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Original article

Immunogenicity of Omicron BA.1-adapted BNT162b2 vaccines: randomized trial, 3-month follow-up

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ABSTRACT

Objectives: The capability of the SARS-CoV-2 Omicron variant to escape immunity conferred by mRNA vaccines has led to the development of Omicron-adapted vaccines. In this study, we aimed to compare the immune response with the ancestral strain and with the BA.1 Omicron variant after administration of the original vaccine and the Omicron-adapted vaccine.

Methods: This is an ongoing phase 3, double-blinded randomized controlled trial, comparing the original BNT161b2 vaccine, monovalent Omicron BA.1-adapted BNT161b2 vaccine, and bivalent combinations. Each vaccine was given at a 30 μg and 60 μg dose. Primary outcomes considered included neutralization titers of SARS-CoV-2 ancestral strain and Omicron BA.1. Exploratory endpoints included neutralization titers for Omicron BA.5, and the incidence of COVID-19 cases.

Results: Overall, 122 individuals (22, 19, 20, 20, 20, 20, and 21 in each arm) completed a 90-day follow-up. Three months after vaccination, adjusting for baseline levels, neutralizing antibody titers were 0.63 (95% CI: 0.3–1.32) and 0.54 (0.24–1.2) for monovalent/60 μg, 0.9 (0.42–1.92) and 2.69 (1.17–6.17) times for monovalent-Omi.BA.1/30 μg, 1.28 (0.6–2.75) and 2.79 (1.21–6.41) times for monovalent-Omi.BA.1/60 μg, 0.96 (0.46–1.97) and 2.07 (0.93–4.58) times for bivalent-Omi.BA.1/30 μg, and 0.79 (0.38–1.63) and 1.95 (0.88–4.32) times for bivalent-Omi.BA.1/60 μg when compared with BNT162b2/30 μg against the ancestral strain and BA.1 variant, respectively.

Discussion: : BA.1-adapted mRNA vaccines lead to a stronger neutralizing antibody response against the Omicron BA.1 sub-variant. **Noam Barda, Clin Microbiol Infect 2023;29:918**

Introduction

In an attempt to counter the vaccine escape capabilities of the SARS-CoV-2 Omicron variant [1], new vaccines were developed that specifically target it. Short-term studies have shown that these

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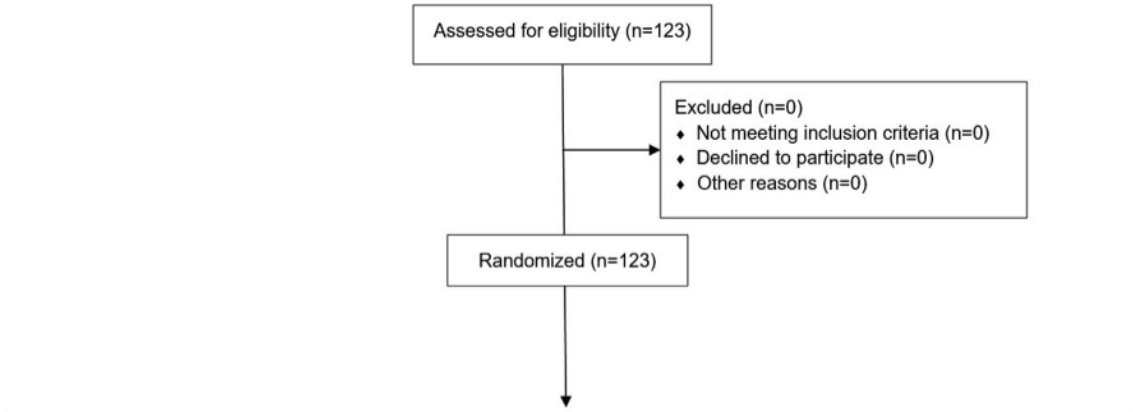

	BNT162b2 30μg	BNT162b2 60μg	BNT162b2OMI 30μg	BNT162b2OMI 60μg	BNT162b2 / BNT162b2OMI 15μg / 15μg	BNT162b2 / BNT162b2OMI 30μg / 30μg
Allocation						
Allocated to intervention	22	20	20	20	20	21
Received allocated intervention	22	19	20	20	20	21
Did not receive allocated intervention	0	1	0	0	0	0
Follow-Up						
Lost to follow-up	0	0	0	0	0	0
Discontinued intervention	0	0	0	0	0	0
Analysis						
Analysed	22	19	20	20	20	21
Excluded from analysis	0	0	0	0	0	0

Fig. 1. Study population flowchart.

novel vaccines indeed lead to a stronger short-term immune response against the Omicron variant [2], but have not reported longer follow-up and were limited to a narrow set of immune response markers.

