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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)

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ABSTRACT

Background: Vaccination remains crucial for protection against severe SARS-CoV-2 infection, especially for people of advanced age, however, optimal dosing regimens are as yet lacking.
Methods: EU-COVAT-1-AGED Part A is a randomised controlled, adaptive, multicentre phase II trial evaluating safety and immunogenicity of a 3rd vaccination (1st booster) in individuals ≥75 years. Fifty-three participants were randomised to full-doses of either mRNA-1273 (Spikevax®, 100 μg) or BNT162b2 (Comirnaty®, 30 μg). The primary endpoint was the rate of 2-fold circulating antibody titre increase 14 days post-vaccination measured by quantitative electrochemiluminescence (ECL) immunoassay, targeting RBD region of Wuhan wild-type SARS-CoV-2. Secondary endpoints included the changes in neutralising capacity against wild-type and 25 variants of concern at 14 days and up to 12 months. Safety was assessed by monitoring of solicited adverse events (AEs) for seven days after on-study vaccination. Unsolicited AEs were collected until the end of follow-up at 12 months, SAEs were pursued for a further 30 days.
Results: Between 08th of November 2021 and 04th of January 2022, 53 participants ≥75 years received a COVID-19 vaccine as 1st booster. Fifty subjects (BNT162b2 n = 25/mRNA-1273 n = 25) were included in the analyses for immunogenicity at day 14.
The primary endpoint of a 2-fold anti-RBD IgG titre increase 14 days after vaccination was reached for all subjects. A 3rd vaccination of full-dose mRNA-1273 provided higher anti-RBD IgG titres (Geometric mean titre)

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D14 mRNA-127310711 IU/mL (95 %-CI: 8003;14336) vs. BNT162b2: 7090 IU/mL (95 %-CI: 5688;8837). We detected a pattern showing higher neutralising capacity of full-dose mRNA-1273 against wild-type as well as for 23 out of 25 tested variants.
Interpretation: Third doses of either BNT162b2 or mRNA-1273 provide substantial circulating antibody increase 14 days after vaccination. Full-dose mRNA-1273 provides higher antibody levels with an overall similar safety profile for people ≥75 years.
Funding: This trial was funded by the European Commission (Framework Program HORIZON 2020).

1. Introduction

Following primary vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), immune response wanes over time [1]. At advanced age, immunosenescence and comorbidities compromise the immune response [2]. Reinforcing immunity in these individuals at high risk for severe coronavirus diseases 2019 (COVID-19) is of particular importance [3]. To overcome decreasing immune response in healthy adults, booster vaccination concepts have been evaluated successfully [4]. To this date, systematic data on age-dependent immune response to vaccination against SARS-CoV-2 is scarce [5].

Continuous viral escape limits the effect of targeted treatments, in particular the effect of monoclonal neutralising antibodies [6]. In contrast, high levels of antibodies against wild-type SARS-CoV-2 effectively neutralise the BA.1 *Omicron* variant [7].

The British COV-BOOST trial showed that the fold-change of anti-Spike IgG titres between first and second booster was more pronounced in individuals >70 years of age when compared to younger adults [8]. This could imply that there may be no immediate ceiling effect of the immune response after a booster dose [8].

Compared to pre-booster levels, a full-dose (100 μg) of mRNA-1273 induced an 80-fold increase in neutralising antibodies (nAB) against the *Omicron* variant versus a 37-fold increase after half-dose (50 μg) [9]. Both messenger ribonucleic acid (mRNA) vaccines, BNT162b2 and full-dose mRNA-1273 were safe and effective as first booster doses in people ≥70 years of age [10].

The present trial evaluates immune response and safety of a third dose (=first booster) in a randomised setting of BNT162b2 (BioNTech/Pfizer, Comirnaty®) versus full-dose (100 μg) mRNA-1273 (Moderna, Spikevax®) in adults ≥75 years of age, who had received a two-dose vaccination priming.

Here, we present first data of the EU-COVAT-1 trial assessing the immune response ≥6 months after completed primary vaccination and 14 days after a first mRNA booster dose including safety data.

2. Methods

2.1. Trial design

EU-COVAT-1 is a multinational, phase 2, randomised clinical trial examining the immunogenicity and reactogenicity of a third vaccination dose (=first booster) of 30 μg BNT162b2 (Comirnaty®) or 100 μg mRNA-1273 (Spikevax®) in adults ≥75 years of age (Table 1). This trial is conducted within the VACCELERATE network. Participating trial sites were selected through the VACCELERATE Site Network, while recruitment of trial participants was supported through the VACCELERATE Volunteer Registry [11,12]. After a favourable opinion of the responsible ethics committee on 8 November 2021 (Ref.: 21-1457_2-AMG-ff) and regulatory approval by the Paul-Ehrlich-Institute (PEI) on 20 October 2021 (Ref.: 4647), enrolment for the trial started at a single centre in Cologne in November 2021 (ClinicalTrials.gov Identifier: NCT05160766, EudraCT Number: 2021-004526-29). This part of the trial is referred to as Part A and was closed for enrolment on 13th of January 2022 in light of recommendations for a fourth vaccination in the targeted age group [13]. For the full protocol, please refer to the web-only supplement. The trial continues with a modified trial design, i.e. with a fourth vaccination as study intervention, which is referred to as Part B. The data collected in Part B will be reported as soon as results are available.

Table 1
Intervention Part A: mRNA-based booster strategies following different prime boost vaccination strategies.

