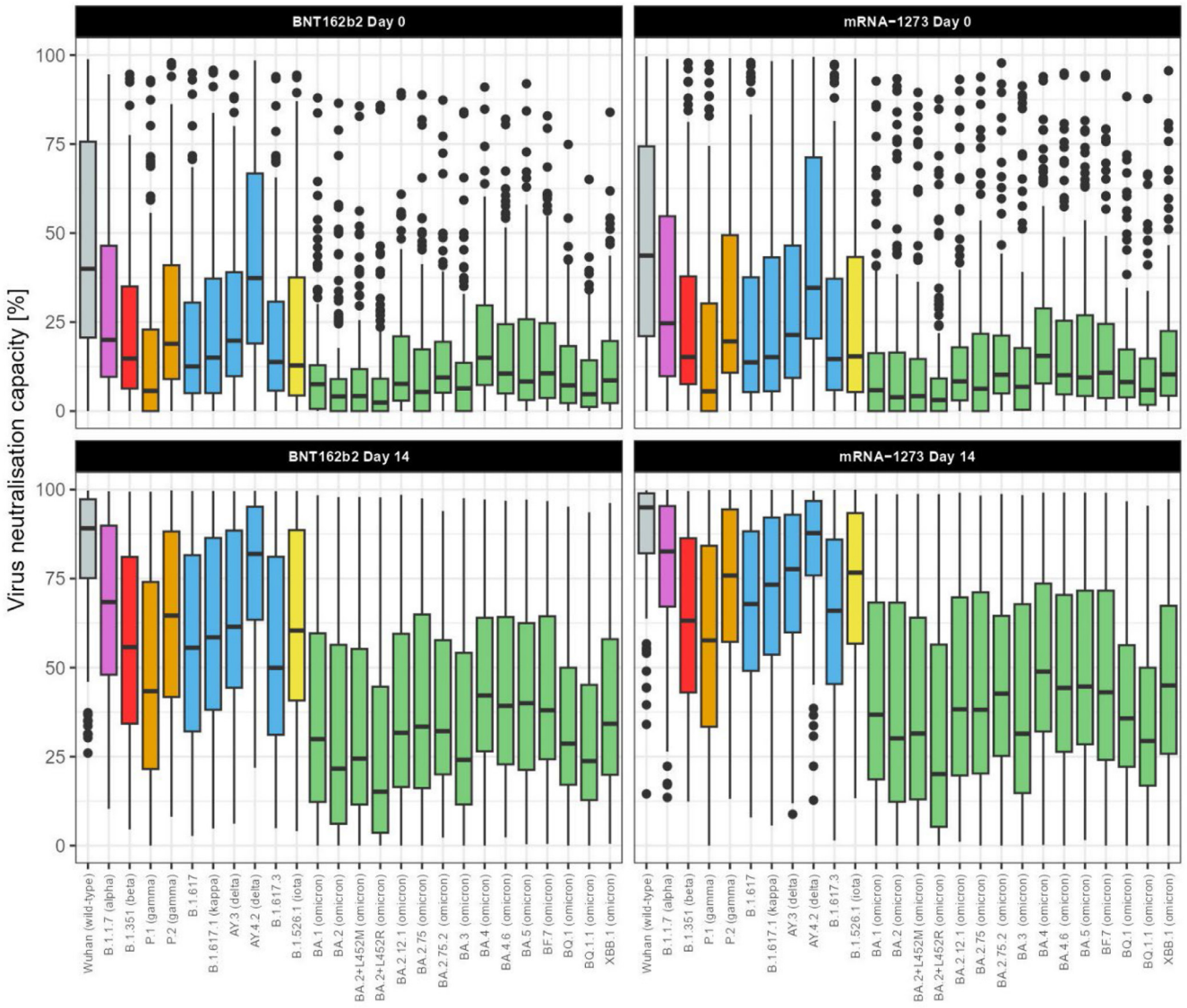

Figure 4. Angiotensin-converting enzyme 2 neutralization activity at baseline (day 0) and at day 14 per initial vaccination group 30 µg BNT162b2 and full-dose (100 µg) mRNA-1273.
mRNA, messenger RNA.

