Supplementary Appendix

Supplement to: Regev-Yochay G, Gonen T, Gilboa M, et al. Efficacy of a fourth dose of Covid-19 mRNA vaccine against omicron. N Engl J Med. DOI: 10.1056/NEJMc2202542

This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Materials

Table of Contents

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Supplementary Methods S1: Study Design, Eligibility, Inclusion & Exclusion Criteria

Study Design

This was an open-labled, controlled intervention study. Two intervention arms were planned and participants were designated to each arm on a time dependent manner. Eligible participants were those enrolled to the Sheba COVID-19 Cohort study (IRB 8008-20), who have been followed for serology testing, had an available test from the recent 60 days with a result of IgG of 700 BAU or below (i.e., below the 40th percentile of the full cohort on December 2021) and had received the third BNT162b2 dose at least 4 months earlier (see below full inclusion/exclusion criteria). Initially volunteers were designated to the BNT162b2 arm, and once approval of the second arm was received, volunteers were designated to the second – mRNA1273 arm, on a first come, first served basis. From the remaining eligible HCW who did not join either arm and did not receive the 4th dose within this study, controls were selected in a 2:1 ratio (See section S2).

Inclusion Criteria:

1. Age: Volunteer must be at least 18 years of age, at the time of signing the informed consent.
2. Sex: Male or Female.
3. Received 3 doses of BNT162b2 with the 3rd dose at least 4 months previously.
4. Have a serology test within the previous 3 months of 700 BAU or less.
5. Responded to the previous vaccine doses, i.e. at least one IgG>100.
6. Medical Conditions: Volunteers with any medical condition are allowed, as long as they adhere to the criteria above.
7. Agreed to attend all visits and signed the informed consent

Exclusion Criteria:

1. Had previously documented SARS-CoV-2 infection (detected by either PCR, anti-S IgG before the first vaccine dose, anti-N IgG at any stage).
2. Had an allergic response to any of the previous BNT162b2 doses.
3. Had history of myo-pericarditis.
4. Reported that they do not feel well or have a fever on the day of vaccination.
5. Pregnant on day of recruitment.

Criteria for premature cessation of the study:

- Increased rates of immediate adverse events, higher than those reported in previous studies (11 per million). https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm)

After informed consent was obtained, participants underwent screening and medical and vaccine history were collected (Supplementary **Table S1**). Blood samples for immunogenicity assessments were collected, a nasopharyngeal swab for SARS-CoV-2 PCR was obtained and the designated vaccine dose was administered; either 30µg of BNT162b2, for those enrolled on December 27-28, 2021, or 50µg of mRNA1273 for those enrolled on January 5-6, 2022.

Follow up visits of the two intervention arms took place on days 7, 14 and 21 and included safety assessment, symptom screen, SARS-CoV-2 PCR nasopharyngeal swab and blood for immunogenicity tests as detailed below. A final assessment of symptoms and SARS-CoV-2 testing (either PCR or rapid Ag tests) was performed on day 30, by telephone, electronic questionnaires and laboratory SARS-CoV-2 testing database. The control group, similarly were invited to perform SARS-CoV-2 PCR on a weekly basis, regardless of symptoms or exposures. To enhance compliance, personal telephone reminders were made to all participants (in all 3 groups).

Supplementary Methods S2: BNT162b2 and mRNA1273 control matching

Age matched (+/-5 years age difference allowed), controls from the sub-cohort of eligible individuals (see study design above) were matched in a 1:2 ratio to each participant in both intervention arms. A single control was allowed to serve as a matched control of both intervention groups. Perfect age and gender matches were preferred.

Supplementary Methods S3: Safety assessment

Safety assessments included monitoring of immediate and late solicited and unsolicited adverse events. Immediate adverse events and allergic reactions were monitored for 30 minutes after vaccine administration, by study physicians or nurses. Solicited adverse event

data were collected by an electronic questionnaire distributed on day 5 after vaccination and on a weekly basis for three consecutive weeks (See **Table S2**). Any participant who did not submit the electronic questionnaire, was directly contacted by research coordinators via telephone calls and missing data was retrieved. Solicited AE included any local reactions as well as systemic reactions, including fever, fatigue, myalgia, headache, lymphadenopathy and other systemic reactions. Severity and duration of any symptom were reported. Participants were instructed to report any unsolicited AE, any medically attended AE, need for medication, ED visits or hospitalization, within the study period.

Supplementary Methods S4- Immunogenicity

SARS-CoV-2 IgG II Quant (Abbott, IL, USA)

Samples were centrifuged in room temperature, at 4000g, for 4 minutes. Serum was tested for IgG antibodies against the SARS-COV-2 spike RBD using the commercial automatic chemiluminescent microparticle immunoassay (CMIA) SARS-CoV-2 IgG II Quant (Abbott, IL,USA) according to manufacturer's instructions.

SARS-CoV-2 Pseudovirus (psSARS-2) Neutralization Assay

SARS-CoV-2 Pseudo-virus (psSARS-2) Neutralization Assay was performed using a propagation-competent VSV-spike similar to the one previously published[1] which was kindly provided by Gert Zimmer, University of Bern, Switzerland and shown to be highly correlative to authentic SARS-CoV-2 virus micro-neutralization assay. Following titration, 100 focus forming units (ffu) of psSARS-2 were incubated with 2-fold serial dilution of heat inactivated (56°C for 30 min) tested sera. After incubation for 60 min at 37°C, virus/serum mixture was transferred to Vero E6 cells that have been grown to confluence in 96-well plates and incubated for 90 min at 37°C. After the addition of 1% methyl cellulose in dulbecco's modified eagle's medium (DMEM) with 2% of fetal bovine serum (FBS), plates were incubated for 24hr and 50% plaque reduction titer was calculated by counting green fluorescent foci using a fluorescence microscope (EVOS M5000, Invitrogen). Sera not capable of reducing viral replication by 50% at 1 to 16 dilution or below were considered non- neutralizing. For clear presentation non- neutralizing samples were marked as a titer of 2.