Cohort	Prime strategy	Intervention Arm	Intervention: Third dose (full dose)	Interval
Cohort 1	BNT162b2 - BNT162b2	1 2	BNT162b2 mRNA-1273	9 ± 3 months from date of 2nd vaccine dose upon enrolment
Cohort 2	mRNA-1273 - mRNA-1273	3 4	BNT162b2 mRNA-1273	
Cohort 3	ChAdOx-1-S - ChAdOx-1-S	5 6	BNT162b2 mRNA-1273	

2.2. Participants

Subjects ≥75 years of age who were primed with homologous ChAdOx-1-S (Oxford/AstraZeneca, Vaxzevria®), BNT162b2 or mRNA-1273 and had no SARS-CoV-2 infection within the last three months were eligible to be enrolled (Table 1). Six to twelve months was set as interval to on-study vaccination. Participants provided written informed consent.

2.3. Randomisation

For randomisation permuted random blocks were used. Subjects were randomly assigned to either 30 μg BNT162b2 or 100 μg mRNA-1273 in a 1:1 ratio. ALEA 17.1. (ALEA Clinical B.V., Abcoude, The Netherlands) was used as electronic randomisation tool and results were documented in the electronic case report form (TrialMaster® 5.0 update 03, Anju Software, Tempe, AZ, USA). No blinding was foreseen for this trial.

2.4. Procedures

After randomisation, vaccine administration was performed by trained site staff via intramuscular (i.m.) injection in the deltoid muscle. For immunogenicity analysis blood was drawn at day 0 (prior to vaccination), day 14 and after 12 months since injection. SARS-CoV-2 anti-Nucleocapsid (N) human Immunoglobulin-G (anti-N IgG) was determined at days 0 and 14. Safety and reactogenicity were determined by the occurrence of adverse events (AEs). Solicited AEs were monitored by means of subject diary for seven days after the 3rd dose. Unsolicited AEs were collected until end of each subject's trial participation. Severe adverse events (SAEs) were pursued for a further 30 days.

Circulating levels of IgG against the SARS-CoV-2 RBD and Nucleocapsid protein were measured at the Centre for Experimental Pathogen Host Research (CEPHR) in Dublin, Ireland, using the Mesoscale Diagnostics (MSD, MD, USA) electrochemiluminescence immunoassay. The results were expressed in IU/ml, based on the first WHO 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.

SARS-CoV-2 Virus Neutralisation Capacity (% inhibition) was estimated using ACE2 neutralisation measurements in serum, performed by the Laboratory of Cell Biology & Histology and Vaccine & Infectious Disease Institute (CBH) in Antwerp, Belgium. Neutralisation Capacity was measured in plasma samples using V-PLEX panels from Mesoscale Discovery (MSD, MD, USA). Antibodies capable of blocking the binding of ACE2 to the following Spike proteins were measured: wild-type, 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, XBB.1. Further details on methodology are provided in the supplement [28].

2.5. Outcome parameters

The rate of 2-fold anti-RBD antibody titre increase against wild-type virus 14 days after 3rd dose was set as primary endpoint. Secondary endpoints included vaccine-induced nAB titre increase against wild-type virus and the change in neutralising capacity against variants of concern (VOC) after 14 days in a subgroup analysis. For long-term immunogenicity after twelve months, anti-RBD IgG titre and nAB against wild-type SARS-CoV-2 were measured. The change in neutralising capacity against VOC after twelve months were assessed in a subgroup.

Safety and reactogenicity were determined by the occurrence of solicited AEs for seven days after the 3rd dose, unsolicited AEs until the end of trial and by the rate of SAEs Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) up to three months after the 3rd vaccination. The present report provides results on reactogenicity and immunogenicity following a 3rd dose on day 0 and day 14.

2.6. Statistical design

The initial sample size calculation yielded 100 probands per arm (i.e., 600 probands totally, including assumed 10 % dropouts, for the 6 planned initial arms). Sample size calculation considered adjustment for multiplicity within each cohort (3 cohorts according to pre-vaccination scheme).

When the sample size was 90 per group (without dropouts, i.e., 100 including 10 % dropouts), two-sided simultaneous 95 % confidence intervals (with Bonferroni adjustment for 2 simultaneous confidence intervals in a cohort) for a proportion using the large sample normal approximation would extend no more than ± 12 % (percentage points) from the observed proportion, i.e., if the observed proportion is 50 % (where the confidence interval is widest), the confidence interval ranged from about 38 % to 62 %.

Part A was closed to further recruitment as of 13th of January 2022 with the massive roll-out of booster campaigns throughout Europe. Therefore, the actual sample size was determined by the number of patients included in Part A before the above-mentioned date, and thus, the precision is smaller than planned.

2.7. Statistical methods

For the binary primary endpoint (subjects with a fold change ≥2 for anti-RBD IgG) absolute counts and frequencies in percent were calculated per randomized treatment arm. The corresponding rate together with the simultaneous two-sided 95 % confidence interval (CI) is reported by implementing a Bonferroni adjusted level of 97.5 % for the Clopper Pearson confidence intervals.

Additionally, 4-fold increase of anti-RBD IgG, Geometric Mean Fold Rise (GMFR) and Geometric Mean Titre (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 (2x mRNA-1273, 2x BNT162b2 and 2x ChAdOx-1-S).

The least square mean differences between mRNA-1273 minus BNT162b2 and corresponding 95 % CI were calculated using the log10 transformed titre values as dependent variable in a generalised linear model (GLM) with the factor booster group (BNT162b2/mRNA-1273) as well as the stratification variables used for randomisation. The mean difference (LS mean diff) on the log10 scale was calculated backwards to the original scale to yield the ratio for GMT values at day 14.

The values for virus neutralisation capacity were analysed descriptively. To check for differences in virus neutralisation capacity values after 14 days an Analysis of Covariance (ANCOVA) was calculated for wild-type and each variant using the factors vaccine regimen (mRNA-1273 vs. BNT162b2) and corresponding baseline value (day 0) as covariate. To visualise the data, heatmaps and boxplots are provided.