est antibody titers [20]. The COV-BOOST trial enrolled participants with a median age of 70 years to receive either BNT162b2 or mRNA-1273 (in a 50-µg dose) booster doses but with lower absolute fold changes in anti-RBD IgG titers than observed in our study [5]. Of note, in our study, a slight disparity of 70% of participants in the BNT162b2 group had a homologous vaccination regimen because they had received three doses of the same vaccine previously.

In a comparative effectiveness trial of first booster doses of mRNA vaccines in US veterans with a median age of 70 years, an overall lower 16-week risk of COVID-19–related outcomes was observed among recipients of mRNA-1273 than recipients of BNT162b2 [21]. Data on long-term effectiveness after booster vaccination show that protection against SARS-CoV-2 infection waned within 6 months but without waning of protection against severe disease [22]. Pending results from the present study, including data on immunogenicity 12 months after second booster vaccination, may further elucidate the role of immunosenescence.

We observed lower seroneutralization activity against more recently emerging SARS-CoV-2 Omicron variants in both study groups. With the emergence of new variants and variant-adapted vaccines, the landscape of SARS-CoV-2 vaccine studies has broadened and novel vaccines have been assessed as boosters, revealing a remarkably high GMT increase in those previously vaccinated with a heterologous priming [23]. However, immune imprinting by primary vaccination against ancestral strains of wild-type SARS-CoV-2 or infection with variants before the Omicron variant may affect immune response to SARS-CoV-2 infection with currently circulating variants or novel vaccines [24]. Of note, in our study, anti-RBD IgG increase (GMT) was lower in participants with previous COVID-19 than in those without. However, this subgroup still achieved higher absolute GMT values and their baseline titers were already significantly higher, which was expected because hybrid immunity provides the highest magnitude of antibody protection [25].

Regarding safety end points and reactogenicity of a second booster in individuals ≥75 years of age, there were no significant differences between BNT162b2 (30 µg) and full-dose mRNA-1273 (100 µg). Local reactions, as well as systemic vaccine-related effects, corresponded to the expected spectrum of AEs described in

previous clinical trials [11,26,27]. Notably, this is the first trial to apply a full-dose of mRNA-1273, whereas it remains to be discussed if the decision to use the double dose of mRNA-1273 may have affected the safety profile.

This trial has several limitations. Changes of vaccination policies in the European Union and the advent of variant-adapted vaccines necessitated a re-design and, later, a stop of recruitment which led to several protocol amendments [11,28]. As a consequence, the initially planned participant number of 550 was not reached and the compared groups remained below calculated statistical sample size. Data on immunogenicity after 12 months are not yet reported; therefore, the effects of immunosenescence in elderly participants with four vaccinations, including some of them with hybrid immunity due to SARS-CoV-2 infection, remains to be finally determined, interpreted, and compared with other studies with similar populations [15]. Immunogenicity assessment at day 14 exactly was not feasible in all participants. Activation of memory responses occurs more quickly than initial adaptive immune responses, but the kinetics of this are poorly studied in older adults. It would be of interest to evaluate whether the responses changed within that period, allowing the evaluation of whether it is appropriate to combine day 8 and day 21 data together with day 14. Furthermore, no clinical end points, i.e. protection against clinical disease and severity were assessed.

With the transition into an endemic viral disease, emerging SARS-CoV-2 variants elucidate mechanisms of immune escape. Although protective anti-RBD antibody titer thresholds have been proposed, these may vary with age and change with time [29]. Thus, an ongoing effort to adapt vaccines, as well as determinants of immune protection, is necessary. In contrast, it has been shown that the cellular response is likely to be conserved against VOCs [30,31]. Future studies should integrate the investigation of T-cell response to reflect a comprehensive picture of vaccine-induced immune response.