Live Micro-neutralization assay

VERO-E6 cells at concentration of 20*103/well were seeded in sterile 96-wells plates with 10% FCS MEM-EAGLE medium, and stored at 37ºC for 24 hours. One hundred TCID50 of wild type, delta and omicron SARS-CoV-2 isolates (isolated from SARS-CoV-2 positive individuals as described previously[2]) were incubated with inactivated sera diluted 1:8 to 1:16,384 in 96 well plates for 60 minutes at 33ºC. Virus-serum mixtures were added to the Vero E-6 cells and incubated for five days at 33ºC after which Gentian violet staining (1%) was used to stain and fix the cell culture layer. Neutralizing dilution of each serum sample was determined by identifying the well with the highest serum dilution without observable cytopathic effect. A dilution equal to 1:10 or above was considered neutralizing.

Supplementary Methods S5 - PCR testing

As part of the study all enrolled HCW (control and intervention arms) were requested to test once a week for the presence of SARS-CoV-2 mRNA by quantitative RealTime-PCR (qRT-PCR). Telephone reminders were made to all participants. Nasopharyngeal swabs were placed in 3mL of universal transport medium (UTM) or viral transport medium (VTM). Test was performed according to manufacturers' instructions on various platforms: Allplex™ 2019-nCoV (Seegene, S. Korea), NeuMoDx™ SARS-CoV-2 assay (NeuMoDx™ Molecular, Ann Arbor, Michigan), Xpert®, Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA).

Supplementary Methods S6 – Vaccine Efficacy

Secondary end points originally included assessment of breakthrough cases. To identify any infection, whether symptomatic or not, nasopharyngeal swabs were obtained on each weekly visit, for SARS-CoV-2 by RT-PCR (Seegene, South Korea). We suspected that the control group could be less motivated to comply with these weekly visits, since, they were not required (or interested in) weekly serology tests. We therefore sent weekly reminders via text messages in addition to the personal telephone reminder. In addition, participants in both arms and in the control group, were requested to perform a SARS-CoV-2 test (either RT-PCR or rapid Ag test) in case of any event of exposure to a detected SARS-CoV-2 infected person or if they developed any potential COVID-19 symptom, including fever, sore throat, headache, myalgia, rhinorrhea, cough or loss of smell or taste. Symptoms were assessed on each weekly visit. All PCR SARS-CoV-2 tests conducted in the hospital or in other settings were reported

to a central reporting system, and participants were actively inquired about results of home rapid antigen tests (via electronic questionnaires or telephone calls).

Breakthrough cases were defined only from day 8 (in each arm as well as in the control group), to exclude early infections due to exposure before vaccine is effective. All breakthrough cases were assessed by electronic questionnaires or telephone calls to define symptom severity at the end of their infection period.

The study was initially not designed to assess vaccine efficacy, since we expected the number of events to be too low, and the population size too small. This analysis was therefore conducted as a prospective observational study as described below.

Supplementary Results S1 - Vaccine efficacy detailed statistical analyses

Cumulative Incidence:

Vaccinated subjects entered follow up 7 days after vaccine day unless they became positive before that. They were followed until being positive or end of follow up (30th Jan 2022). The Moderna (mRNA1273) group were vaccinated a week after the BNT (BNT162b2) group. The control group started follow-up on 27th December 2021, but since the vaccinated follow-up started 7 days after vaccine day, the follow-up of the controls for BNT is analyzed only from the 3rd Jan 2022, and the controls for Moderna only from 10th Jan 2022. The controls were followed until they were vaccinated, became positive or until end of follow-up, whichever occurred first. The cumulative incidence of each treatment group and its control are given in Table A1 below.

Table A1: Cumulative incidence with 95% confidence interval

	group	day	cuminc	lowerCI	upperCI
1	BNT Control	23	0.2148884	0.1519313	0.2731719
2	BNT Control	28	0.2525738	0.1849619	0.3145769
3	BNT	23	0.1699346	0.1082381	0.2273627
4	BNT	28	0.1830065	0.1193810	0.2420351

	group	day	cuminc	lowerCI	upperCI
1	Mod Control	17	0.2558150	0.1800064	0.3246150
2	Mod Control	19	0.2558150	0.1800064	0.3246150

3 Moderna 17 0.2068966 0.1296463 0.2772903

4 Moderna 19 0.2068966 0.1296463 0.2772903

Poisson Regression:

The Poisson regression model, adjusting for calendar day and age-group, starting all vaccinated persons on the eighth day following their vaccination, and controls on Jan 3rd 2002, gives, in Table A2, the following estimated parameters (intercept and calendar day effects not given here):

Table A2: Estimated parameters, standard errors, z-values and P-values from the Poisson regre ssion of breakthrough infections

	Estimate	Std. Error	z value	P-value
BNT	-0.3574	0.2252	-1.5874	0.11
Moderna	-0.1139	0.2424	-0.4698	0.64
agec40-59	-0.3336	0.2280	-1.4629	0.14
agec60+	-0.8786	0.2629	-3.3423	0.0008

The estimates in the above table are log incidence rate ratios. For the vaccine groups, the comparative group is the control group. For the age groups, the comparative group is the 18-39y group. Vaccine efficacy is calculated by 1 minus the exponentiated parameter estimate, and is shown below, in Table A3, with its 95% confidence interval.

Table A3: Vaccine efficacy against infection with 95% confidence interval

	efficacy	lower_CI	upper_CI
BNT	0.3005	-0.0875	0.5501
Moderna	0.1077	-0.4352	0.4452

Cox regression:

We used calendar days as the time-axis, starting at 3rd Jan 2022. Participants in the vaccine groups were entered at their date of vaccination by left truncation. The estimated coefficients from the model are shown below in Table A4:

Table A4: Output from the Cox regression model: log hazard ratios (HR),
standard errors (se), and p-values

n= 692, number of events= 128

	log HR	se(log HR)	p-value
BNT	-0.3586	0.2252	0.11

Moderna	-0.1138	0.2424	0.64
agec40-59	-0.3365	0.2281	0.14
agec60+	-0.8848	0.2629	0.00076

The estimates in the above table are log hazard ratios. For the vaccine groups, the comparative group is the control group. For the age groups, the comparative group is the 18-39y group. Comparison with Table A2 shows that the results are almost identical to the estimates of the log incidence rate ratios.

Secondary analyses of vaccine efficacy against infection:

In a secondary analysis, we examined and compared the vaccine effects during 8-14 days after vaccination with their effects 15-29 days after vaccination. This was achieved by adding two extra covariates into the Poisson regression model (one for each vaccine) that represented the difference in the log incidence rate ratios between the two periods. The parameter estimates from this Poisson regression model are shown below in Table A5 (intercept and calendar day effects not shown here).