For the analysis of Part A, data were exported on 13 March 2023, whereas the database has not yet been locked as the trial is still on-going.

3. Results

A total of 53 subjects were enrolled for Part A from 08 November 2021 to 04 January 2022 at the single trial site in Cologne, Germany. The final data base lock is projected to November 2023. Thus, we are reporting preliminary data. The follow up of trial participants from Part A was completed in January 2023. One subject consented to participate and was randomised but did not receive vaccination due to an acute SARS-CoV-2 infection on day 0. This subject was excluded from the analysis. A total of 25 of 52 subjects received BNT162b2 as 3rd dose, twenty-seven subjects received mRNA-1273 (Fig. 1). For two out of the 27 subjects receiving mRNA-1273 a blood sample at day 14 was not available due to difficult venepuncture.

Participants baseline characteristics are summarised in Table 2. Most frequent comorbidities were vascular disorders (e.g. hypertension), which was 56 % in the BNT162b2 group and 70 % in the mRNA-1273 group (Table 2). Regarding baseline characteristics of subjects, no substantial difference between the two groups was observed. For safety, only AEs of grading 1 or 2 were reported. For investigational medicinal product (IMP)-related AEs within seven days after vaccination, there was no substantial difference between the two vaccination groups (Fig. 2). In general, more subjects experienced AEs in the mRNA-1273 group. The most frequent AEs in both groups were injection site discomfort, injection site induration and fatigue (see panel A in Fig. 2). Other infrequently reported AEs were arthralgia and myalgia after vaccination with 100 μg mRNA-1273 (see panel B in Fig. 2). No serious adverse events were reported. The number of subjects with no AE related to IMP was lower in the mRNA-1273 group (7 % vs. 20 %). The number of subjects with IMP-related AEs (grade 1) was approximately the same, with 12 reported AEs in the BNT162b2 group versus ten AEs in the mRNA-1273 group, respectively. There were more subjects (n = 15) with at least one grade 2 AE related to IMP in the mRNA-1273 group (Table 3). In follow-up to month 12, eleven subjects in the BNT162b2 group (44 %) reported SARS-CoV-2 infection between day 0 and the end of trial (month 12) and eight subjects in the mRNA-1273 group (30 %). In both groups anti-N IgG was at lower limit of quantification (LLOQ) at baseline Visit 01 (day 0) as well as on Visit 02 (day 14)7.

In both vaccine groups all subjects experienced a two-fold increase in anti-RBD IgG titres at 14 days. Similar kinetics were observed when exploring the fold-change ≥4 for anti-RBD IgG (Table 4). There was a higher GMFR in the mRNA-1273 group. Based on the priming regimen, descriptive subgroup analyses for both vaccination groups showed that subjects with an mRNA priming regimen (2x mRNA-1273 or 2x BNT162b2) had higher GMT at day 14 compared to a 2x ChAdOx-1-S as priming regimen. Fig. 3 shows that absolute values were higher in the mRNA-1273 group and Fig. 4 shows the vaccination effect on anti-RBD levels separately for each intervention arm according to their priming regimen. For the mRNA-1273 group, higher values at day 14 were observed with GMT at day 14 of 10711 IU/mL (95 %-CI: 8003; 14336)