In conclusion, a second booster vaccination with either BNT162b2 or mRNA-1273 yielded a substantial antibody titer increase 14 days after vaccination in participants of advanced age. Full-dose mRNA-1273 (100 µg) provided a higher antibody titer than BNT162b2 (30 µg), with an overall similar safety profile for participants aged ≥75 years.

Declarations of competing interest

JS has received research grants by the German Federal Ministry of Education and Research (BMBF), Noscendo and Basilea Pharmaceuticals; has received speaker honoraria by AbbVie, Hikma, Pfizer and Gilead; has been a consultant to Gilead, Produkt&Markt GmbH, Alvea Vax and Micron Research and has received travel grants by German Society for Infectious Diseases (DGI) and Meta-Alexander Foundation, all outside the submitted work. 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. JSG has received speaker honoraria from Gilead and Pfizer, outside of the submitted work. MZ has received honoraria for lecturing courses by Pfizer Malaysia; is now an employee with AiCuris AG. RS has received lecture honoraria from Pfizer and Hikma, 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 collaborations from AbbVie. PWGM has received honoraria and/or grant funding from Gilead, Janssen, MSD, ViiV Healthcare, GSK, and AstraZeneca, outside of the submitted work. SMK has received grants from Pfizer, MSD, Huvepharma, AiCuris, Astra Zeneca, Mylan, Janssen pharma. 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 and the State of North Rhine-Westphalia; Consulting fees Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited, Noxxon N.V. and Pfizer Pharma; Honoraria for lectures from Akademie für Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, BioRad Laboratories Inc., Datamed GmbH, European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Ruesselsheim, HELIOS Kliniken GmbH, Lahn-Dill-Kliniken GmbH, medupdate GmbH, MedMedia GmbH, MSD Sharp & Dohme GmbH, Pfizer Pharma GmbH, Scilink Comunicación Científica SC, streamedup! GmbH and University Hospital and LMU Munich; Participation on an Advisory Board from Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited and Pfizer Pharma; A pending patent currently reviewed at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Other non-financial interests from Elsevier, Wiley and Taylor & Francis online outside the submitted work. OAC reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from AbbVie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pfizer, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, AbbVie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, Shionogi; payment for expert testimony from Cidara; participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi, and The Prime Meridian Group. Kristin G-I Mohn 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. The remaining authors have no competing interest to declare.

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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.

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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

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Author contributions

OAC obtained funding. 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, TW, BZ, LMB, JG, JAN, SCM, JMN, RS, PK, and OAC enrolled participants. JFI, RN, CG, GS, AGL, PM, SKS, AH, HG, KL, and CL were responsible for laboratory analyses. All authors read and approved the final manuscript.

Consent for publication

Written informed consent obtained by every enrolled participant ensures permission to publish research findings.

Availability of data and materials

Individual participant data will be made available when the trial is completed. 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 will follow the recommendations on authorship published by the International Committee of Medical Journal Editors and the VACCELERATE Publication Policy V01.0 from December 20, 2021.

Roles and responsibilities

The sponsor, the University of Cologne, is represented by Professor Oliver A. Cornely. Overall project coordination, correspondence with ethics committees and Competent Authority, data management, safety management, and central monitoring are performed by the CTCC for Germany. Project coordination and correspondence with ethics committees and competent authorities were performed by ECRIN for all other countries. Statistical design, randomization, and data analysis were performed by the CeDAS. The services of the BioBank Antwerp, Antwerp, Belgium (ID: BE 71030031000" BioBank Antwerp [BB190007], BBMR-ERIC, Belgian [BIORESOURCE]) are used for the 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.2024.107161.