In this study, we present a 3-month interim analysis of a randomized trial designed to compare the immunogenicity and safety of monovalent Omicron BA.1 and bivalent-BNT162b2/Omicron-BA.1 vaccines with the original BNT162b2 vaccine, given as a fourth dose. This unblinding and analysis at 3 months were pre-planned, so as to provide data for an important public health question as soon as possible.

Methods

Study setting and design

This is an ongoing phase 3, double-blinded, randomized controlled parallel-group trial. The recruitment to the study was performed from the healthcare workers of a large tertiary medical centre and from the general public (using internet advertisements). Individuals were eligible to participate if they were ≥60 years old, had received three doses of the BNT162b2 vaccine with the last dose received ≥4 months prior, and were without evidence of

Table 1
Baseline characteristics of the study population

Variable	Overall *N* = 122	BNT162b2 30 μg *N* = 22	BNT162b2 60 μg *N* = 19	BNT162b2 OMI 30 μg *N* = 20	BNT162b2 OMI 60 μg *N* = 20	BNT162b2 15 μg/BNT162B2 OMI 15 μg *N* = 20	BNT162b2 30 μg/BNT162B2 OMI 30 μg *N* = 21
Age (y), median (IQR)	67.2 (63.7, 70.6)	67.7 (64.6, 72.6)	67.2 (63.9, 69.6)	68.5 (64.6, 73.3)	66.6 (63.1, 70.7)	66.5 (63.8, 69.0)	66.2 (64.0, 69.9)
Sex, *N* (%)							
Female	61 (50)	10 (45)	9 (47)	12 (60)	10 (50)	8 (40)	12 (57)
Male	61 (50)	12 (55)	10 (53)	8 (40)	10 (50)	12 (60)	9 (43)
BMI, median (IQR)	26.2 (24.0, 28.9)	27.3 (24.7, 28.1)	24.2 (23.5, 27.0)	26.4 (23.8, 29.3)	25.1 (22.8, 27.5)	27.5 (25.1, 30.8)	26.9 (23.9, 29.0)
Missing	1	1	0	0	0	0	0
Healthcare workers, *N* (%)	44 (36)	9 (41)	9 (47)	6 (30)	8 (40)	5 (25)	7 (33)
Number of comorbidities, *N* (%)							
0	64 (52)	11 (50)	12 (63)	10 (50)	10 (50)	11 (55)	10 (48)
1	32 (26)	6 (27)	4 (21)	5 (25)	7 (35)	5 (25)	5 (24)
2	26 (21)	5 (23)	3 (16)	5 (25)	3 (15)	4 (20)	6 (29)

BMI, body mass index. Baseline characteristics of the study population, overall, and by vaccine group.

Table 2
Immunological findings for the primary outcomes. Geometric mean titers, geometric mean fold rise, and geometric mean ratios (compared with the original vaccine) of neutralization titers against the ancestral strain and against the BA.1 Omicron strain for each of the study arms

