Supplementary Appendix

Supplement to: Canetti M, Barda N, Gilboa M, et al. Six-month follow-up after a fourth BNT162b2 vaccine dose. N Engl J Med. DOI: 10.1056/NEJMc2211283

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

Six Months Follow-up of a Fourth BNT162b2 Vaccine Dose

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Supplementary Methods S1- Study setting and design

This is a prospective cohort study conducted among health care workers (HCW) of the Sheba Medical Center (SMC), the largest tertiary medical center in Israel, staffed by 15,287 HCW, including employees (physicians, nurses and nurse aids, paramedical personnel, and administration and logistic staff), students, volunteers, and retired personnel.

The Sheba HCW COVID Cohort was established before the rollout of the first two vaccine doses in December 2020. All HCW at SMC were offered to join the study. Upon recruitment, personal and clinical data were collected. All participants were requested to perform a serology test every 4 weeks and received electronic reminders to do so through emails and text messages. All HCW in SMC were required to undergo antigen rapid diagnostic tests (Ag-RDT) or quantitative real-time polymerase chain reaction (qRT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detection in the event of exposure to an infected person or if they exhibited any symptoms consistent with coronavirus disease 2019 (COVID-19). In addition, during the Omicron variant of concern (VOC) surge, HCW were encouraged to test weekly and received reminders through emails, text messages, or phone calls to do so. HCW who were infected with SARS-CoV-2 received daily electronic questionnaires or telephone calls to collect data on symptoms and disease severity. Further information regarding recruitment and follow-up of this cohort has been previously reported in detail (1-4).

The current study had two aims: First, to compare long-term dynamics of immunogenicity following receipt of the fourth BNT162b2 vaccine dose to immunogenicity dynamics following the second and third doses. Second, to estimate the long-term vaccine effectiveness (VE) of a fourth vaccine dose compared to having received three doses at least four months earlier. All HCW at SMC who received at least two BNT162b2 vaccine doses and were not infected with COVID-19 prior to vaccination were potentially included in the study. In the immunogenicity analysis following the second, third and fourth vaccine doses, we included all individuals who performed at least one serology test during the study period: January 2021 to July 2022. In the VE analysis, we included all HCW who received three BNT162b2 vaccine doses at least four months earlier and were not previously infected with COVID-19. In the three-dose arm, participants were followed from December 27, 2021, and in the four-dose arm, follow-up began on the day of the receipt of the fourth dose (as early as December 27, 2021). Individuals could potentially contribute time to both arms. In both arms, participants were followed until a positive SARS-CoV-2 test or the end of follow-up period on July 10, 2022, for up to 182 days (26 weeks) following receipt of each vaccine dose.

Given the surge of Omicron cases in Israel and the waning of the third vaccine dose, a campaign to administer a fourth mRNA Pfizer-BioNTech (BNT162b2) vaccine dose was launched in Israel on January 2, 2022. The vaccine was offered to high-risk groups [i.e., individuals who were 60 years old

or older, health care workers (HCW), and immunosuppressed patients] for whom at least four months have passed since the receipt of the third vaccine dose (5). Omicron was the dominant variant in Israel, responsible for close to 100% of infections. BA.1 was the dominant strain until March 2022, then replaced by BA.2 until June 2022, which since then had been replaced by BA.5 as the dominant strain.

The protocol was approved by the Institutional Review Board of SMC and written informed consent was obtained from all study participants.

Supplementary Methods S2- Exclusion of HCW with hybrid immunity

To verify that only SARS-CoV-2 naïve HCW are included we excluded positive cases. History of SARS-CoV-2 infection was determined based on documentation of previous Ag-RDT and qRT-PCR conducted in SMC or in other medical institutions (including community settings) reported to a country-wide electronic system. Participants were also actively inquired about the results of home rapid antigen tests (via electronic questionnaires or telephone calls). Additionally, to identify any undetected cases, we assessed the individual serology result dynamics and we defined SARS-CoV-2 previous infection by sero-response: Our previous results (7-9) demonstrated a substantial increase in IgG levels following vaccination or infection which was maintained for 30 days, after which a slow consistent decline was observed. Therefore, an uncharacteristic increase in IgG levels of >500 BAU or >1000 BAU in HCW with previous IgG results of <700 or >700, respectively was considered as a sero-response due to SARS-CoV-2 infection.