References

[1] Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med* 2021;**385**:e84. doi:10.1056/NEJMoa2114583.
[2] Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 2021;**593**:130–5. doi:10.1038/s41586-021-03398-2.
[3] Pawelec G, Bronikowski A, Cunnane SC, Ferrucci L, Franceschi C, Fülöp T, et al. The conundrum of human immune system "senescence". *Mech Ageing Dev* 2020;**192**:111357. doi:10.1016/j.mad.2020.111357.
[4] Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;**398**:2093–100. doi:10.1016/S0140-6736(21)02249-2.
[5] Munro APS, Feng S, Janani L, Cornelius V, Aley PK, Babbage G, et al. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. *Lancet Infect Dis* 2022;**22**:1131–41. doi:10.1016/S1473-3099(22)00271-7.
[6] Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* 2021;**398**:2258–76. doi:10.1016/S0140-6736(21)02717-3.
[7] Monge S, Rojas-Benedicto A, Olmedo C, Mazagatos C, José Sierra M, Limia A, et al. Effectiveness of mRNA vaccine boosters against infection with the SARS-CoV-2 omicron (B.1.1.529) variant in Spain: a nationwide cohort study. *Lancet Infect Dis* 2022;**22**:1313–20. doi:10.1016/S1473-3099(22)00292-4.
[8] Moderna. Moderna announces preliminary booster data and updates strategy to address omicron variant [press release], 2021, https://investors.modernatx.com/news/news-details/2021/Moderna-Announces-Preliminary-Booster-Data-and-Updates-Strategy-to-Address-Omicron-Variant/default.aspx; 2021 [accessed 20 July 2024].
[9] Salmanton-García J, Wipfler P, Valle-Simón P, Merakou C, Kopsidas I, Bethe U, et al. VACCELERATE Site Network. VACCELERATE Site Network: real-time definition of clinical study capacity in Europe. *Vaccine* 2023;**41**:3915–22. doi:10.1016/j.vaccine.2023.05.006.
[10] Salmanton-García J, Stewart FA, Heringer S, Koniordou M, Álvarez-Barco E, Argyropoulos CD, et al. VACCELERATE Volunteer Registry: a European study participant database to facilitate clinical trial enrolment. *Vaccine* 2022;**40**:4090–7. doi:10.1016/j.vaccine.2022.05.022.
[11] Neuhann JM, Stemler J, Carcas AJ, Frías-Iniesta J, Akova M, Bethe U, et al. Immunogenicity and reactogenicity of a first booster with BNT162b2 or full-dose mRNA-1273: a randomised VACCELERATE trial in adults ≥75 years (EU-COVAT-1). *Vaccine* 2023;**41**:7166–75. doi:10.1016/j.vaccine.2023.10.029.
[12] Durier C, Ninove L, Lefebvre M, Radenne A, Desaint C, Ropers J, et al. Neutralizing antibodies against SARS-CoV-2 variants following mRNA booster vaccination in adults older than 65 years. *Sci Rep* 2022;**12**:20373. doi:10.1038/s41598-022-24409-w.
[13] El Yousfi M, Mercier S, Breuillé D, Denis P, Papet I, Mirand PP, et al. The inflammatory response to vaccination is altered in the elderly. *Mech Ageing Dev* 2005;**126**:874–81. doi:10.1016/j.mad.2005.03.008.
[14] Siegrist CA, Aspinall R. B-cell responses to vaccination at the extremes of age. *Nat Rev Immunol* 2009;**9**:185–94. doi:10.1038/nri2508.
[15] Saiag E, Alcalay Y, Marudi O, Orr-Urtreger A, Hagin D. Cellular and humoral immune response to the fourth Pfizer-BioNTech COVID-19 vaccine dose in individuals aged 60 years and older. *Vaccine* 2023;**41**:914–21. doi:10.1016/j.vaccine.2022.12.035.
[16] Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet* 2022;**400**:1305–20. doi:10.1016/S0140-6736(22)01656-7.