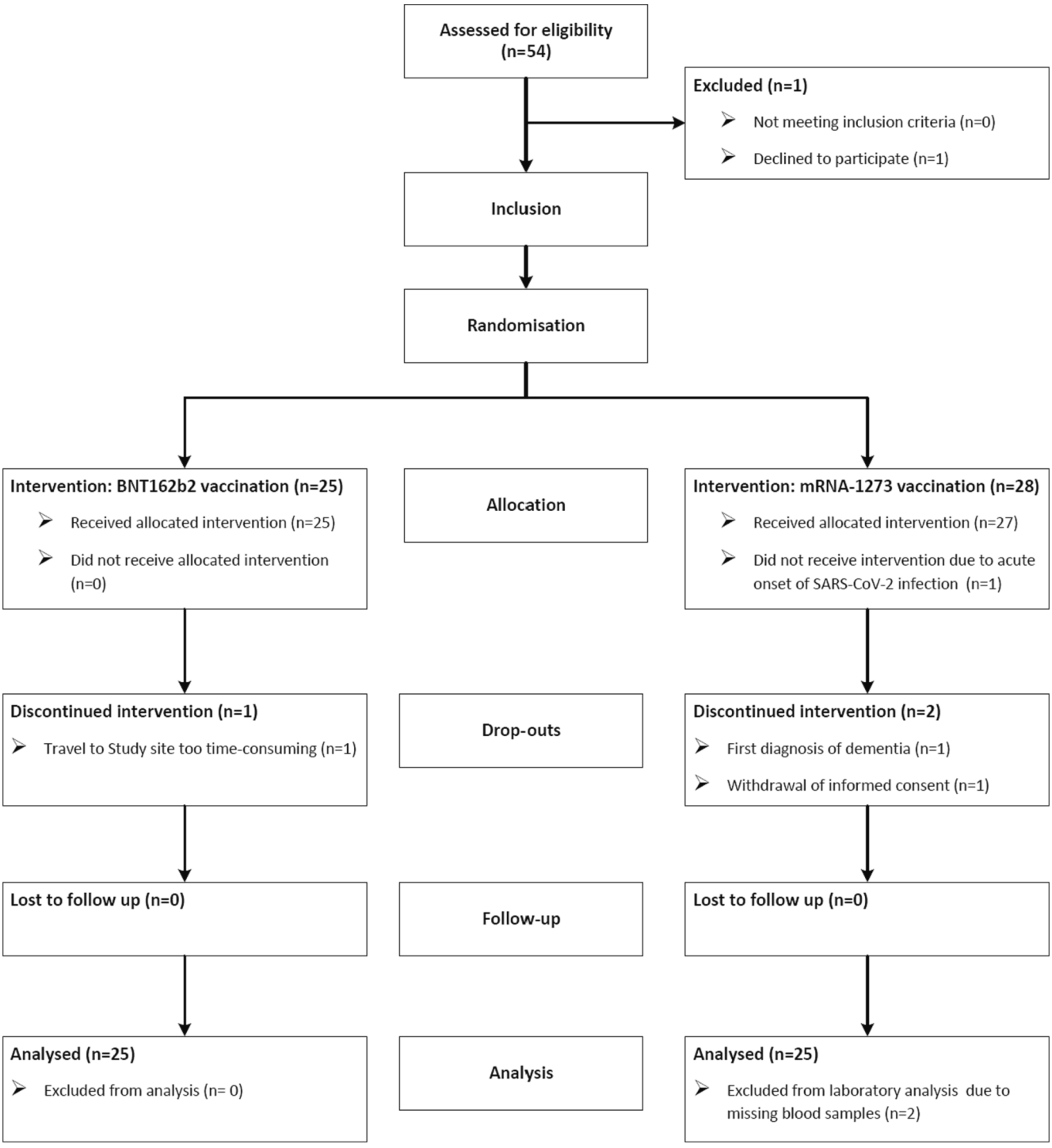

Fig. 1. CONSORT Diagram (Day 0 - Day 14) Drop outs are given for the full study duration.

and 7090 IU/mL (95 %-CI: 5688; 8837) for BNT162b2 and mRNA-1273, respectively (Table 4, Fig. 3 A/B) and a ratio $\frac{GMT_{\text{mRNA}-1273}}{GMT_{\text{BNT162b2}}}$ at day 14 of 1.51026 (95 %CI: 1.08539; 2.10143). After 14 days the observed values for virus neutralisation capacity were lower for omicron variants compared to other variants (Fig. 5). When checking for differences in virus neutralisation capacity, values after 14 days show consistent patterns in the mRNA-1273 group with higher mean values compared to the BNT162b2 group (Fig. 5). When displaying the virus neutralisation capacity in a heatmap (Fig. 6), plasma of subjects in the mRNA-1273 group show an overall higher virus neutralisation compared to the BNT162b2 group, especially for wild-type, B.1.1.7 (alpha variant) and AY.4.2 (delta variant). In exploratory ANCOVA analyses, the mean differences between the two groups yielded statistical significance for the wild-type and 23 out of 25 variants (not corrected for multiplicity) (Table 5). The estimated mean differences between mRNA-1273 minus BNT162b2 varied between 9 and 16 percentage points (Table 5).

4. Discussion

There is scarce data for the vaccination response in the elderly (age group ≥75 years) from randomised controlled trials. However, there is evidence that age-related immunosenescence is partly due to reduced B

Table 2
Baseline characteristics.

	BNT162b2 n = 25	*mRNA-1273*n = 27*
Age (years)		
Mean ± SD	77.7 ± 2.8	78.6 ± 3.2
Median [Min; Max]	77.0 [75; 87]	78.0 [75; 85]
Sex		
Female	9 (36 %)	11 (41 %)
Male	16 (64 %)	16 (59 %)
Body mass index (kg/m^2)		
Mean ± SD	25.7 ± 3.1	24.6 ± 4.0
Median [Min; Max]	25.6 [20.3; 32.8]	24.1 [16.8; 32.6]
Priming vaccine regimen		
2x BNT162b2	16 (64 %)	14 (52 %)
2x ChAdOx-1-Si	6 (24 %)	9 (33 %)
2x mRNA-1273	3 (12 %)	4 (15 %)
Time between 1st and 2nd vaccination in days		
Mean ± SD	40 ± 19	46 ± 26
Median [Min; Max]	42 [21; 84]	42 [21; 111]
Time between 2nd and study vaccination in days		
Mean ± SD	202 ± 20	203 ± 24
Median [Min; Max]	192 [185; 255]	190 [184; 273]
Most frequent Comorbidities as per Standard Organ Class		
Cardiac disorders	9 (36 %)	10 (37 %)
Metabolism and nutrition disorders	10 (40 %)	15 (56 %)
Vascular disorders	14 (56 %)	19 (70 %)

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

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.

and T cell responses [14,15]. As a consequence, immune response to vaccines is expected to be impaired in the elderly [16]. In a pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales, age (≥80 years), comorbidities (≥5 comorbidities), male sex, immunosuppression and chronic kidney disease (stage 5) were detected as risk factors for severe coronavirus disease [17]. Individuals at risk for developing a severe SARS-CoV-2 infection such as the elderly with comorbidities could therefore benefit from booster vaccinations to improve immunity against SARS-CoV-2 [18]. Currently recommended booster vaccination dosages by German authorities are 50 µg for mRNA-1273 (Spikevax®) and 30 µg for BNT162b2 (Comirnaty®), respectively [19]. However, in-depth data on immunogenicity are needed to provide optimal dosing regimens that offer adequate protection for different populations, particularly for these individuals at risk.