Supplementary Methods S3- Study variables

In the immunogenicity analysis, the exposure of interest was the number of vaccine doses received and the period of time elapsed since receipt of the vaccine dose. Two immunologic outcomes of interest were considered: anti-receptor binding domain (RBD) immunoglobulin G (IgG) levels and neutralizing antibody titers. IgG samples were collected using kits produced by either Beckman-Coulter or Abbott (detailed below). The SARS-CoV-2 pseudovirus neutralization assay was performed using green fluorescent protein reporter-based pseudotyped virus, with a vesicular stomatitis virus backbone coated by SARS-CoV-2 S protein (a complete description of the laboratory methods is included below). Covariates considered in this analysis included individuals' age and sex.

In the vaccine effectiveness analysis, we compared individuals who received three vaccine doses at least four months earlier with individuals who received four vaccine doses at specific intervals following vaccination (7-181, 7-35, 36-102, and 103-181 days). The outcome of interest was SARS-CoV-2 infection. SARS-CoV-2 infection was defined as either a positive SARS-CoV qRT-PCR test, a

positive Ag-RDT, or an increase in IgG levels that could not be attributed to vaccine receipt (see below). Covariates considered in this analysis included individuals' age, sex, and professional role (physician, nurse, paramedical personnel, and administration and logistic staff).

All study variables are described in Table S1 below.

Supplementary Methods S4- Immunogenicity

IgG II assays

IgG samples from before receipt of the third dose using the SARS-CoV-2 RBD IgG assay (Beckman-Coulter, CA, U.S.A.), or after receipt of the third dose using the SARS-CoV-2 IgG II Quant (Abbott, IL, USA) test. These commercial tests were performed according to the manufacturer's instructions. To present all IgG Antibody levels in Binding Antibody Units (BAU) per the World Health Organization (WHO) standard measurements we imputed the Abbott-based BAU values from the Beckman-Coulter assay results, based on an independent sample of 215 individuals with both Abbott BAU and Beckman-Coulter levels (see below a detailed explanation).

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 with the spike Wuhan (original) strain similar to the one previously published (2). 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 S5- Imputation of IgG results

The model to correct IgG values from the Beckman kit to the Abbott kit used for some of the post-second dose serology tests is a linear regression using a single predictor, the log-transformed results from the Beckman kit, modeled using a penalized restricted cubic spline, with the outcome being the

log-transformed results from the Abbott kit. The model was trained on a dataset of 215 observations for which both kits were used.
Internal validation of the model, for both discrimination and calibration, was done using optimism corrected bootstrapping (6) with 50 repetitions, via the R package rms (7).
Overall, the model shows very good performance in converting results from the Beckman kit to the Abbott kit. See Figure S3 below.

Supplementary Methods S6- Model prediction plots

The plots compare the values predicted from the multivariable immunogenicity models to that of the crude observed values. A separate model was fit after each vaccine dose, with IgG and neutralizing antibody levels as the outcome, and time since vaccination, age, and sex as the predictors. Time was modeled using a natural cubic spline with 4 degrees of freedom. To account for repeated measurements, a random intercept and slope (by time since vaccination) were included for each individual. For each outcome and for each vaccine dose the crude measurements are plotted, a with an overlaid non-parametric Locally Weighted Scatterplot Smoother (LOESS) overlaid in red (representing the mean of observed values) and the mean of the weekly predictions for the model plotted in black (representing the mean of predicted values). A good fit is shown for the estimation of IgG and neutralizing antibody titers after the second, third, and fourth vaccine doses.
See Figure S4 below.

Supplementary Methods S7- SARS-CoV-2 positive cases

SARS-CoV-2 infection was determined by either positive SARS-CoV-2 qRT-PCR or positive Ag-RDT. Nasopharyngeal swabs were placed in 3mL of universal transport medium (UTM) or viral transport medium (VTM). qRT-PCR tests were performed according to the manufacturer's instructions using Allplex™-2019 nCoV (Seegene, S. Korea) platform. Ag-RDT were performed according to manufacturer's instructions using STANDARD Q COVID-19 Ag (SD BIOSENSOR, S. Korea).