Outcome	Visit	BNT162b2		BNT162b2 OMI		BNT162b2/BNT162b2 OMI	
		30 μg	60 μg	30 μg	60 μg	15 μg/15 μg	30 μg/30 μg
Geometric mean titer							
Direct neutralization–ancestral strain (titer)	0	557 (361.7–857.7)	382.4 (176.3–829.3)	419.3 (228.1–770.5)	315.2 (188–528.4)	803.4 (347.8–1855.8)	256 (135.1–485)
	1	1854.9 (1134.4–3033)	1241.4 (624.3–2468.6)	1321.9 (739.5–2363.1)	1499.2 (838.6–2680.4)	2549.1 (1306.2–4974.9)	1845.8 (1087.4–3133.1)
	2	4390 (2924.3–6590.3)	2048.4 (1007.8–4163.7)	3010 (1606.2–5640.8)	3807.8 (2092.7–6928.6)	5287.7 (3205.1–8723.5)	2521.4 (1388.9–4577.4)
	3	2246.3 (1308.7–3855.7)	1166.1 (617.5–2202.1)	1765.3 (705.1–4419.6)	1949.1 (941.9–4033.4)	2314.5 (1229–4358.6)	1255.6 (679.3–2320.6)
Direct neutralization–BA.1 (titer)	0	28.5 (10.8–75.6)	26.4 (10.8–64.4)	12.9 (3.5–47.2)	29.5 (11.4–76.8)	63.3 (19.2–208.1)	14.2 (6.1–33)
	1	146.1 (102.5–208.2)	101.6 (48.6–212.6)	184.4 (81.1–419)	315.2 (164.6–603.5)	330.5 (124.2–879.3)	222.9 (125.7–395.1)
	2	401.7 (236.7–681.9)	188.1 (88.9–398.2)	574.7 (333.2–991.1)	764.8 (394.6–1482.4)	1062 (509.6–2213.2)	477.7 (236–967.1)
	3	154 (74–320.2)	94.5 (45.7–195.3)	327.9 (111–968.6)	512 (268–978)	435 (191.2–989.2)	245.8 (108.1–558.7)
Geometric mean fold rise							
Direct neutralization–wild-type	1	3.3 (2.5–4.5)	3.1 (1.8–5.2)	3.1 (2–4.6)	4.8 (3–7.5)	2.9 (1.2–6.8)	6.3 (3.9–10.2)
	2	7.5 (5–11.4)	5 (2.5–10)	6.5 (4.3–10.1)	12.4 (6.7–22.9)	6 (3.4–10.5)	8.6 (4.1–17.8)
	3	3.4 (2–5.7)	2.6 (1.3–5.2)	3.4 (1.6–7.2)	6.2 (2.7–14.2)	3 (1.6–5.6)	3.7 (2–6.7)
Direct neutralization–BA.1	1	5.5 (2.4–12.6)	3.7 (1.9–7.6)	15.6 (6.2–39.2)	10.7 (5.1–22.2)	4.7 (1.6–13.3)	12.3 (7–21.4)
	2	14.7 (6–36.5)	6.9 (3–15.9)	37.3 (12.6–110)	26 (10.7–63.2)	15 (6.2–36.7)	26.3 (13.8–49.9)
	3	5 (1.8–13.9)	2.3 (1.2–4.4)	17.4 (5.6–53.7)	11.3 (4.9–25.9)	7.2 (2.7–19.1)	12.2 (7.2–20.8)
Geometric mean ratio							
Direct neutralization–wild-type	1	REF	0.8 (0.44–1.48)	0.83 (0.45–1.51)	1.13 (0.62–2.04)	1.05 (0.58–1.93)	1.44 (0.79–2.62)
	2	REF	0.56 (0.29–1.05)	0.77 (0.41–1.46)	1.18 (0.63–2.23)	0.98 (0.52–1.85)	0.8 (0.43–1.5)
	3	REF	0.63 (0.3–1.32)	0.9 (0.42–1.92)	1.28 (0.6–2.75)	0.96 (0.46–1.97)	0.79 (0.38–1.63)
Direct neutralization–BA.1	1	REF	0.69 (0.33–1.43)	1.78 (0.86–3.65)	2.06 (1.02–4.18)	1.5 (0.73–3.08)	1.79 (0.88–3.64)
	2	REF	0.47 (0.23–0.97)	1.75 (0.84–3.64)	1.85 (0.9–3.81)	1.89 (0.91–3.92)	1.37 (0.67–2.8)
	3	REF	0.54 (0.24–1.2)	2.69 (1.17–6.17)	2.79 (1.21–6.41)	2.07 (0.93–4.58)	1.95 (0.88–4.32)

previous SARS-CoV-2 infection (per clinical history, PCR, or rapid antigen). Participants were randomized in a 1:1:1:1:1:1 ratio to receive one of the following: BNT162b2/30 μg, BNT162b2/60 μg, monovalent Omicron BA.1-adapted BNT161b2 vaccine versions (BNT162b2-Omi.BA.1/30 μg, Omi.BA.1/60 μg), and bivalent combinations (bivalent-Omi.BA.1/30 μg [BNT162b2/15 μg + BNT162b2-Omi.BA.1/15 μg] or bivalent-Omi.BA.1/60 μg [BNT162b2/30 μg + BNT162b2-Omi.BA.1/30 μg]).