Regarding reactogenicity of a 3rd vaccination dose in individuals ≥75 years of age, we found no significant differences between BNT162b2 (30 µg) and full-dose mRNA-1273 (100 µg). Local reactions as well as systemic vaccine-induced reactions corresponded to the expected spectrum described in previous clinical trials [20,21]. It has been reported with different vaccines that in individuals of advanced age reactogenicity mostly remains at lower threshold and that cell-mediated immunity after vaccination is altered [14,22]. In our trial, both neutralisation capacity and anti-RBD IgG titre were significantly higher with full-dose mRNA-1273 (100 µg) showing an improved antibody-mediated protection for people ≥75 years of age. In a pooled analysis of national prospective cohort studies in the UK, the rate of severe COVID-19 events like COVID-19-related hospitalisation or death among individuals who received mRNA-1273 (3.0 events per 1000 person-years) as the booster dose was lower than that for individuals who received BNT162b2 (9.0 events per 1000 person-years) as booster [17]. In a comparative effectiveness trial of third doses of mRNA vaccines in US veterans with a median age of 70 years, Dickerman et al. observed an overall lower 16-week risk of COVID-19-related outcomes among recipients of the mRNA-1273 vaccine compared with recipients of the BNT162b2 vaccine [23]. Present data on long-term effectiveness after booster vaccination show that protection against SARS-CoV-2 infection waned gradually through month six. Long-term protection against infection may be compromised by factors of immune imprinting but not in regard to severe COVID-19

Table 3
Grading of AE related to IMP for BNT162b2 versus mRNA-1273.

	BNT162b2 n = 25	*mRNA-1273* n = 27*
Subjects with no AE related to IMP	5 (20 %)	2 (7 %)
Subjects with at least one AE of worst Grade 1 related to IMP	12 (48 %)	10 (37 %)
Subjects with at least one AE of worst Grade 2 related to IMP	8 (32 %)	15 (56 %)
Subjects with at least one AE of worst Grade 3 or higher related to IMP	0	0
Subjects with at least one SAE[#] related to IMP	0	0

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

n = number of subjects, AE = Adverse Event, SAE = Severe Adverse Event, IMP = Investigational Medicinal Product.

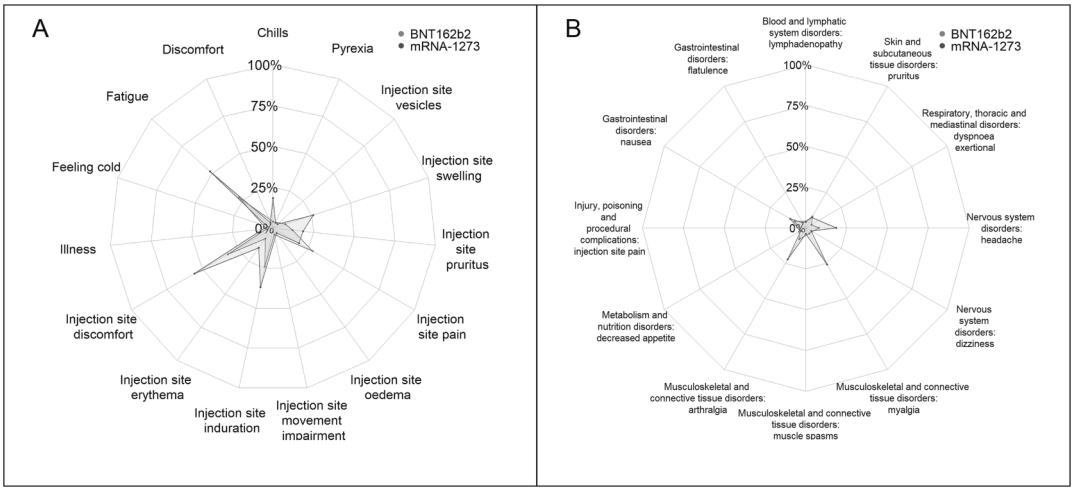

Fig. 2. Spider chart of most frequent AEs 7 days after on-study vaccination (BNT162b2 = red net, mRNA-1273 = turquois net). Plot A shows AEs reported for the system organ class "general disorders and administration site conditions". Plot B shows AEs for other system organ classes (SOC).

Table 4
Descriptive statistics for the primary and exploratory endpoints.

	Anti-SARS-CoV-2 receptor-binding domain (RBD) human IgG	
	BNT162b2 N = 25	***mRNA-1273 N = 25***
Primary Endpoint (overall)		
Overall Proportion Fold Change ≥2 from Day 0 to Day 14	25/25 (100 %) (97.5 %-CI: 83.9 % −100 %)	25/25 (100 %) (97.5 %-CI: 83.9 % −100 %)
Primary Endpoint separately for each intervention arm based on priming regimen		
2x BNT162b2	16/16 (100 %)	13/13 (100 %)
Proportion Fold Change >= 2 from Day 0 to Day 14	(97.5 %-CI: 76 % −100 %)	(97.5 %-CI: 71.4 % −100 %)
2x ChAdOx-1-S	6/6 (100 %)	8/8 (100 %)
Proportion Fold Change >= 2 from Day 0 to Day 14	(97.5 %-CI: 48.2 % −100 %)	(97.5 %-CI: 57.8 % −100 %)
2x mRNA-1273	3/3 (100 %)	4/4 (100 %)
Proportion Fold Change >= 2 from Day 0 to Day14	(97.5 %-CI: 23.2 % − 100 %)	(97.5 %-CI: 33.4 % −100 %)
Exploratory Analysis (overall)		
Proportion Fold Change ≥4 from Day 0 to Day 14	25/25 (100 %) (97.5 %-CI: 83.9 % − 100 %)	25/25 (100 %) (97.5 %-CI: 83.9 % − 100 %)
GMFR from Day 0 to Day 14	55.7 (95 %-CI: 39.9–77.7)	120.5 (95 %-CI: 80.6–180.2)
GMT at Day 14	7090 (95 %-CI: 5688; 8837)	10,711 (95 %-CI: 8003; 14336)
GMT Day 14 subgroup analysis for each cohort based on priming regimen		
2x BNT162b2	6590.1 IU/mL (95 %CI: 4899.2; 8864.6) N = 16	12065.7 IU/mL (95 %-CI: 7831.9; 18588.2) N = 13
2x ChAdOx-1-S	6240.5 IU/mL (95 %-CI: 4654.39; 8367.23) N = 6	7101.8 IU/mL (95 %-CI: 4299.3; 11731.2) N = 8
2x mRNA-1273	13512.2 IU/mL (95 %-CI: 4642; 39331.7) N = 3	16548.2 IU/mL (95 %-CI: 6564.5; 41715.9) N = 4
Equivalence (overall)		
LS mean Diff mRNA-1273 – BNT162b2 at Day 14	0.17905 (95 %CI: 0.035588; 0.32252)	
Ratio $\frac{GMT_{\text{mRNA}-1273}}{GMT_{\text{BNT162b2}}}$ at day 14	1.51026 (95 %CI: 1.08539; 2.10143)	