Table A5: Estimated parameters, standard errors, z-values and P-values from the Poisson regre ssion secondary analysis of breakthrough infections

	Estimate	Std. Error	z value	P-value
BNT (8-14)	0.1068	0.5231	0.2043	0.8381
BNT (15+ v 8-14)	-0.4416	0.2468	-1.7897	0.0735
Moderna (8-14)	-0.7208	0.4422	-1.6301	0.1031
Moderna (15+ 8-14)	0.1787	0.2887	0.6190	0.5359
agec40-59	-0.3293	0.2280	-1.4440	0.1487
agec60+	-0.8714	0.2629	-3.3152	0.0009

The estimates in the above table are log incidence rate ratios. For the vaccine groups 8-14 days, the comparative group is the control group. For the age groups, the comparative group is the 18-39y group. The second and fourth rows of the table show that there is no statistically significant difference between the effects in the first 14 days following vaccination and the effects thereafter, but there is a hint that the Pfizer BNT vaccine may have an increased effect after 14 days.

Vaccine efficacy against symptomatic disease:

We repeated the Poisson regression model analysis on the breakthrough infections that caused

symptomatic disease. The results are shown in Table A6 below:

Table A6: Estimated parameters, standard errors, z-values and P-values from the Poisson regre ssion of breakthrough infections causing symptomatic
disease

	Estimate	Std. Error	z value	P-value
BNT	-0.5640	0.2529	-2.230	0.026
Moderna	-0.3764	0.2784	-1.352	0.18
agec40-59	-0.2996	0.2464	-1.216	0.22
agec60+	-0.9183	0.2898	-3.169	0.0015

The estimates in the above table are log incidence rate ratios. For the vaccine groups, the comparative group is the control group. For the age groups, the comparative group is the 18-39y group. Vaccine efficacy is calculated by 1 minus the exponentiated parameter estimate, and is shown below, in Table A7, with its 95% confidence interval. The protection against symptomatic disease appears somewhat stronger than against infection.

Table A7: Vaccine efficacy against infection with 95% confidence interval

	efficacy	lower_CI	upper_CI
BNT	0.4311	0.0660	0.6535
Moderna	0.3137	-0.1845	0.6023

Supplementary Table S1 – Study general comorbidity computer-based questionnaire

	Question	Answer1	Answer2
1	What is your date of birth?		
2	What is your gender?	Male	Female
3	What is your current height in m?		
4	What is your current weight in kg?		
5	Did you undergo a SARS-CoV-2 Anti-spike IgG test before receiving the first dose of the vaccine?	Yes	No
6	Do you suffer from systemic hypertension (systolic blood pressure above 140) for which you are pharmaceutically treated?	Yes	No
7	Do you suffer from dyslipidemia (total cholesterol above 200 or LDL cholesterol above 160) for which you are pharmaceutically treated?	Yes	No
9	Do you suffer from an autoimmune disease for which you are pharmaceutically treated?	Yes	No
10	Do you have diabetes (HbA1C>6.5 or fasting blood sugar>126) for which you are pharmaceutically treated?	Yes	No
11	Do you suffer from heart disease for which you are pharmaceutically treated?	Yes	No
12	Do you suffer from lung diseases such as asthma, COPD, and pulmonary fibrosis treated for which you are pharmaceutically treated?	Yes	No
13	Do you suffer from any coagulation disorder resulting in hemorrhage or thrombosis for which you are pharmaceutically treated?	Yes	No
14	Are you immunosuppressed (organ transplant recipient, currently undergoing biologic therapy/chemotherapy, treated with corticosteroids, underwent a splenectomy, or diagnosed with HIV)?	Yes	No
15	Have you ever had a serious allergic reaction (anaphylaxis) that required immediate treatment?	Yes	No
16	Do you have liver disease as cirrhosis, hepatitis, liver cancer, or a metabolic disorder?	Yes	No

17	Do you have kidney disease (a creatinine level of >1.2 mg/dL or GFR<60) for which you are pharmaceutically treated?	Yes	No
18	Are you currently pregnant (as confirmed by a beta-HCG blood test and fetal heartbeat detection on ultrasonography)?	Yes	No

The questionnaire was reviewed and approved by the Institutional review board of the Sheba Medical Center**.**

Supplementary Table S2 – Adverse Event computer-based questionnaire

	Question	Answer 1	Answer 2	Answer 3
	Local symptoms:			
1	Did you experience pain in the injection site?	Yes	No	
2	Did you experience redness of the injection site?	Yes	No	
3	Did you experience swelling of the injection site?	Yes	No	
4	Did you experience itching at the injection site?	Yes	No	
5	Did you experience local lymph node swelling?	Yes	No	
6	Did you experience other local symptoms? If so, please elaborate	Yes	No	
7	How long did the local symptoms last (in days)?			
8	How would you rate the severity of the local symptoms on a scale of 1-10 (1- mild, 10- severe with major functional impairment)?			
	Systemic symptoms:			
9	Did you experience a fever above 37.5? How many days did it last?	Yes	No	Number of days:___
10	Did you experience fatigue? How many days did it last?	Yes	No	Number of days:___
11	Did you experience myalgia? How many days did it last?	Yes	No	Number of days:___
12	Did you experience generalized lymphadenopathy? How many days did it last?	Yes	No	Number of days:___
13	Did you experience headache? How many days did it last?	Yes	No	Number of days:___
14	Did you experience facial nerve palsy? How many days did it last?	Yes	No	Number of days:___
15	Did you experience paresthesia? How many days did it last?	Yes	No	Number of days:___
16	Did you experience an allergic reaction? If so, please elaborate. How many days did those symptoms last?	Yes	No	Number of days:___

17	How would you rate the severity of the systemic symptoms on a scale from 1-10 (1- mild, 10- severe with major functional impairment)?			
18	Did you have any laboratory abnormality? If so, please elaborate.	Yes	No	
19	Did you experience any other symptoms? How many days did they last? If so, please elaborate.	Yes	No	Number of days:___
20	Did you require medical leave due to your symptoms? If so, how long were you absent from work for?	Yes	No	Number of days:___
21	Did you seek medical attention due to your symptoms? If so, please elaborate	Yes	No	
22	Did you require hospitalization?	Yes	No	