After the eligibility criteria were confirmed, participants signed informed consent, nasopharyngeal swabs for SARS-CoV-2 were performed, and blood samples for immunogenicity assays were drawn. The vaccine was administered by a study nurse. Immune responses were further assessed on days 7, 30, and 90. Participants were required to report any of the following symptoms, irrespective of the perceived aetiology or significance: a new diagnosis of COVID-19, fever, chills, sore throat, diarrhoea, vomiting, new or increased cough, shortness of breath, muscle pain, or loss of taste/smell. If any of these symptoms were reported, a local SARS-CoV-2 test was performed (home rapid antigen test), followed by a SARS-CoV-2 RT-PCR. The vaccine assignment was unblinded on day 90.

Allocation (randomization) of participants to vaccine groups was performed using an interactive response system. Study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments. In case of an emergency, the principal investigator had the sole responsibility for determining if unblinding of a participant's study intervention assignment was warranted. This trial is a preregistered sub-study of a larger study (Study C4591031; NCT04955626). All participants provided informed consent. The study was approved by the Sheba Medical Center institutional review board. For the trial protocol and complete trial description and methods (including laboratory methods), see the supplementary appendix.

The primary immunogenicity endpoints of this study were the neutralization titers of SARS-CoV-2 ancestral strain and the BA.1 variant of concern. Exploratory endpoints included neutralization titers for the Delta and BA.5 variants of concern, serum IgG and IgA antibody levels (ancestral strain receptor-binding domain (RBD)), T-cell activation by the spike protein, and incidence of COVID-19 cases.

Statistical analysis

The study population was described with appropriate statistics for each variable type. Outcomes were log-transformed, using base-10 for IgG and IgA levels and base 2 for other outcomes.

The geometric mean titer of each endpoint was estimated at each planned visit, with a 95% CI based on modelling the log-transformed values with Student's t-distribution. The geometric mean fold rise (GMFR), compared with the levels before receipt of the trial vaccine dose, was similarly estimated, with 95% CIs estimated by modelling the difference in the log-transformed values with Student's t-distribution. The serologic response was evaluated at each visit as the empirical proportion of individuals with any (non-zero) response. To compare the increase of neutralizing antibody levels against the different strains at different post-vaccination time points, a separate analysis of covariance model was fit at each time point, with the log-transformed antibody levels as the outcome, the vaccination group as the exposure (using the lower dose of the reference strain vaccine as the baseline), and the log-transformed pre-vaccination antibody levels as a covariate. The