Cases were also defined as positive when an uncharacteristic increase in IgG levels was observed. Our previous results (8-10) demonstrated a substantial increase in IgG levels following vaccination or infection which was maintained for 30 days, after which a slow consistent decline was observed. Therefore, an uncharacteristic increase in IgG levels of >500 BAU or >1000 BAU in HCW with previous IgG results of <700 or >700, respectively was considered as a sero-response due to SARS-CoV-2 infection.

Supplementary Methods S8- Statistical analysis

The study population for each analysis was described using appropriate summary statistics for each variable.

Immunogenicity

IgG and neutralizing antibody titers were log-transformed for all analyses, using base 10 for IgG levels and base 2 for neutralizing antibody titers. Crude IgG and neutralizing antibody levels up to 182 days after the second, third, and fourth vaccine doses were plotted, overlaid with a non-parametric LOESS.

To compare adjusted antibody levels at each week following receipt of the second, third, and fourth vaccine doses, a separate model was fit after each vaccine dose, with IgG and neutralizing antibody levels as the outcome, and time since vaccination, age, and sex as the predictors. Time was modeled using natural cubic splines with 4 degrees of freedom. To account for repeated measurements, a random intercept and slope (by time since vaccination) were included for each individual. Model fit was assessed by comparing observed to predicted antibody values at each week. Adjusted predictions were then compared between the three models at each week following vaccination using the full study population as the standard population. The predictions were exponentiated back to their original scale.

IgG samples were presented using BAU of the SARS-CoV-2 IgG II Quant (Abbott, IL, USA) test. Some early IgG levels (of samples obtained before receipt of the third vaccine dose) were tested using the SARS-CoV-2 RBD IgG assay (Beckman-Coulter, CA, U.S.A.). These were imputed to BAU results using a model previously reported (8,11), as explained above.

Confidence intervals for the antibody level estimates following each vaccine dose at each week were derived using the percentile bootstrap method, with 1000 repetitions. Each repetition included a bootstrap sampling of the population used to develop the Beckman-Coulter to Abbott model and the populations following each vaccine dose. In this analysis, missing outcome data was accounted for by use of the mixed model, under a missing at random assumption.

Vaccine effectiveness

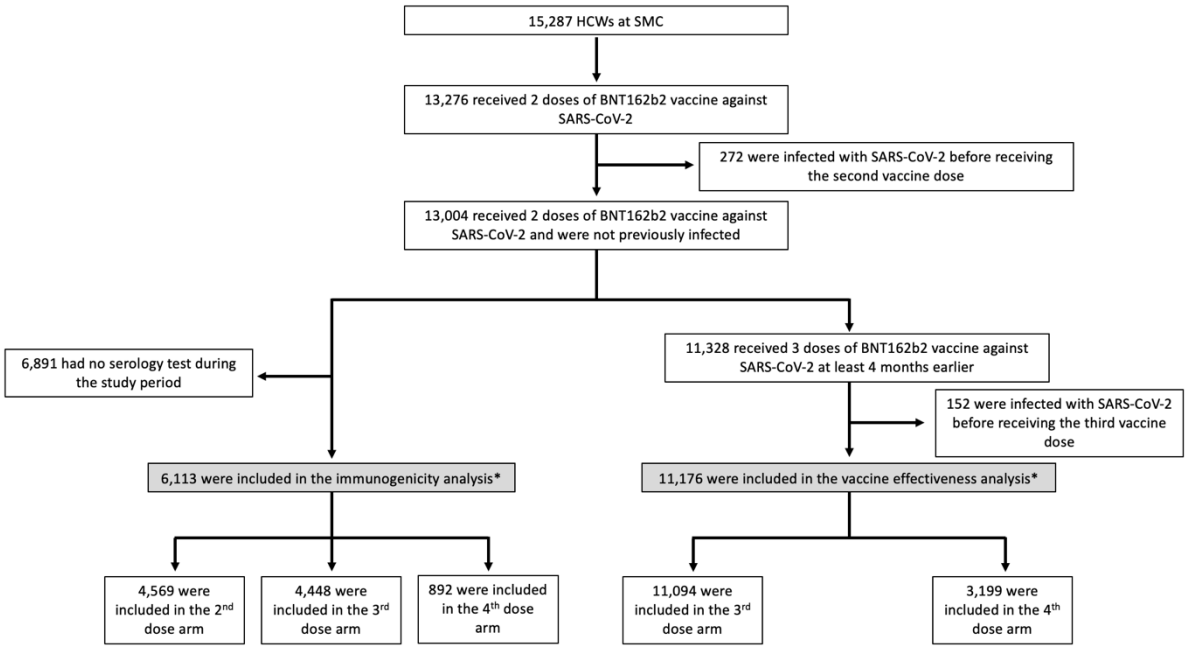
Cumulative incidence curve for SARS-CoV-2 infection was derived and plotted using the Kaplan-Meier method. Adjusted hazard ratios, comparing individuals who received three vaccine doses with individuals at different periods following the fourth dose (7-181, 7-35, 36-102, and 103-181 days post-vaccination) were estimated using Cox proportional hazards regression. This analysis was adjusted for age, sex, and professional role. Vaccination group (third dose, 7-181, 7-35 from fourth dose, 36-102 from fourth dose, and 103-181 from fourth dose) was modeled as a time-varying covariate,