The questionnaire was reviewed and approved by the Institutional review board of the Sheba Medical Center**.**

Supplementary Table S3: Trial population; Characteristics of participants at enrollment

		BNT162b2	Control (BNT162b2)	mRNA1273	Control (mRNA1273)
Number of participants		154	308	120	239
Male sex		63 (40.9%)	90 (29.2%)	39 (32.5%)	61 (25.5%)
Age	Mean, Median (Range)	59.0, 60.8, (30-85)	59.2, 61.3, (30-89)	55.1, 56.0, (29-87)	56.0, 56.7, (29-89)
	18-45	33 (21.4%)	57 (18.5%)	33 (27.5%)	51 (21.3%)
	46-60	44 (28.6%)	88 (28.6%)	44 (36.7%)	95 (39.7%)
	>60	77 (50%)	163 (52.9%)	43 (35.8%)	93 (38.9%)
Number of comorbidities	0	92 (59.7%)	194/268 (72.4%)	81 (67.5%)	149/203 (73.4%)
	1	41 (26.6%)	52/268 (19.4%)	28 (23.3%)	39/203 (19.2%)
	≥2	21 (13.6%)	22/268 (8.2%)	11(9.2%)	15/203 (7.4%)
Immunosuppressed		3 (1.9%)	4/267 (1.5%)	2 (1.7%)	1/203 (0.5%)
BMI (kg/m^2)	Mean, Median (Range)	26.6, 26.0 (18.7-57.1) n=149	26.1, 25.5, (17.7-43.6) n=242	25.9, 24.7 (19.4-42.2) n=117	26.0, 25.5 (17.7-43.0) n=193

Supplementary Table S4a – Local adverse events

	BNT, age<60	**BNT, age>60**	**mRNA 1273, age<60**	**mRNA 1273, age>60**	**Total**
	(N=75)	(N=79)	(N=73)	(N=47)	(N=274)
Any local symptoms, (%, 95% CI)	66 (88%, 80.6-95.4%)	55 (69.6%, 59.5-79.8%)	61 (83. 6%, 75.1-92.1%)	38 (80.9%, 70-92. %)	220 (80.3%, 75.6-85%)
Mild (1-3), (%, 95% CI)	40 (53.3%, 42.0-64.6%)	32 (40.5%, 29.7-51. 3%)	33 (45.2%, 33.8-56.6%)	25 (53.2%, 38.9-67.7%)	130 (47.5%, 41.5-53.4%)
Moderate (4-6), (%, 95% CI)	17 (22. 7%, 13.2-32.1%)	12 (15.2%, 7.3-23.1%)	16 (21.9%, 12.4-31.4%)	7 (14.9%, 4.7-25.1%)	52 (19%, 14.3-23.6%)
Severe (7-10), (%, 95% CI)	3 (4%, -0.4-8.4%)	3 (3.8%, -0.4-8.0%)	7 (9.6%, 2.8-16.3%)	4 (8.5%, 0.5-16.5%)	17 (6.2%, 3.4-9.1%)
Any local symptoms - duration (days)					
Mean, (95% CI)	1.53, (1.2-1.8)	1.5, (1.2-1. 9)	2.2, (1.3-3)	1.6, (1.6-3.4)	1.7, (2-1.4)
Median (SD)	1 (1.3)	1 (1.6)	2 (3.6)	2 (1.1)	2 (2.2)
25th, 75th %tile	1 ,2	0 ,2	1 ,3	0 ,2	1 ,2
Min, Max	0 ,7	0 ,10	0 ,30	0 ,5	0 ,30
Erythema/redness, (%, 95% CI)	6 (8%, 1.9-14.1%)	3 (3.8%, -0.4-8.0%)	8 (11%, 3.8-18.1%)	5 (10.6%, 1.8-19.4%)	22 (8.0%, 4.8-11.2%)
Induration/swelling, (%, 95% CI)	10 (13.3%, 5.6-21.0%)	6 (7.6%, 1.8-13.4%)	10 (13.7%, 5.8-21.6%)	7 (14.9%, 4.7-25.1%)	33 (12.0%, 8.2-16%)
Pain and/or tenderness, (%, 95% CI)	64 (85.3%, 77.3-93.3%)	54 (68.4%, 58.1-78.6%)	61 (83. 6%, 75.1-92.1%)	37 (78.7%, 67.0-90.4%)	216 (78.8%, 74-83. 7%)

Supplementary Table S4b – Systemic adverse events

	BNT, age<60 (N=75)	**BNT, age>60** (N=79)	**mRNA 1273, age<60** (N=73)	**mRNA 1273, age>60** (N=47)	**Total** (N=274)
Any systemic symptoms, (%, 95% CI)	38 (50.7%, 39.4-62%)	28 (35.4%, 24.9-46%)	42 (57.5%, 46.2-68.9%)	25 (53.2%, 38.9-67.5%)	133 (48.5%, 42.6 -54.5%)
Mild (1-3), (%, 95% CI)	17 (22.7%, 13.2-32.2%)	9 (11.4%, 4.4-18.4%)	18 (24.7%, 14.8-34.5%)	12 (25.5%, 13.1-38%)	21 (7.7%, 4.5-10.8%)
Moderate (4-6), (%, 95% CI)	9 (12%, 4.6-19.35%)	5 (6.3%, 1-11.7%)	14 (19.2%, 10.2-28.2%)	5 (10.6%, 1.8-19.5%)	10 (3.6%, 1.4-5.9%)
Severe (7-10), (%, 95% CI)	7 (9.3%, 2.8-15.9%)	6 (7.6%, 1.8-13.4%)	3 (4.1%, -0.4-8.7%)	2 (4.3%, -1.5-10.0%)	8 (2.9%, 0.9-4.9%)
Any systemic symptoms - duration (days)					
Mean, (95% CI)	1.6, (1.0-2.1)	1.0, (0.6-1.4)	1.4, (0.7-2.0)	1.2, (0.6-1.7)	1.3, (1.63-1.0)
Median (SD)	0 (2.4)	0 (1.9)	1 (3.0)	1 (1.9)	0 (2.4)
25th, 75th %tile	0 ,2	0 ,1	0 ,2	0 ,2	0 ,2
Min, Max	0 ,14	0 ,10	0 ,24	0 ,9	0 ,24
Fever > 37.5, (%, 95% CI)	8 (10.7%, 3.7-17.7%)	3 (3.8%, -0.4-8.0%)	5 (6.9%, 1.1-12.6%)	1 (2.1%, -2-6.3%)	18 (6.6%, 3.6-9.5%)
Fever > 37.5 - duration					
Mean, (95% CI)	1.5, (1.2-1.8)	1.3, (1.0-1.5)	1.3, (1.0-1.5)	0.8, (0.6-1.0)	1.3, (1.4-1.1)
Median (SD)	1 (1.5)	1 (1.1)	1.5 (1)	1 (0.8)	1 (1.2)
25th, 75th %tile	1 ,1.8	0 ,2	0.25 ,2	0 ,1.5	0.3 ,2
Min, Max	0 ,5	0 ,3	0 ,2	0 ,2	0 ,5
Fatigue, (%, 95% CI)	25 (33.3%, (22.7-44%)	17 (21.5%, (12.5-30.6%)	31 (42.5%, (31.1-53.8%)	18 (38.3%, (24.4-52.2%)	91 (33.2%, 27.6-38.8%)
Fatigue - duration					