N represents the number of subjects, in the brackets (95 %-CI: LL; UL) the lower (LL) and upper limits (UL) of 95 %-confidence intervals (95 %-CI) are reported, GMFR = Geometric Mean Fold Rise, GMT = Geometric Mean Titre, LS mean Diff = least square mean difference, receptor-binding domain = RBD.

disease [24]. We observed a lower GMT at day 14 in subjects who had received 2x ChAdOx-1-S as in comparison to a mRNA priming regimen (2x mRNA-1273 or 2x BNT162b2) as a heterologous booster regimen [25]. Available evidence suggests that heterologous booster vaccine regimens, especially those combined with an adenoviral vector-based vaccine, elicit a more durable cellular immune response [26]. However, this may not be true for elderly subjects due to their reduced immune response and for vaccination efficacy against emerging variants [25]. The trial has several limitations. Firstly, EU-wide changes of vaccination policies forced a redesign and stop of recruitment of the present trial assessing immunogenicity of a 3rd vaccination dose (Part A) in January 2022 [27]. Secondly, as a consequence the initially planned sample size could not be reached. Cohorts to be compared remained small. However, the trial design was subsequently changed, and recently enrolled subjects received a 4th vaccination as study vaccination (Part B). The target sample size for Part B is 550 subjects [27]. And thirdly, the EU-COVAT-1 Part A was planned as a multinational trial. With the change of vaccination policies, Part A of the trial was subsequently carried out at a single trial centre. Further obtained data for Part A, including data on cellular immune response at month three and twelve after third dose will provide more information on the impact of long-term protection and immunological memory as compared to other studies [16].

To conclude 3rd doses of either BNT162b2 or mRNA-1273 provide significant antibody increase 14 days after vaccination. Full-dose mRNA-1273 (100 μg) provides significantly higher antibody levels with an overall similar safety profile for people ≥75 years.

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of the Faculty of Medicine, University of Cologne, Germany. All patients provided written informed consent before start of trial participation.

Consent for publication

Written informed consent obtained by every enrolled subject 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.

Role of funding source

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.

CRediT authorship contribution statement

Julia M. Neuhann: Methodology, Investigation, Visualization, Writing – original draft. **Jannik Stemler:** Investigation, Visualization, Writing – original draft. **Antonio J. Carcas:** Investigation, Writing – review & editing. **Jesús Frías-Iniesta:** Investigation, Writing – review & editing. **Murat Akova:** Validation, Writing – review & editing. **Ullrich Bethe:** Methodology, Project administration, Writing – original draft. **Sarah Heringer:** Methodology, Project administration, Writing – original draft. **Jon Salmanton-García:** Visualization, Writing – review & editing. **Lea Tischmann:** Methodology, Project administration, Writing – review & editing. **Marouan Zarrouk:** Methodology, Project administration, Writing – review & editing. **Arnd Cüppers:** Methodology, Project administration, Writing – review & editing. **Jan Grothe:** Investigation, Writing – original draft. **Alejandro Garcia Leon:** Investigation, Writing – review & editing. **Patrick Mallon:** Investigation, Writing – review & editing. **Riya Negi:** Investigation, Writing – review & editing. **Colette Gaillard:** Investigation, Writing – review & editing. **Gurvin Saini:** Investigation, Writing – review & editing. **Christine Lammens:** Investigation, Writing – review & editing. **An Hotterbeekx:** Investigation, Writing – review & editing. **Katherine Loens:** Investigation, Writing – review & editing. **Surbhi Malhotra-Kumar:** Investigation, Writing – review & editing. **Herman Goossens:** Investigation, Writing – review & editing. **Samir Kumar-Singh:** Investigation, Writing – review & editing. **Franz König:** Methodology, Formal analysis, Visualization, Writing – original draft. **Lusine Yeghiazaryan:** Methodology, Formal analysis, Visualization, Writing – original draft. **Martin Posch:** Methodology, Formal analysis, Writing – review & editing. **Philipp Koehler:** Methodology, Supervision, Visualization, Writing – original draft. **Oliver A. Cornely:** Conceptualization, Methodology, Validation, Supervision, Visualization, Writing – original draft.