Calendar time was used as the time scale, to further adjust for the differing disease prevalence over time. Individuals who were diagnosed with SARS-CoV-2 during the first 7 days of follow-up were excluded from the vaccine effectiveness analysis, as the fourth dose was assumed to not yet have an effect at that point. Vaccine effectiveness was defined as one minus the hazard ratio.

Analyses were performed with the use of R software, version 4.1.2

Figure S1- Study design flow chart

Overall, of the 15,287 HCW at SMC, 13,004 received two BNT162b2 vaccine doses and were not diagnosed with a SARS-CoV-2 infection before receiving the second vaccine dose. Of them, 6,113 HCW had at least one serology test during the study period and were thus included in the immunogenicity analysis. For the VE analysis, 11,176 HCW received three BNT162b2 vaccine doses at least four months earlier, were not diagnosed with a SARS-CoV-2 infection before receiving the three vaccine doses, and were therefore included (Figure S1).



*Individuals could contribute test/time to multiple arms. HCW; health care workers, SMC; Sheba Medical Center, SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

Figure S2- Crude infection cumulative incidence

Crude cumulative incidence (derived using the Kaplan-Meier estimator) of infection, comparing three-dose recipients (at least four months after its receipt) and four-dose recipients. The time-axis used is calendar time, with follow-up for both groups starting on December 27, 2021, and ending on July 10, 2022. The initial increase and subsequent decrease in the "at-risk" population is a consequence of using calendar time as the time scale in the survival analysis. As individuals are included in the risk-set only after vaccination (V4 arm) or after 4 months have passed since receipt of the third dose (V3 arm), the overall risk-set tends to initially increase in size