Mean, (95% CI)	3.4, (2.7-4.1)	2, (1.7-2.3)	2.6, (1.6-3.7)	1.5, (1.1-1.9)	2.5, (2.9-2.1)
Median (SD)	2 (3)	2 (1.5)	2 (4.4)	1 (1.3)	2 (3.1)
25th, 75th %tile	1 ,5	1 ,3	1 ,2.25	1 ,2	1 ,3
Min, Max	0 ,14	0 ,6	1 ,24	0 ,5	0 ,24
Myalgia, (%, 95% CI)	21 (28%, (17.8-38.2%)	10 (12.7%, (5.3-20%)	23 (31.5%, (20.9-42.2%)	13 (27.7%, (14.9-40.4%)	67 (24.5%, 19.4-29.6%)
Myalgia - duration					
Mean, (95% CI)	3.0, (2.4-3.7)	1.8, (1.6-2.14)	1.8, (1.6-2.0)	1.5, (1.3-1.7)	2.2, (2.4-1.9)
Median (SD)	2 (2.9)	2 (1.3)	2 (0.9)	2 (0.7)	2 (1.9)
25th, 75th %tile	1 ,5	1 ,2.5	1 ,2	1 ,2	1 ,2
Min, Max	0 ,14	0 ,5	1 ,4	0 ,2	0 ,14
Lymphadenopathy, (%, 95% CI)	7 (9.3%, 2.8-15.9%)	1 (1.3%, -1.2-3.7%)	4 (5.5%, 0.3-10.7%)	1 (2.1%, -2-6.2%)	13 (4.7%, 2.2-7.3%)
Lymphadenopathy - duration					
Mean, (95% CI)	3.1, (2.6-3.6)	0.5, (0.3-0.7)	2.4, (1.8-3.0)	1, (0.5-1.5)	2.1, (2.-1.8)
Median (SD)	3.5 (2.2)	0 (1)	2 (2.7)	0 (1.7)	1.5 (2.3)
25th, 75th %tile	1 ,5	0 ,1.5	0.5 ,4.5	0 ,3	0 ,3.8
Min, Max	0 ,6	0 ,2	0 ,7	0 ,3	0 ,7
Headache, (%, 95% CI)	21 (28%, 17.8-38.2%)	13 (16.5%, 8.3-24.6%)	17 (23.3%, 13.6 -33%)	8 (17.0%, 6.3-27.8%)	59 (21.5%, 16.7-26.4%)
Headache - duration					
Mean, (95% CI)	3.5, (2.8-4.1)	2.1, (1.6-2.5)	3.0, (1.8-4.3)	2, (1.4-2.6)	2.8, (3.2-2.4)
Median (SD)	3 (3)	1 (2.0)	1.8 (5.4)	2 (2)	2 (3.5)
25th, 75th %tile	1 ,5	1 ,3	1 ,3	0.8 ,2.3	1 ,3
Min, Max	0 ,14	0 ,7	0 ,24	0 ,7	0 ,24
Arthralgia, (%, 95% CI)	7 (9.3%, 2.8-15.9%)	6 (7.6%, 1.8-13.4%)	6 (8.2%, 1.9-14.5%)	4 (8.5%, 0.5-16.5%)	23 (8.4%, 5.1-11.7%)

Arthralgia - duration					
Mean, (95% CI)	3.8, (2.8-4.8)	3, (2.3-3.7)	5.7, (3.6-7.7)	1.2, (0.9-1.5)	3.4, (4-2.8)
Median (SD)	2 (4.4)	2 (3.3)	2 (9)	1.5 (1)	2 (5.0)
25th, 75th %tile	1.3 ,4.8	0.5 ,4.5	1.8 ,8.3	0 ,2	1 ,3
Min, Max	0 ,14	0 ,10	1 ,24	0 ,2	0 ,24
Paresthesia, (%, 95% CI)	2 (2.7%, -1-6.3%)	1 (1.3%, -1.2-3.7%)	1 (1.4%, -1.3-4.0%)	0 (0%, 0-0%)	4 (1.5%, 0.0-2.9%)
Paresthesia - duration					
Mean, (95% CI)	7.0, (5.5-8.6)	0.3, (0.1-0.4)	0.5, (0.3-0.7)	0, (0-0)	2.1, (2.6-1.6)
Median (SD)	7 (7)	0 (0.5)	0.5 (0.7)	0 (0)	0 (4.5)
25th, 75th %tile	0.1 ,14	0 ,0.8	-	-	0 ,1
Min, Max	0.1 ,14	0 ,1	0 ,1	0 ,0	0 ,14
Allergic reaction, (%, 95% CI)	1 (1.3%, -1.3-3.9%)	1 (1.3%, -1.2-3.7%)	0 (0%, 0-0%)	1 (2.1%, -2-6.3%)	3 (1.0%, -0.1-2.3%)
Absence from work - duration (days)					
Mean, (95% CI)	1.8, (1.8-2.1)	1.2, (0.7-1.0)	1, (1-1)	3.3, (1.6-3.4)	1.8, (1.8-1.4)
Median (SD)	1 (1.2)	1 (0.4)	-	2 (3.21)	1 (1.5)
25th, 75th %tile	1 ,2.5	1 ,1.25	-	1 ,7	1 ,2
Min, Max	1 ,5	1 ,2	1 ,1	1 ,7	1 ,7