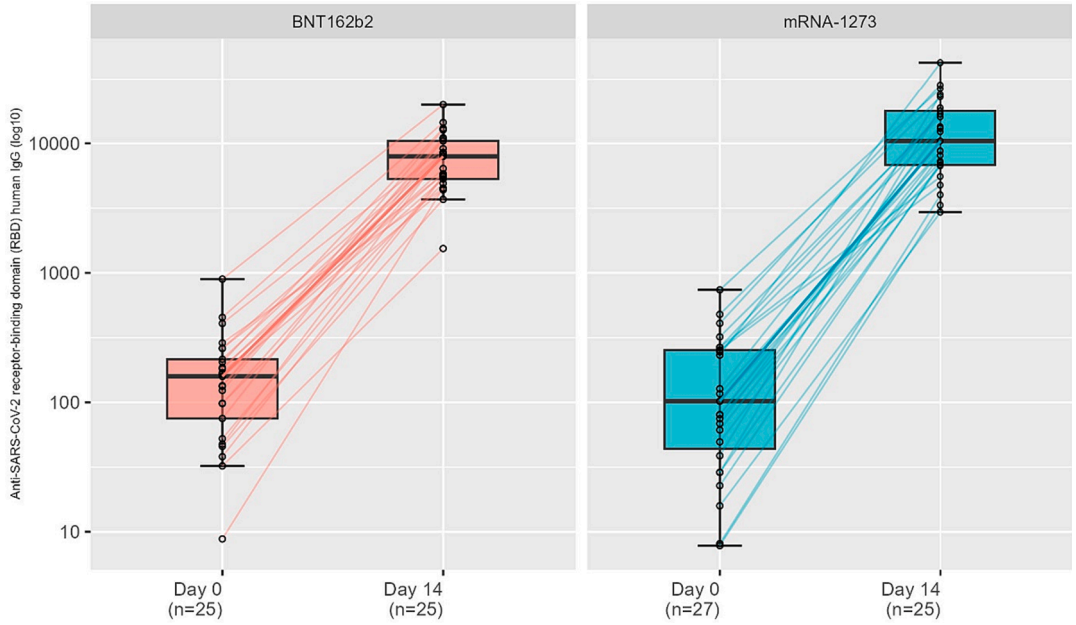

Fig. 3. A & B: Kinetics of anti-RBD IgG. Boxplot images represent the median (black line in the middle of each boxplot) of anti-RBD protein IgG titres at baseline (day 0) and 14 days after vaccination with 30 μg BNT162b2 (red, 3A) and after vaccination with a full-dose (100 μg) mRNA-1273 in green (3B) [IU/mL]. The vaccination effect on anti-RBD levels for all subjects from day 0 to day 14 is demonstrated as solid lines connecting the paired samples for each subject at multiple timepoints. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

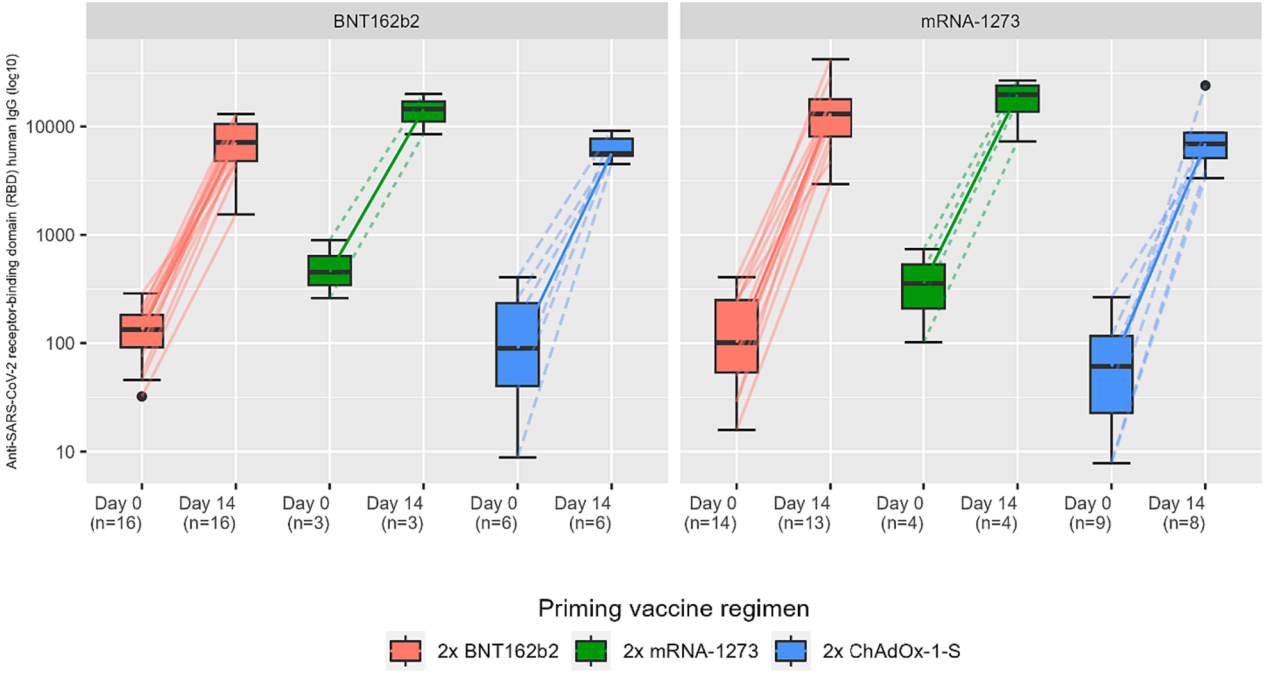

Fig. 4. A & B: Kinetics of anti-RBD IgG by priming vaccine regimen. Boxplot images represent the median (black line in the middle of each boxplot) of anti-RBD protein IgG titres at baseline (day 0) and 14 days after vaccination with BNT162b2 and with mRNA-1273 per priming vaccine regimen [IU/mL]. Solid lines connect samples from the same participants at 2 time points.

