Comparing Immunogenicity and Efficacy of Two Different mRNA-based COVID-19 Vaccines as a Fourth Dose; Six-Month Follow-up, Israel, 27 December 2021 to 24 July 2022

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Supplementary Methods S1 – Immunologic Methods

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

Samples were centrifuged at room temperature, at 4000g, for 4 minutes. Serum was tested for immunoglobulin G (IgG) antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) spike receptor binding domain (RBD) using the commercial automatic chemiluminescent microparticle immunoassay (CMIA) SARS-CoV-2 IgG II Quant (Abbott, IL, USA) according to the manufacturer's instructions. The geometric mean titers (GMT) are presented in binding antibody units (BAU).

SARS-CoV-2 Pseudovirus (psSARS-2) neutralization assay

SARS-CoV-2 Pseudovirus (psSARS-2) neutralization assay was performed using a propagation-competent vesicular stomatitis virus spike and shown to be highly correlative to authentic SARS-CoV-2 virus micro-neutralization assay (1). 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 24 hours, 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.

Supplementary Methods S2 – SARS-CoV-2 Cases

Cases were defined as positive in one of three scenarios:

1. Positive SARS-CoV-2 quantitative real-time polymerase chain reaction (qRT-PCR) test. These tests were performed using the Allplex™-2019 nCoV (Seegene, S. Korea) platform.
2. Positive antigen rapid diagnostic test (Ag-RDT) test. These tests were performed using STANDARD Q COVID-19 Ag (SD BIOSENSOR, S. Korea).
3. an observation of an uncharacteristic increase in IgG levels, defined as >500 BAU or >1000 BAU in healthcare workers (HCW) with previous IgG results of <700 or >700, respectively.

Supplementary Methods S3 – SARS-CoV-2 Symptoms and Disease Severity Questionnaire

1. What was the highest Fever measurement in the past 24 hours?
    - Under 37
    - 37-37.4
    - 37.5-37.9
    - 38-38.9
    - 39-39.9
    - Over 40
2. What was the lowest saturation measured in the past 24 hours?
    - Above 96
    - Under 96
    - Not measured
3. Please mark all symptoms that you experienced in the past 24 hours:
    - Cough
    - Dyspnea
    - Myalgia
    - Throat pain
    - Headache
    - Chest pain
    - Fatigue
    - Rhinorrhea
    - Diarrhea
    - Anosmia
    - Other- please elaborate
    - I did not experience any symptom
4. How would you describe your functional status?
    - I am hospitalized
    - I cannot get out of bed
    - I feel unwell and spend most day in bed
    - I feel less well than usual
    - I feel well as usual

Supplementary Table S1 – Variable Definitions

Variable	Values	Definition
A. Exposure		
Vaccine type	BNT162b2/ mRNA1273	Vaccine type received upon enrollment
B. Immunological outcomes		
IgG	Numeric	Anti-RBD IgG GMT tested on days 0 and 180.
Neutralizing antibodies	Numeric	Neutralizing antibodies GMT on days 0 and 180.
C. Clinical outcomes		
SARS-CoV-2 infection	0/1	Positive SARS-CoV-2 qRT-PCR test, a positive Ag-RDT, or an uncharacteristic IgG increase after a decline from peak vaccination levels was already observed (>500 or >1000 from previous levels of <700 or >700, respectively)
SARS-CoV-2 substantial disease	0/1	Positive SARS-CoV-2 participant who spent two or more days mostly in bed due to feeling unwell
D. Covariates		
Age	Numeric	Participant's age upon enrollment
Sex	Female/ male	Participant's sex
BMI	Numeric	BMI calculated as weight/m^2 upon enrollment
Immunosuppression	0/1	Including organ transplant recipient, currently undergoing biological therapy or chemotherapy, treated with corticosteroids, underwent splenectomy, or diagnosed with HIV
Number of comorbidities	0, 1, +2	Including hypertension, dyslipidemia, autoimmune disease, diabetes, heart disease, lung disease, coagulation disorder, liver disease, and kidney disease

Abbreviations: IgG- anti-RBD immunoglobulin G, GMT- geometric mean titers, SARS-CoV-2- severe acute respiratory syndrome coronavirus 2, qRT-PCR- quantitative real-time polymerase chain reaction, Ag-RDT- antigen rapid diagnostic test, BMI- body mass index, HIV- human immunodeficiency virus.

Supplementary Table S2 – Baseline Characteristics of the Study Population

Characteristics of the study population following application of all eligibility criteria. IQR: Interquartile Range.

Variable	Entire Population N=700	Control N=426	mRNA1273 N=120	BNT162b2 N=154
Age, Median (IQR)	58 (46, 67)	58 (46, 67)	56 (46, 64)	61 (47, 70)
Sex, N (%)				
Female	490 (70%)	318 (75%)	81 (68%)	91 (59%)
Male	210 (30%)	108 (25%)	39 (32%)	63 (41%)
Professional Role, N (%)				
Physicians	-	-	35 (29%)	41 (27%)
Nurses	-	-	21 (18%)	34 (22%)
Paramedical personnel	-	-	35 (29%)	34 (22%)
Administrative personnel	-	-	26 (22%)	43 (28%)
Other	-	-	3 (2.5%)	2 (1.3%)

Supplementary Table S3 – Immune Markers

The geometric mean titer for each vaccination type and measurement at baseline and at 6-month follow-up and the geometric mean fold rise when comparing values at 6 months and at baseline. BAU: Binding Antibody Units, GMT: Geometric Mean Titer, GMFR: Geometric Mean Fold Rise.

		Baseline		Six Months		
Measurement	Vaccination Type	N	GMT	N	GMT	GMFR*
IgG (BAU)	mRNA1273	119	336 (286-394)	40	593 (480-734)	1.58 (1.27-1.97)
	BNT162b2	154	326 (293-363)	44	388 (323-467)	1.16 (0.98-1.37)
Neutralizing Antibodies (Titer)	mRNA1273	118	339 (279-413)	39	452 (338-605)	1.04 (0.74-1.45)
	BNT162b2	154	430 (361-512)	45	272 (196-378)	0.75 (0.51-1.1)

* GMFR values were estimated using only those individuals with measurements at both baseline and six months.

Supplementary Table S4 – Vaccine Efficacy

Number of individuals analyzed, total follow-up days contributed, number of cases, the incidence rate, and the hazard ratio (estimated using a Cox proportional hazards model adjusted for age and sex with the controls as baseline) over the six-month follow-up period. Only individuals with non-missing data regarding infection symptoms were included in the analysis for substantial disease. CI: Confidence Interval.

Outcome		N	Follow-up Days Contributed	Positive Cases	Incidence Rate per 1000 days	Hazard Ratio (95% CI)
Infection	Controls	426	22,342	150	6.71	Reference
	mRNA1273	120	13,835	70	5.06	0.82 (0.62-1.09)
	BNT162b2	154	17,849	89	4.99	0.86 (0.65-1.13)
Substantial Disease	Controls	393	19,051	48	2.52	Reference
	mRNA1273	108	12,311	7	0.57	0.28 (0.13-0.62)
	BNT162b2	140	16,065	14	0.87	0.51 (0.27-0.95)

References

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.