Supplementary Table S5 – Immunogenicity Summary Table

A. IgG				
		All available samples of trial participants (n=700)		
Pre-trial Period				
Post-dose 2	IgG (n tested) GMT (95%CI)	 949.9 (869-1039)		
Pre-dose 3	IgG (n tested) GMT (95%CI)	 63.8 (59-69)		
Post-dose 3	IgG (n tested) GMT (95%CI)	 2131 (1933-2349)		
Trial period				
		BNT162b2 4th dose group	mRNA1273 4th dose group	Control group
n		154	120	426
Pre-dose 4	IgG (n tested) GMT (95%CI)	N=154 326.3 (293-363)	N=120 335.2 (285.5-393.5)	N=424 421.7 (403-441)
1 week post dose 4	IgG (n tested) GMT (95%CI)	N=149 1476 (1268-1718)	N=110 2341 (1917-2860)	
2 weeks post dose 4	IgG (n tested) GMT (95%CI)	N=142 2975 (2607-3394)	N=105 3502 (2965-4137)	N=50 340 (303-381)
3 weeks post dose 4	IgG (n tested) GMT (95%CI)	N=138 2684 (2372-3038)	N=89 3729 (3132-4440)	
B. Neutralizing Ab				
		All available samples of trial participants (n=700)		
Pre-trial Period				
Post-dose 2	Neut (n tested) GMT (95%CI)	 306.4 (251-374)		
Pre-dose 3	Neut (n tested) GMT (95%CI)	 59.1 (49-71)		
Post-dose 3	Neut (n tested) GMT	 2628		

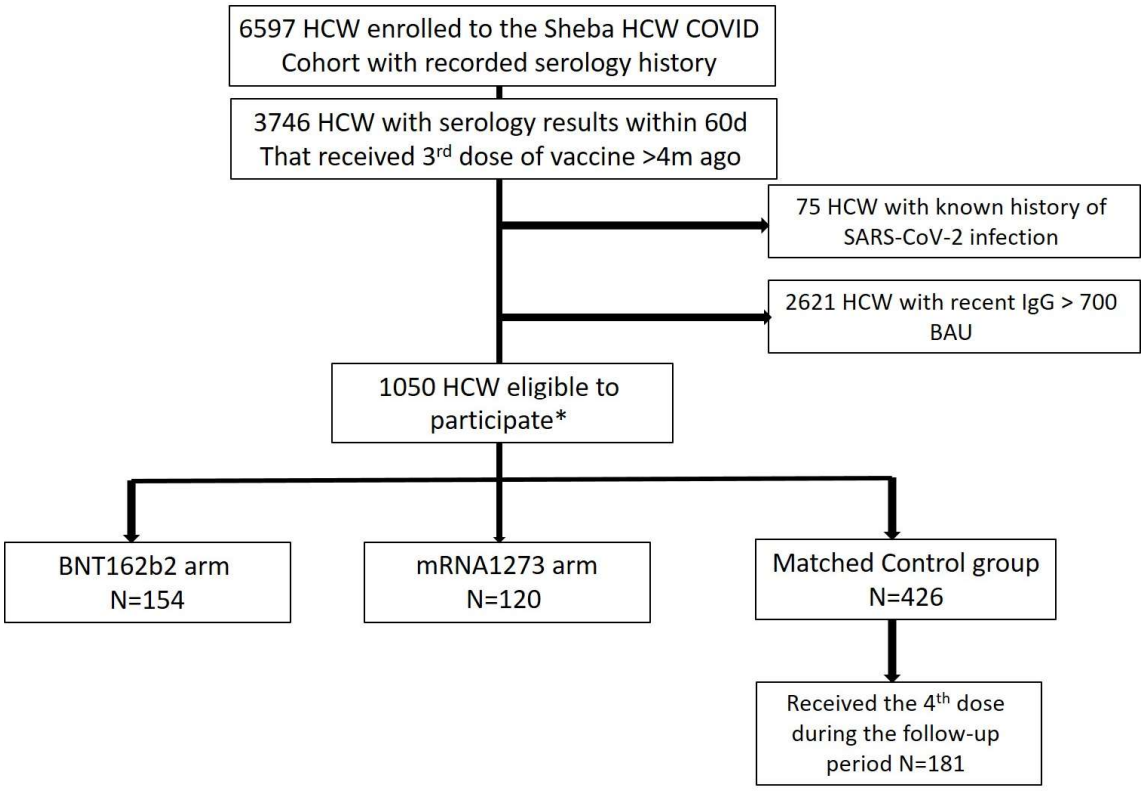
	(95%CI)	(2312-2987)		
Trial period				
		BNT162b2 4th dose group	mRNA1273 4th dose group	Control group
n		154	120	426
Pre-dose 4	Neut (n tested) GMT (95%CI)	N=154 429.6 (360-512)	N=119 336.6 (277-409)	N=323 362.9 (320-412)
1 week post dose 4	Neut (n tested) GMT (95%CI)	N=149 2801 (2293-3421)	N=111 3423 (2721-4308)	
2 weeks post dose 4	Neut (n tested) GMT (95%CI)	N=142 3788 (3184-4507)	N=106 5192 (4099-6578)	N=38 363.9 (227-585)
3 weeks post dose 4	Neut (n tested) GMT (95%CI)	N=137 3501 (2976-4119)	N=84 3510 (2884-4272)	