[17] Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: the challenge of immune changes with aging. *Semin Immunol* 2018;**40**:83–94. doi:10.1016/j.smim.2018.10.010.
[18] Cunningham AL, Levin MJ. Herpes zoster vaccines. *J Infect Dis* 2018;**218**:S127–33. doi:10.1093/infdis/jiy382.
[19] Lynch SM, Guo G, Gibson DS, Bjourson AJ, Rai TS. Role of senescence and aging in SARS-CoV-2 infection and COVID-19 disease. *Cells* 2021;**10**. doi:10.3390/cells10123367.
[20] Liu X, Munro APS, Wright A, Feng S, Janani L, Aley PK, et al. Persistence of immune responses after heterologous and homologous third COVID-19 vaccine dose schedules in the UK: eight-month analyses of the COV-BOOST trial. *J Infect* 2023;**87**:18–26. doi:10.1016/j.jinf.2023.04.012.
[21] Dickerman BA, Gerlovin H, Madenci AL, Figueroa Muñiz MJ, Wise JK, Adhikari N, et al. Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans. *Nat Microbiol* 2023;**8**:55–63. doi:10.1038/s41564-022-01272-z.
[22] Chemaitelly H, Ayoub HH, Tang P, Coyle P, Yassine HM, Al Thani AA, et al. Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting: a retrospective population-based cohort study. *Lancet Infect Dis* 2023;**23**:816–27. doi:10.1016/S1473-3099(23)00058-0.
[23] Wu JD, Li JX, Liu J, Wang HM, Zhou GH, Li J, et al. Safety, immunogenicity, and efficacy of the mRNA vaccine CS-2034 as a heterologous booster versus homologous booster with BBIBP-CorV in adults aged ≥18 years: a randomised, double-blind, phase 2b trial. *Lancet Infect Dis* 2023;**23**:1020–30. doi:10.1016/S1473-3099(23)00199-8.
[24] Yisimayi A, Song W, Wang J, Jian F, Yu Y, Chen X, et al. Repeated Omicron exposures override ancestral SARS-CoV-2 immune imprinting. *Nature* 2024;**625**:148–56. doi:10.1038/s41586-023-06753-7.
[25] Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis* 2023;**23**:556–67. doi:10.1016/S1473-3099(22)00801-5.
[26] Kanokudom S, Assawakosri S, Suntronwong N, Auphimai C, Nilyanimit P, Vichaiwattana P, et al. Safety and immunogenicity of the third booster dose with inactivated, viral vector, and mRNA COVID-19 vaccines in fully immunized healthy adults with inactivated vaccine. *Vaccines (Basel)* 2022;**10**:86. doi:10.3390/vaccines10010086.
[27] Shapiro Ben David S, Shamir-Stein N, Baruch Gez S, Lerner U, Rahamim-Cohen D, Ekka Zohar A. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. *Clin Immunol* 2021;**232**:108860. doi:10.1016/j.clim.2021.108860.
[28] Neuhann JM, Stemler J, Carcas A, Frías-Iniesta J, Bethe U, Heringer S, et al. A multinational, phase 2, randomised, adaptive protocol to evaluate immunogenicity and reactogenicity of different COVID-19 vaccines in adults ≥75 already vaccinated against SARS-CoV-2 (EU-COVAT-1-AGED): a trial conducted within the VACCELERATE network. *Trials* 2022;**23**:865. doi:10.1186/s13063-022-06791-y.
[29] Kenny G, O'Reilly S, Wrigley Kelly N, Negi R, Gaillard C, Alalwan D, et al. Distinct receptor binding domain IgG thresholds predict protective host immunity across SARS-CoV-2 variants and time. *Nat Commun* 2023;**14**:7015. doi:10.1038/s41467-023-42717-1.
[30] Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* 2022;**603**:488–92. doi:10.1038/s41586-022-04460-3.
[31] López D. Predicted HLA class I and Class II epitopes from licensed vaccines are largely conserved in new SARS-CoV-2 omicron variant of concern. *Front Immunol* 2022;**13**:832889. doi:10.3389/fimmu.2022.832889.