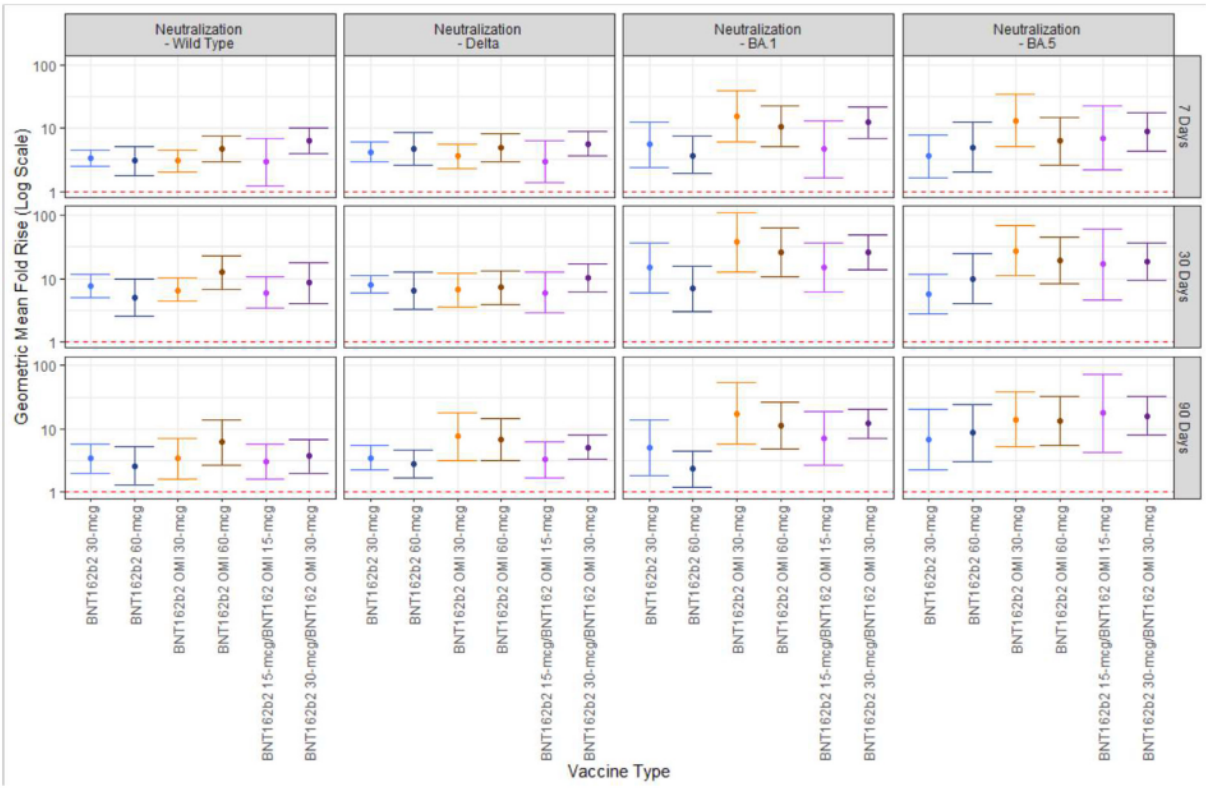

Fig. 2. Geometric mean fold rise by each vaccine type at each visit. Estimates of the geometric mean fold rise of neutralization titers, compared with baseline levels, at each visit and their 95% CI. The *Y* axis is log-scaled. A dashed red line is drawn at the null value of 1. Samples obtained after a COVID-19 infection were excluded.

coefficient and CI for the vaccination group were exponentiated to report the multiplicative change on the original scale.

Vaccine efficacy was analysed by estimating the incidence proportion (risk) of infection for each vaccine type as the empirical proportion of infection, with 95% CIs estimated using the Clopper-Pearson Method. The risk difference between each vaccine type and the reference vaccine was estimated as the difference in the empirical probabilities, with 95% CIs estimated using the Miettinen-Nurminen Method. To increase power, this analysis was repeated by pooling together each vaccine type (BTN162b2, monovalent-Omi.BA.1 and bivalent-Omi.BA.1) into a single arm, regardless of the dose.

No hypothesis tests were done, so no adjustment for multiple comparisons was needed. All analyses were performed on all participants that were randomized without differentiation between Intention to treat (ITT) and per protocol (PP). There were no missing data in the study population. Analysis was performed using the R statistical programming language, version 4.1.2.

Results

Overall, 122 individuals completed a follow-up of 90 days (Fig. 1). The median (interquartile range) age was 67 (64–71), and 50% were women (Table 1 and Table S1).

After the fourth dose administration, a rapid increase in antibody neutralization titers was observed against the SARS-CoV-2 ancestral strain and BA.1 Omicron variant in all vaccine groups. Three months after vaccination, titers declined to levels similar to 1 week after vaccination. For example, neutralization levels for the BA.1 strain after the 60-μg bivalent vaccine rose from a titer of 14 (95% CI: 6–33) pre-vaccination to 223 (95% CI: 126–395) after 1 week, to 478 (95% CI: 236–967) after 1 month, and then declined to 246 (95% CI: 108–559) at 3 months (Table 2). A similar trend was observed for the other variants of concern. Higher doses of each of the three vaccine types did not result in increased neutralizing antibody titers (Fig. S1 and Table S2).

The GMFR of neutralizing titers against the ancestral strain was six- to eight-fold compared with baseline and was similar after all three vaccines regardless of the dose administered. The GMFR of neutralizing titers against the BA.1 Omicron variant was higher at 1 and 3 months after vaccination with either monovalent-Omi.BA.1 or bivalent-Omi.BA.1 compared with BNT162b2 (Table 2 and Fig. 2). For example, after vaccination with the higher-dose bivalent vaccine, direct neutralization levels against BA.1 were 26-fold (95% CI: 14–50) greater than the baseline after 1 month and 12-fold (95% CI: 7–21) greater than the baseline after 3 months, whereas they were only 7-fold (95% CI: 3–16) and 2-fold (95% CI: 1–4) greater than the baseline at the same time point after vaccination with the double-dose ancestral strain vaccine. Neutralization of the Delta variant behaved similarly to the ancestral strain, whereas the neutralization of the BA.5 Omicron variant behaved similarly to BA.1 (Fig. S2 and Table S3).