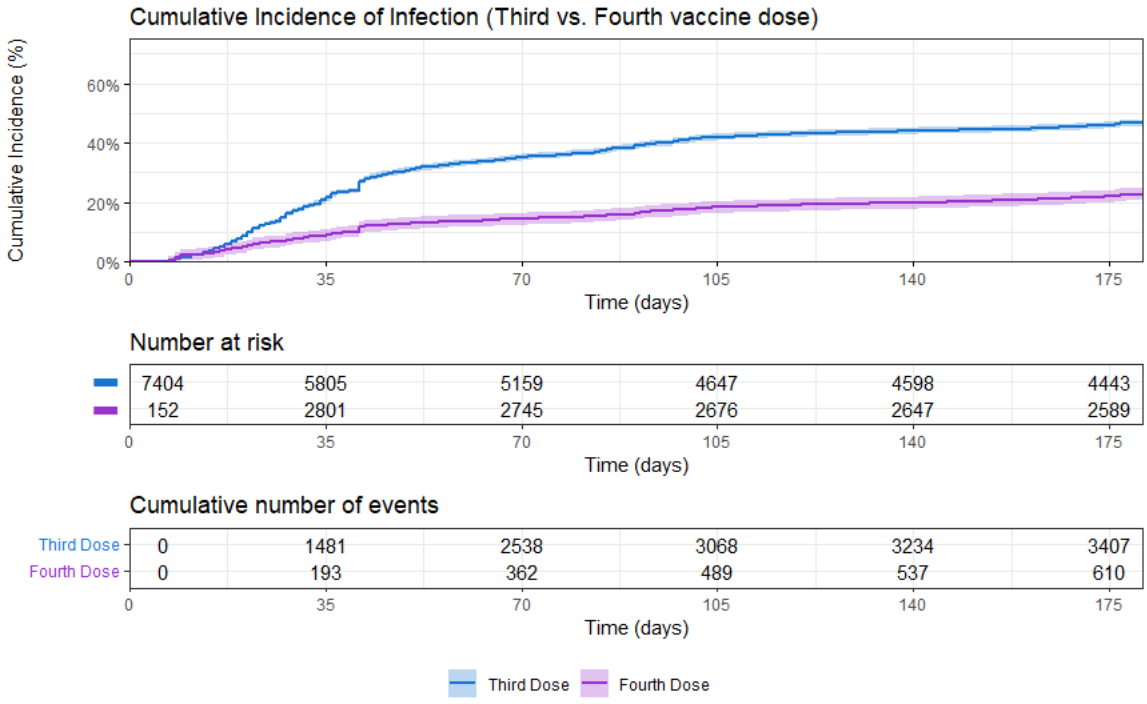
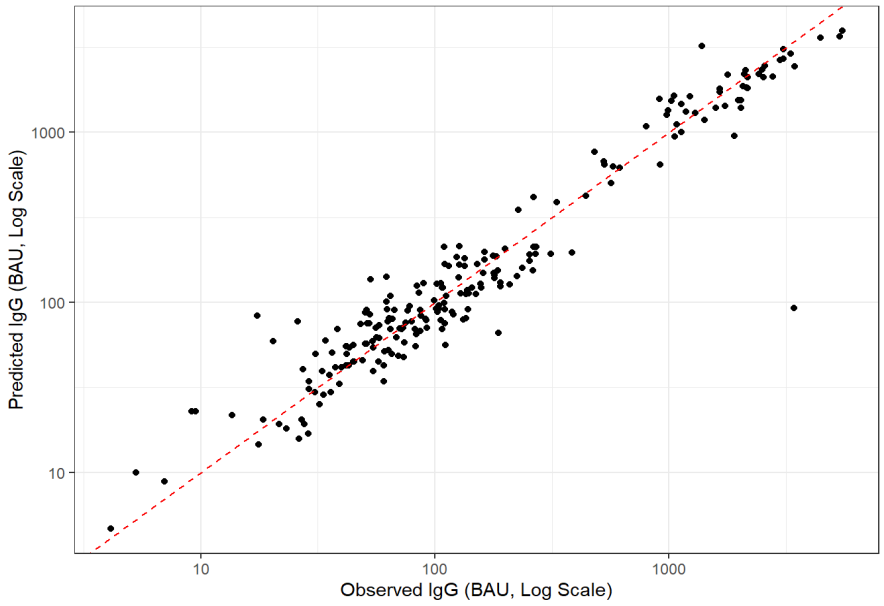
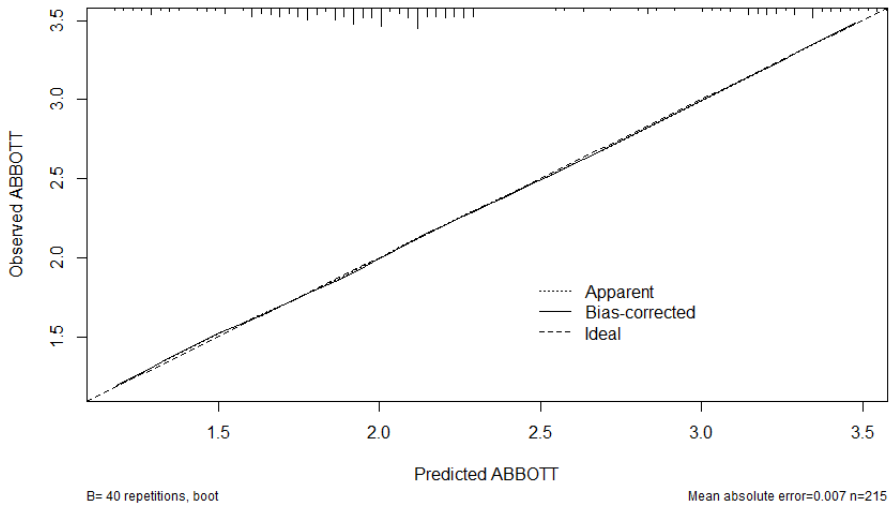


Figure S3- Imputation of IgG results model

Scatter plot of observed vs. predicted values:



Model Calibration:

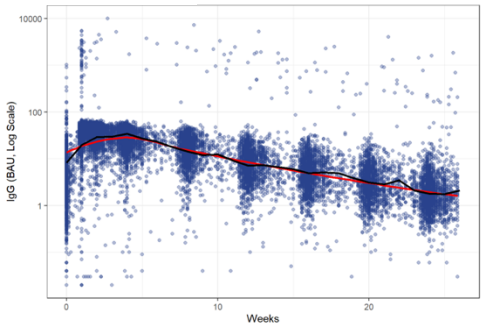


Model Performance:

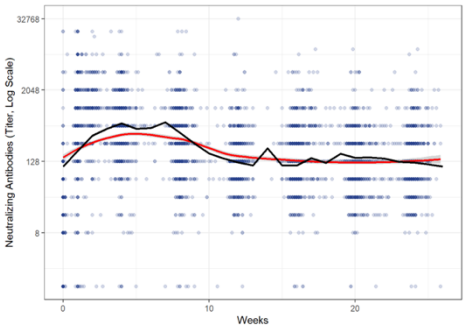
Statistic	Apparent	Training	Test	Optimism	Corrected
R2	0.918	0.921	0.917	0.0041	0.914
MSE	0.036	0.034	0.036	-0.0019	0.038

Figure S4- Model prediction plots

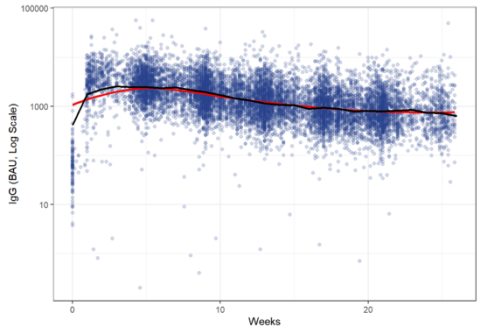
IgG: V2



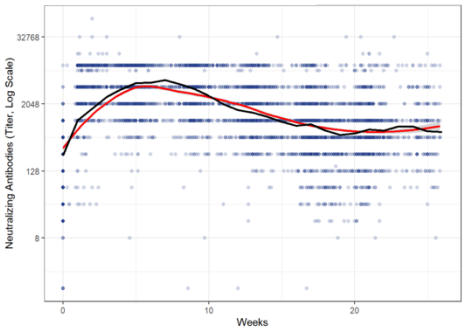
Neutralizing antibodies: V2



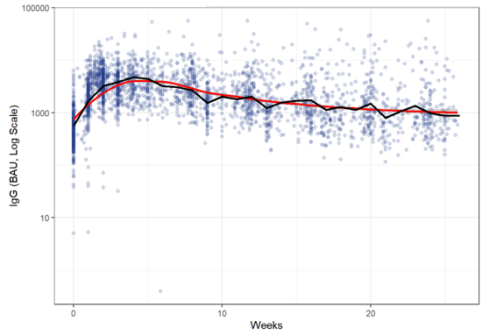
IgG: V3



Neutralizing antibodies: V3



IgG: V4



Neutralizing antibodies: V4

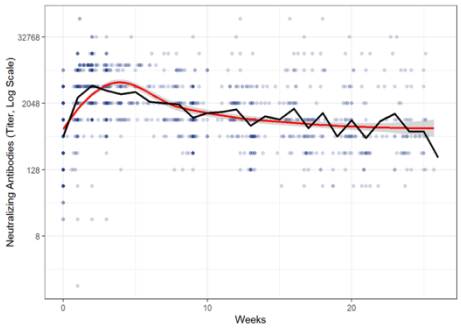


Table S1- Variable definitions

Variable	Values	Definition
A. Exposure		
Vaccine dose	Second, third, and fourth BNT162b2 vaccine doses	Number of doses received at each point
B. Immunological outcomes		
IgG	Numeric in BAU	Anti-RBD IgG GMT results during the study period
Neutralizing antibodies	Numeric in titer	Neutralizing antibodies GMT results during the study period
C. Clinical outcome		
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)
D. Covariates		
Age	Numeric (years)	Participant's age
Sex	Female/ male	Participant's sex
BMI	Numeric	Calculated as weight/height^2
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

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.