Supplementary Table S6 –Breakthrough infections and vaccine efficacy

		BNT162b2	Control (BNT)	mRNA1273	Control (mRNA1273)
N enrolled		154	308	120	239
N followed		153	307	116	149
Exposure days*		3808	4755	1923	2327
Study period		Dec 27, 2021-Jan 30, 2022	Dec 27, 2021-Jan 30, 2022	Jan 5, 2022-Jan 30, 2022	Jan 5, 2022-Jan 30, 2022
Infected Participants (days 1 - end of study)		29	47	28	43
Breakthrough** cases (days 8 – end of study)		28	46	24	36
Breakthrough** symptomatic disease		22	42	17	33
Cum incidence of SARS-CoV-2 infections***(95%CI)		18.3% (11.9-24.2%)	25.3% (18.5-31.5%)	20.7% (11.3-27.8%)	25.6% (18.0-32.5%)
Cum incidence of symptomatic COVID-19 disease		14.4% (8.5-19.9%)	23.9% (17.3-30.1%)	15.6% (8.5-22.1%)	23.9% (16.4-30.7%)
Vaccine efficacy against infection		30.0% (-8.8%-55%)	Ref	10.8% (-43%-44%)	Ref
Vaccine efficacy against disease		43.1% (6.6%-65.4%)	Ref	31.4% (-18.4-60.2%)	Ref
Characteristics of breakthrough infections					
		BNT162b2	Control-B	mRNA1273	Control-M
Total breakthrough infections		28	46	24	36
Symptoms	Asymptomatic	7 (25.0%)	3 (6.5%)	7 (29.2%)	3 (8.3%)
	Mild w/o fever	18 (64.3%)	30 (65.2%)	16 (66.6%)	26 (72.2%)
	Fever <48h	2 (7.1%)	4 (8.7%)	1 (4.2%)	5 (13.9%)
	Fever for > 48h	0 (0%)	8 (17.4%)	0 (0%)	2 (5.5%)
	Required ED / hospitalization	0 (0%)	0 (0%)	0 (0%)	0(0%)
Gender	Male	9 (36%)	6 (14.2%)	9 (39.1%)	3 (9.1%)
Age	Mean, Median (Range)	53.79, 57.5 (30-85)	53.13, 54.4 (32-78)	51.84, 52.62 (32-72)	49.53, 50.51 (29-78)
	18-45	11 (44%)	14 (32.6%)	6 (26.1%)	12(33.3%)
	46-60	4 (16%)	20 (46.5%)	10 (43.5%)	18 (50.0%)
	>60	10 (40%)	9 (20.9%)	3 (13%)	3 (8.3%)
Comorbidities	2 or more	3/25 (12%)	3/35 (12%)	2/19 (10.5%)	2/31 (6.5%)
Immunosuppression		2/25 (8%)	0/35	0/19 (0%)	1/31 (3.2%)
BMI (mean)		25.46	25.11 (n=33)	26.27	24.88 (n=29)
Days since last vaccine dose (mean, median)		20.8, 21	20.84, 22	15.83, 15	15.94, 15
Lowest N-gene Ct (Geomean (95%CI)		(n=20) 25.3 (22.8-28.2)	(n=34) 24.7 (23-26.6)	(n=17) 25.1 (22.1-28.5)	(n=27) 24.9 (23.4-26.6)
Pre-infection IgG GMT (95%CI)		n=25 1890.3 (1301.1-2746.2)	n=31 336.88 (290.31-390.9)	n= 23 3413.7 (2576.8-4522.4)	n=22 315.61 (253.77-392.5)
Pre-infection neut GMT (95%CI)		n=25 1937.5 (1157.4-3243.6)	n=10 274.37 (139.08-541.29)	n=23 3774.5 (2251.8 – 6327.0)	n=5 388.02 (105.2-1431.3)

*Exposure days are counted from day 8 after 4th dose until end of study
**Breakthrough cases and their exposure days were counted starting from day 8 after 4th dose until the end of study period on Jan 30, 2022
***Follow up: BNT-28d, mRNA1273-19d)

Supplementary Figure S1: Study source cohort, screening and participant eligibility and enrollment



Supplementary Figure S2: Solicited local and systemic adverse events following the 4th dose of BNT162b2 or mRNA1273

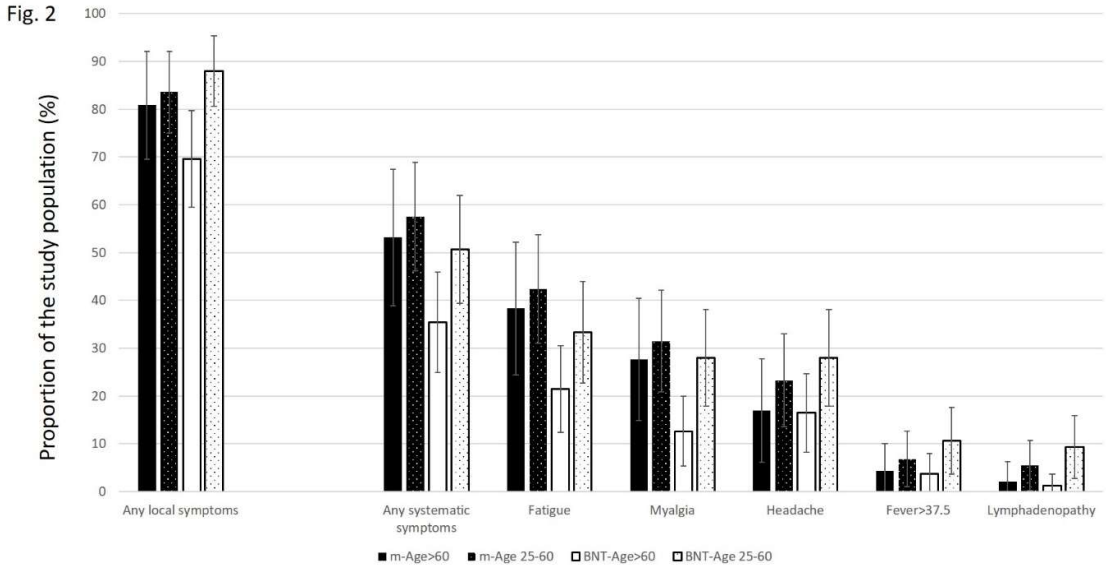


Figure S2: Solicited local and systemic adverse events following the 4th dose of BNT162b2 or mRNA1273. Black denotes recipients of mRNA1273, white denotes recipients of BNT162b2. Dotted denotes the younger population (<60 years of age). The proportion of participants reporting each AE among each age group in the two different vaccine recipients, is presented and its 95%CL.