The serologic response was high for all vaccines at all time points, at no point dropping below 90% (Table S4).

Three months after vaccination, adjusting for baseline levels, neutralizing antibody titers against the ancestral strain were 0.9 (95% CI: 0.42–1.92) times for monovalent-Omi.BA.1/30 μg and 0.96 (95% CI: 0.46–1.97) for bivalent-Omi.BA.1/30 μg when compared with BNT162b2/30 μg. For BA.1, however, they were 2.69 (95% CI: 1.17–6.17) times higher for monovalent-Omi.BA.1/30 μg and 2.07 (95% CI: 0.93–4.58) times higher for bivalent-Omi.BA.1/30 μg when compared with BNT162b2/30 μg (Table 2 and Fig. 3). No clear differences in the kinetics of IgG and IgA antibody levels against ancestral RBD were observed between the groups. Spike-specific T-cell activation peaked at 1 week, and was then higher for all

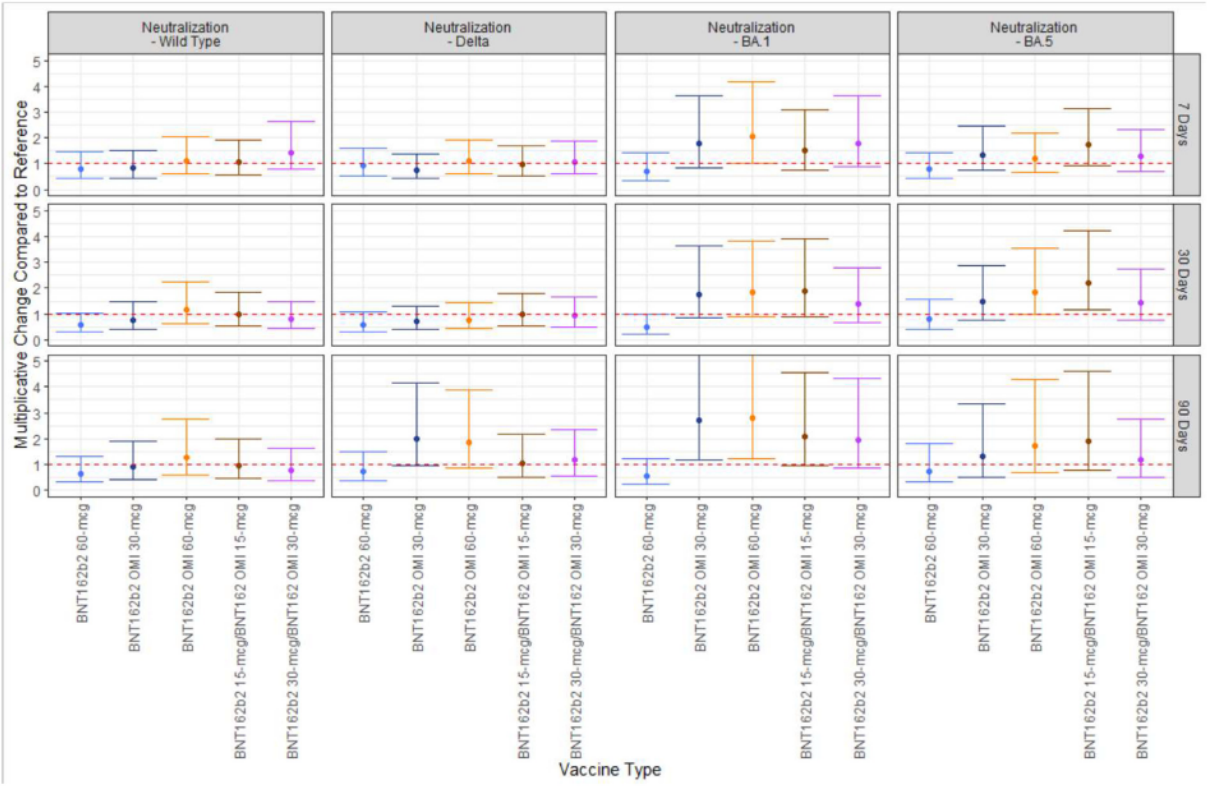

Fig. 3. Adjusted geometric mean ratio by each vaccine type at each visit. The geometric mean ratio of neutralization titers, adjusted for baseline levels, between each vaccine and the reference—BNT162b2/30 μg. This was estimated using a separate analysis of covariance model fit at each time point, with the log-transformed antibody levels as the outcome, the vaccination group as the exposure (using the lower dose of the reference strain vaccine as the baseline), and the log-transformed pre-vaccination antibody levels as a covariate. The coefficient and CI for each vaccination group were exponentiated to report the multiplicative change on the original scale. In both panels, a dashed red line is drawn at the null value of 1. Samples obtained after a COVID-19 infection were excluded.

investigational vaccines compared with BNT162b2/30 μg, particularly, 2.44-fold (95% CI: 1.04–5.69) higher after monovalent-Omi.BA.1/30 μg (Fig. S3 and Table S5).

During the study period, a BA.2\5 surge took place in Israel [3]. Infection proportions after both monovalent vaccines were similar: 24% (95% CI: 12–40%) after BNT162b2 and 28% (95% CI: 15–44%) after monovalent-Omi.BA.1. Observed infection proportions after the bivalent-Omi.BA.1 vaccines were lower, 12% (95% CI: 4–26%) (Table S6 and Fig. S4).

Discussion

This randomized trial aimed to estimate the effect of the novel Omicron-adapted BNT162b2 vaccines when given alone or as a bivalent vaccine together with the reference strain BNT162b2 vaccine. We find that the neutralizing antibody levels against the BA.1 Omicron variant, after Omicron-adapted vaccines, increased when compared with the original vaccine.