Table S2- Baseline characteristics of participants included in the immunogenicity analysis

	Overall (N= 6,113)	**V2* (N= 4,569)**	**V3* (N= 4,448)**	**V4* (N= 892)**
Sex				
Female	4,436 (73)	3,313 (73)	3,323 (75)	578 (65)
Male	1,677 (27)	1,256 (27)	1,125 (25)	314 (35)
Age	48 (37-59)	49 (39-60)	49 (38-60)	63 (51-71)
BMI (kg/m²)	25 (22.3-28.1)	25 (22.3-28.1)	25.1 (22.4-28.2)	25.9 (23.4-28.7)
Missing data	2,748 (45)	1,269 (28)	2,015 (45)	297 (33)
Comorbidities				
0	3,228 (77)	3,165 (77)	2,192 (75)	450 (65)
1	664 (16)	657 (16)	500 (17)	154 (22)
≥2	291 (7)	288 (7)	222 (8)	88 (13)
Missing data	1,930 (32)	459 (10)	1,534 (34)	200 (22)
Immunosuppression	36 (1)	35 (1)	28 (1)	12 (2)
Missing data	1,931 (32)	459 (10)	1,535 (35)	201 (23)
Profession				
Physician	1,090 (18)	825 (18)	725 (16)	192 (22)
Nurse	1,931 (32)	1,370 (30)	1,494 (34)	153 (17)
Paramedical personnel	1,264 (21)	1,013 (22)	898 (20)	191 (21)
Administrative personnel	1,828 (30)	1,361 (30)	1,331 (30)	356 (40)

Numbers are presented as N (%) or median (interquartile range). V2, second vaccine dose, V3, third vaccine dose, V4, fourth vaccine dose, BMI, body mass index. *The number of individuals who contributed at least one immunological test to each group. Each participant could contribute to more than one group.

Table S3- Baseline characteristics of participants included in the vaccine effectiveness analysis

	Overall (N= 11,176)	**V3* (N= 11,094)**	**V4 days 7-35* (N= 3,145)**	**V4 days 36-102* (N= 2,877)**	**V4 days 103-181* (N= 2,600)**
Sex					
Female	7,784 (70)	7,736 (70)	2,069 (66)	1,904 (66)	1,741 (67)
Male	3,392 (30)	3,358 (30)	1,076 (34)	973 (34)	859 (33)
Age	49 (36-65)	49 (36-65)	68 (57-75)	69 (59-76)	70 (61-76)
BMI (kg/m^2)	25 (22.4-28.1)	25 (22.4-28.1)	25.8 (23.1-28.7)	25.9 (23.5-29)	26 (23.4-29.1)
Missing data	8,099 (72)	8,088 (73)	2,224 (71)	2,091 (73)	1,965 (76)
Comorbidities					
0	3,513 (78)	3,467 (79)	798 (68)	658 (67)	529 (68)
1	675 (15)	657 (15)	236 (20)	205 (21)	159 (20)
≥2	288 (7)	281 (6)	138 (12)	118 (12)	94 (12)
Missing data	6,699 (60)	6,689 (60)	1,973 (63)	1,896 (66)	1,818 (70)
Immunosuppression	37 (1)	37 (1)	15 (1)	13 (1)	10 (1)
Missing data	6,700 (60)	6,690 (60)	1,974 (63)	1,897 (66)	1,819 (70)
Profession					
Physician	2,130 (19)	2,106 (19)	662 (21)	571 (20)	487 (19)
Nurse	2,827 (25)	2,810 (25)	670 (21)	622 (22)	567 (22)
Paramedical personnel	2,516 (23)	2,495 (23)	599 (19)	548 (19)	486 (19)
Administrative personnel	3,703 (33)	3,683 (33)	1,214 (39)	1,136 (39)	1,060 (41)
Days contributed	1,377,157	941,267	87,879	184,535	163,476

Numbers are presented as N (%) or median (interquartile range). Days contributed is presented as person-days. V3, third vaccine dose, V4, fourth vaccine dose, BMI, body mass index. *The number of individuals who contributed time to each study period. Each participant could contribute time to more than one group.