Supplementary Figure S3: Neutralizing antibody titers after 3 doses of BNT162b2, and a fourth dose of either BNT162b2 or mRNA1273

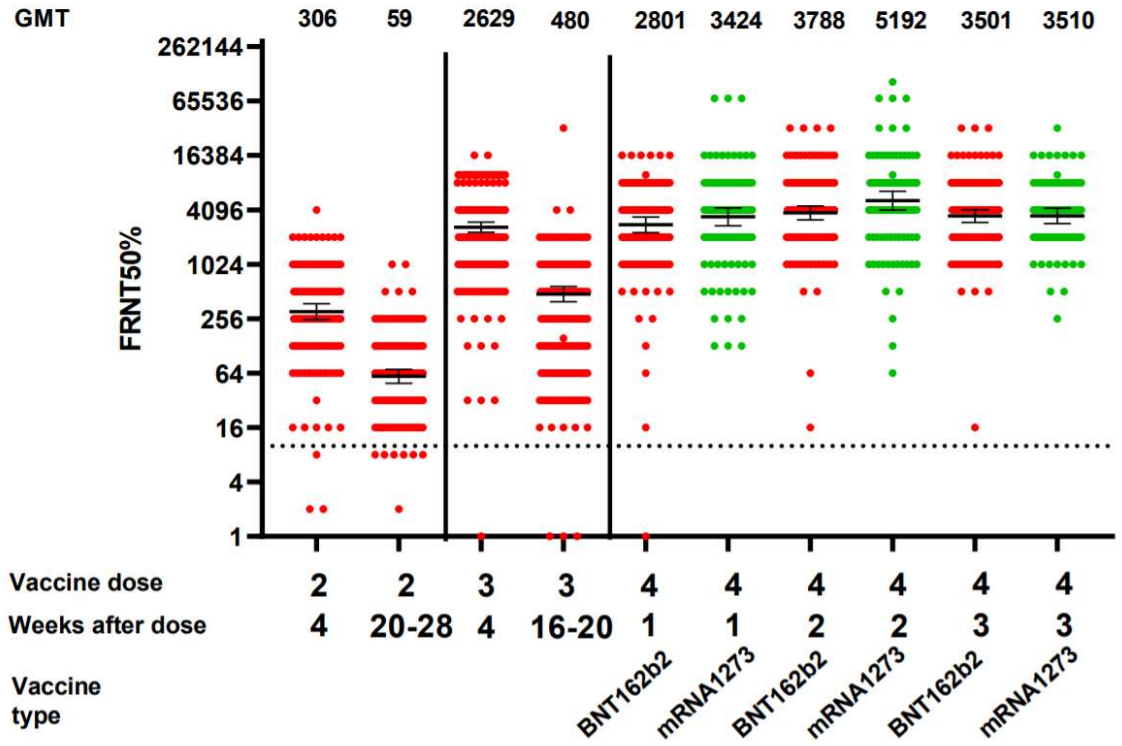
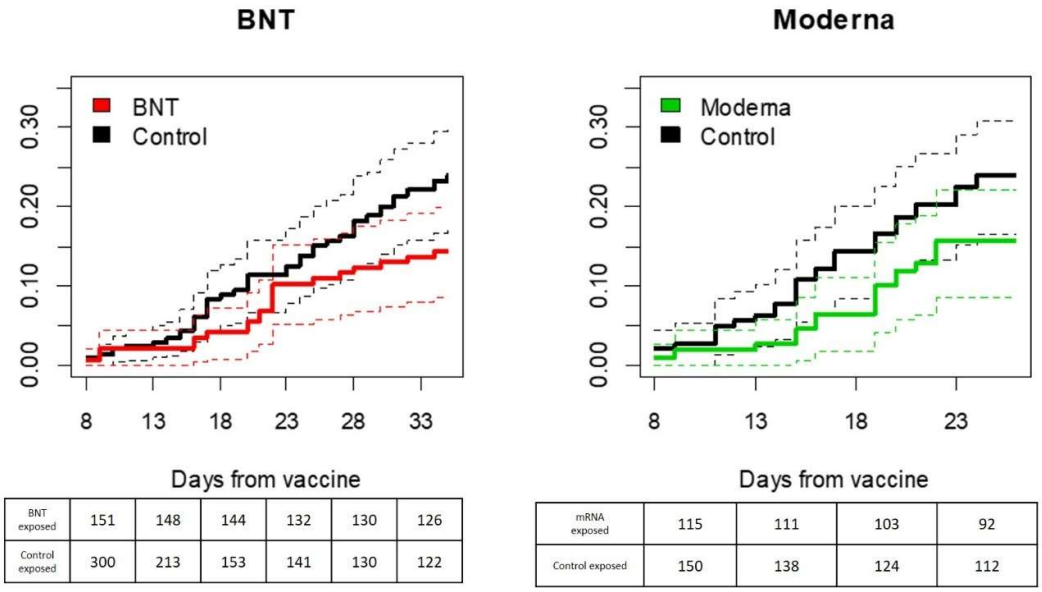


Figure S3: Neutralizing antibody titers after 3 doses of BNT162b2, and a fourth dose of either BNT162b2 or mRNA1273, Geometric mean titers (GMT) are presented and their 95%CI. Red denotes response among BNT162b2 recipients; Green denotes response among mRNA1273 recipients.

Supplementary Figure S4: Cumulative incidence of symptomatic SARS-CoV-2 infections, among BNT162b2 and mRNA1273 recipients and their matched controls



BNT exposed	151	148	144	132	130	126
Control exposed	300	213	153	141	130	122

mRNA exposed	115	111	103	92
Control exposed	150	138	124	112

Figure S4: Cumulative incidence of symptomatic SARS-CoV-2 infections, among BNT162b2 and mRNA1273 recipients and their matched controls. 95%CI are depicted by the dotted lines.

Clinical trial Protocol

See Appendix A.

References:

1. Nemet I, Kliker L, Lustig Y, Zuckerman N, Erster O, Cohen C, Kreiss Y, Alroy-Preis S, Regev-Yochay G, Mendelson E, Mandelboim M. Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. N Engl J Med. 2022 Feb 3;386(5):492-494. doi: 10.1056/NEJMc2119358. Epub 2021 Dec 29. PMID: 34965337.

2. **Bibliography**

1. Lustig Y, Sapir E, Regev-Yochay G, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. Lancet Respir Med 2021;9(9):999–1009.
2. Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. N Engl J Med 2022;386(5):492–494.