The importance of antibody levels as correlates of protection against COVID-19 infection has been previously described [4–6]. Over the 90-day follow-up, we found neutralizing antibody levels against the Omicron variant to be increased in individuals who received the novel vaccines. This increase was moderate (~1.5–2-fold greater), but persisted throughout the study period. These findings are similar to findings from shorter-term studies [2]. Within each vaccine type, we did not find that higher vaccine doses resulted in a stronger immune response.

Waning of the immune response after receipt of the original vaccine [7,8], correlated with decreased vaccine effectiveness over time [9,10], has been previously described. Here we report that the waning of the immune response is also evident over a 3-month follow-up period after receipt of the Omicron-adapted vaccines. Further studies with longer follow-ups will be needed to ascertain the degree of this waning and its association with long-term vaccine effectiveness.

In this study, the analysis of vaccine efficacy was exploratory, and the sample size was too small to draw strong conclusions. Despite this, an encouraging signal was found, with somewhat lower infection proportions after receipt of the bivalent vaccine. Larger studies are needed to better estimate the relative effectiveness of these novel vaccines.

In conclusion, neutralization titers against the BA.1 Omicron variant are moderately increased after monovalent-Omi.BA.1 or bivalent-Omi.BA.1 vaccination. Findings against the BA.5 variant are similar. Waning of the immune response is clearly evident 90 days after vaccination and is not affected by a higher dosage.

Author contributions

Conception and design: N.B., G.R.-Y., Y.L., and D.H. Data collection and laboratory work: Y.L., V.I., D.Z., K.A., Y.W.-O., S.A., L.K., B.A.-K., E.B.-A., M.C., R.K., and M.M. Analysis and interpretation of the results: N.B., Y.L., G.J., D.H., and G.R.-Y. Supervision of study conduct and laboratory work: Y.L., E.M., R.D., D.H., Y.K., M.M., and G.R.-Y. Draft manuscript preparation: N.B., Y.L., G.J., and G.R.-Y. All authors reviewed the results and approved the final manuscript.

Transparency declaration

GR-Y served as a member of an Advisory Board of Moderna and MSD; received consulting fees from Medison; and speaking fees from Teva, MSD, Pfizer, Astrazeneca, and Medison. YL received a

grant from Pfizer outside the submitted work. All other authors declare of no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.03.007.

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