Declaration of Competing Interest

JN no conflicts declared. JS has received research grants by the Ministry of Education and Research (BMBF) and Basilea Pharmaceuticals; has received speaker honoraria by AbbVie, 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. AJC no conflicts declared. 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. 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

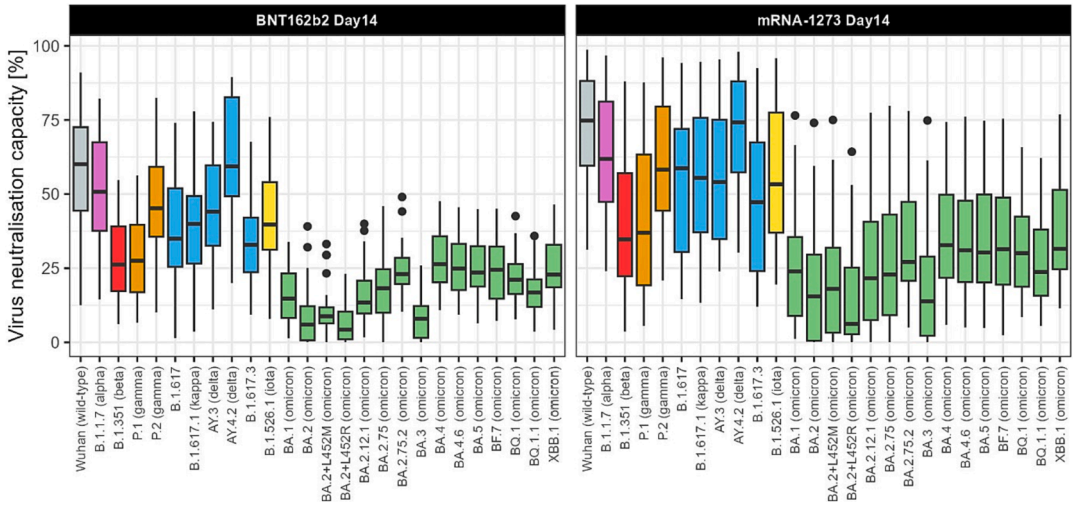

Fig. 5. Boxplot for virus neutralisation capacity values. Wild-type is in grey colour, sub-lineages of VOC have similar colours, e.g., blue boxplots are related to delta variants. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. Heatmap for virus neutralisation capacity at day 14. The colour represents the observed mean value at day 14 for the variant and vaccine group. In the cells the mean ± standard deviations are given.

these activities are paid to the Institution. UB no conflicts declared. SH no conflicts declared. JSG has received speaker honoraria from Gilead and Pfizer, outside of the submitted work. LT no conflicts declared. MZ has received honoraria for lecturing courses by Pfizer Malaysia; is now an employee with AiCuris AG. AC no conflicts declared. JG no conflicts declared. AGL no conflicts declared. PM has received honoraria from Gilead and AstraZeneca, outside of the submitted work. RN no conflicts declared. CG no conflicts declared. GS no conflicts declared. AH no conflicts declared. SKS no conflicts declared. KL no conflicts declared. CL no conflicts declared. HG no conflicts declared. SMK has received grants from Pfizer, MSD, Huvepharma, AiCuris, Astra Zeneca, Mylan, Janssen pharma. FK no conflicts declared. LY 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) 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

Table 5
Results of ANCOVA models for virus neutralisation capacity values.

Variant	Mean difference mRNA-1273 – BNT162b2 [Lower and upper boundary of 95 %-CI]	p-value
Wild-type	12.6 [1.2; 23.9]	0.03143
B.1.1.7 (alpha)	12.2 [0.3; 24.0]	0.04405
B.1.351 (beta)	14.2 [2.6; 25.8]	0.01744
P.1 (gamma)	14.2 [2.3; 26.2]	0.02039
P.2 (gamma)	15.2 [3.4; 27.0]	0.01255
B.1.617	16.7 [4.6; 28.7]	0.00787
B.1.617.1 (kappa)	16.1 [4.0; 28.3]	0.01039
AY.3 (delta)	14.6 [2.5; 26.7]	0.01925
AY.4.2 (delta)	10.2 [-0.0; 20.4]	0.05004
B.1.617.3	15.8 [3.8; 27.7]	0.01067
B.1.526.1 (iota)	15.1 [2.9; 27.3]	0.01627
BA.1 (omicron)	9.3 [0.0; 18.7]	0.04989
BA.2 (omicron)	10.2 [0.5; 19.9]	0.04066
BA.2 + L452M (omicron)	11.9 [2.3; 21.5]	0.01634
BA.2 + L452R (omicron)	9.2 [0.9; 17.5]	0.03104
BA.2.12.1 (omicron)	10.8 [1.1; 20.4]	0.02939
BA.2.75 (omicron)	9.8 [-0.5; 20.2]	0.06146
BA.2.75.2 (omicron)	9.3 [0.6; 17.9]	0.03706
BA.3 (omicron)	9.3 [0.2; 18.3]	0.04512
BA.4 (omicron)	10.3 [1.5; 19.1]	0.02259
BA.4.6 (omicron)	11.6 [2.3; 20.9]	0.01583
BA.5 (omicron)	11.9 [3.2; 20.6]	0.00856
BF.7 (omicron)	11.5 [1.9; 21.1]	0.01953
BQ.1 (omicron)	10.8 [3.3; 18.3]	0.00570
BQ.1.1 (omicron)	10.5 [3.0; 17.9]	0.00704
XBB.1 (omicron)	11.7 [2.6; 20.7]	0.01268

ANCOVA = Analysis of Covariance, 95 %-Confidence Interval = 95 %-CI.

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, The Prime Meridian Group; A patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Stocks from CoRe Consulting, EasyRadiology; Other interests from DGHO, DGI, ECMM, EHA, ISHAM, MSG-ERC, Wiley.

Data availability

Data will be made available on request.

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Anti-RBD 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; neutralising 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.

Roles and responsibilities

The sponsor, the University of Cologne, is represented by Professor Oliver A. Cornely. Project coordination, correspondence with ethics committees and Competent Authority, data management, safety management and central monitoring are performed by the CTCC. Statistical design 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 storage of the generated samples and aliquots.

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 20 December 2021.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.10.029.

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