Table S4- Adjusted weekly antibody level ratios following each vaccine dose

	IgG		Neutralizing antibodies	
Week	**Ratio V3:V2 (95% CI)**	**Ratio V4:V3 (95% CI)**	**Ratio V3:V2 (95% CI)**	**Ratio V4:V3 (95% CI)**
0	3.8 (3.3-4.4)	0.4 (0.3-0.4)	2.9 (2.3-3.9)	1.5 (1.3-1.8)
1	2 (1.8-2.4)	0.9 (0.8-1)	3.4 (2.9-3.9)	4.1 (3.6-4.6)
2	1.3 (1.2-1.5)	1.7 (1.5-1.9)	4 (3.6-4.4)	3.7 (3.3-4.2)
3	1.1 (1-1.2)	2.2 (2-2.4)	4.7 (4.3-5.1)	1.7 (1.5-1.9)
4	1.1 (1-1.2)	2.1 (2-2.3)	5.7 (5.1-6.2)	0.9 (0.8-1)
5	1.3 (1.2-1.5)	1.8 (1.6-2)	6.9 (6.2-7.6)	0.5 (0.5-0.6)
6	1.8 (1.6-1.9)	1.4 (1.3-1.6)	8.1 (7.4-9)	0.4 (0.3-0.5)
7	2.4 (2.2-2.6)	1.2 (1.1-1.3)	9.3 (8.5-10.2)	0.4 (0.3-0.4)
8	3.1 (2.8-3.4)	1.1 (1-1.1)	10.4 (9.6-11.33)	0.4 (0.3-0.4)
9	3.6 (3.2-4)	1 (1-1.1)	11.1 (10.3-12.2)	0.4 (0.4-0.5)
10	3.8 (3.4-4.3)	1.1 (1-1.1)	11.5 (10.6-12.6)	0.5 (0.5-0.6)
11	3.8 (3.4-4.3)	1.2 (1.1-1.2)	11.5 (10.5-12.6)	0.6 (0.6-0.7)
12	3.7 (3.3-4.1)	1.3 (1.2-1.4)	11 (10.1-12.1)	0.8 (0.7-0.9)
13	3.5 (3.1-3.9)	1.4 (1.3-1.5)	10.2 (9.4-11)	0.9 (0.8-1)
14	3.4 (3-3.8)	1.5 (1.4-1.6)	9.1 (8.5-9.9)	1 (0.9-1.1)
15	3.4 (3-3.8)	1.5 (1.4-1.6)	8 (7.5 -8.6)	1.1 (0.9-1.2)
16	3.4 (3.1-3.8)	1.5 (1.4-1.6)	6.9 (6.5-7.4)	1.1 (1-1.3)
17	3.5 (3.2-3.9)	1.5 (1.4-1.6)	5.9 (5.5-6.3)	1.2 (1.1-1.4)
18	3.7 (3.3-4.1)	1.5 (1.4-1.5)	5 (4.6-5.3)	1.3 (1.1-1.5)
19	3.8 (3.5-4.2)	1.4 (1.3-1.5)	4.2 (3.9-4.5)	1.4 (1.2-1.6)
20	4 (3.6-4.4)	1.4 (1.3-1.5)	3.6 (3.3-3.9)	1.5 (1.3-1.8)
21	4.1 (3.8-4.5)	1.4 (1.3-1.5)	3.3 (3-3.6)	1.7 (1.4-2.1)
22	4.3 (3.9-4.7)	1.4 (1.3-1.5)	3 (2.8-3.3)	1.9 (1.5-2.4)
23	4.5 (4.1-4.9)	1.4 (1.3-1.5)	2.9 (2.5-3.2)	2.2 (1.6-2.8)
24	4.6 (4.2-5)	1.4 (1.3-1.6)	2.8 (2.4-3.2)	2.5 (1.8-3.3)
25	4.8 (4.4-5.2)	1.4 (1.3-1.6)	2.7 (2.2 -3.2)	2.8 (1.9-3.9)

Levels are adjusted predictions using a separate model after each vaccine dose, with IgG and neutralizing antibody levels as the outcome, and time since vaccination, age, and sex as the predictors. Time was modeled using natural cubic splines with 4 degrees of freedom. To account for repeated measurements, a random intercept and slope (by time since vaccination) were included for each individual. The full study population was used as the standard population. The predictions were exponentiated back to their original scale. V2, second vaccine dose; V3, third vaccine dose, V4; fourth vaccine dose; GMT, geometric mean titer; CI, confidence interval; IgG, anti-RBD immunoglobulin G;

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