Supplementary Appendix

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

Fourth Dose of BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Setting

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Author contributions

O.M., J.G.W. and M.M.A., contributed equally. All authors conceived and designed the study. O.M., J.G.W., M.M.A. and N.D. participated in data extraction and analysis. All authors wrote the manuscript. All authors critically reviewed the manuscript and decided to proceed with publication. R.D.B. and N.D. supervised the study and vouch for the data and analysis.

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Methods S1 - Functional form and fit for Poisson regression models

⇨ $\log(\text{incidence rate}) = \log(\text{events} / \text{time}) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n$

⇨ $\log(\text{events}) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n + \log(\text{time})$

- Events = number of individuals with the outcome of interest
- Time = Number of person-days of follow-up
- Coefficients (x_1-x_n) include:
  - Time-varying exposure (specific to each model*)
  - Age
  - Sex
  - Local COVID-19 burden (the day previously)
  - Population sector
  - Number of CDC risk factors for severe COVID-19
  - Number of hospital admissions in the past 3 years
  - Calendar month of third vaccine dose
  - Calendar date (of each day of follow-up)

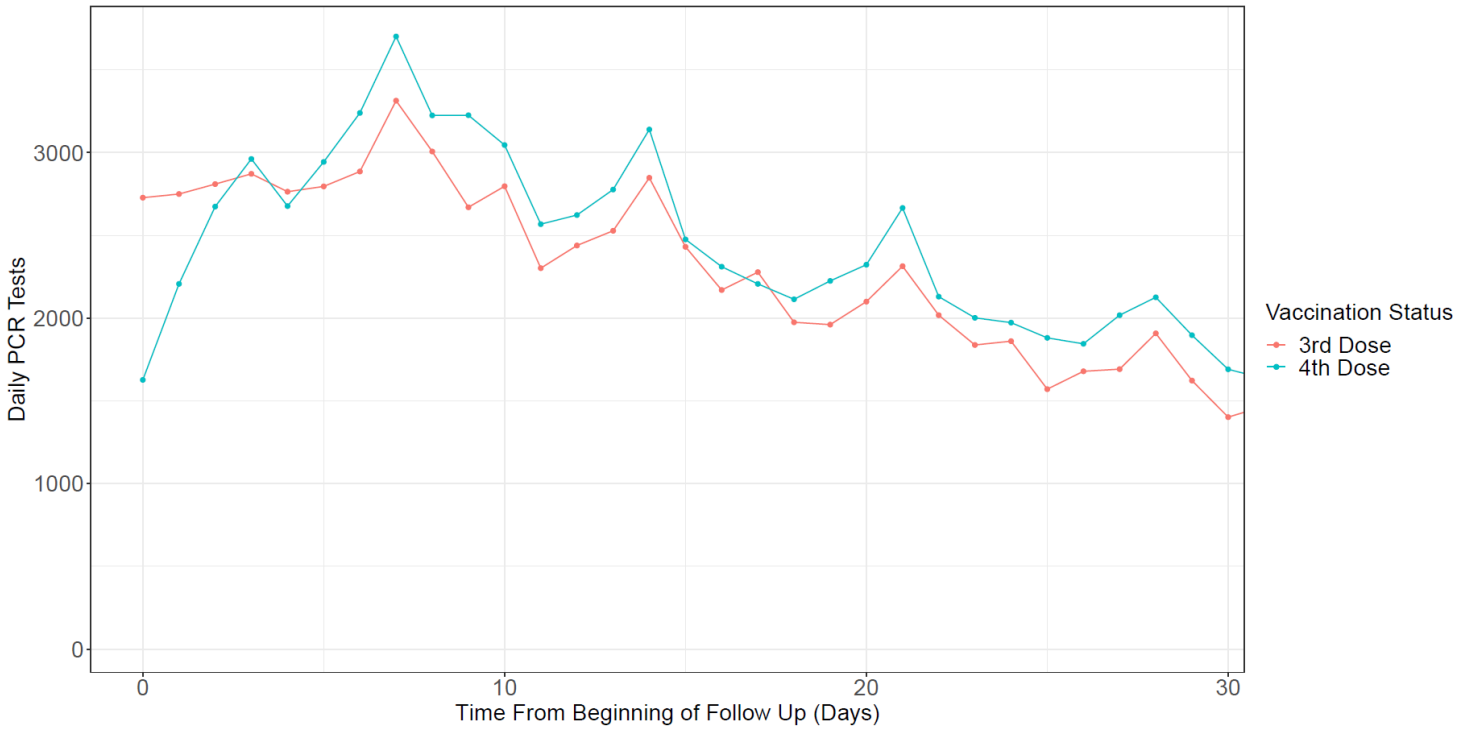
* 1. {no exposure, days 1-4 following 4th vaccine dose, days 5-6, and day 7+}

2. {no exposure, days 1-4, days 5-6, days 7-13, and day 14+}

3. {no exposure, and each day of follow-up treated as a separate category}

⇨ Chi-squared goodness-of-fit test of residual deviance: P = 1

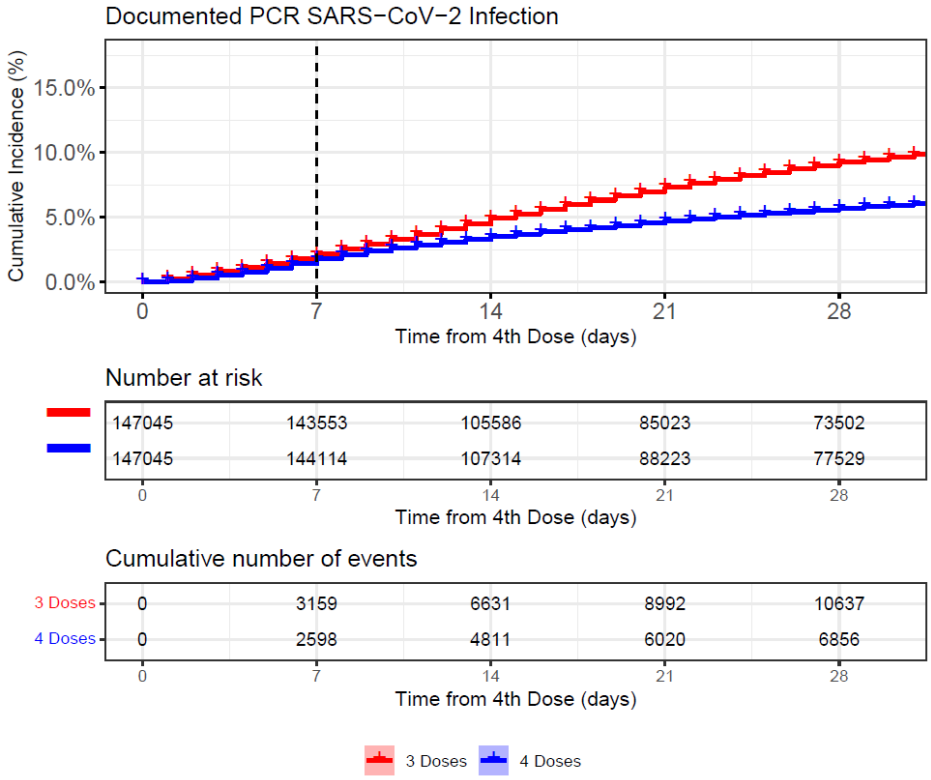
Figure S1 – SARS-CoV-2 PCR tests in the matched exposure groups over the study period



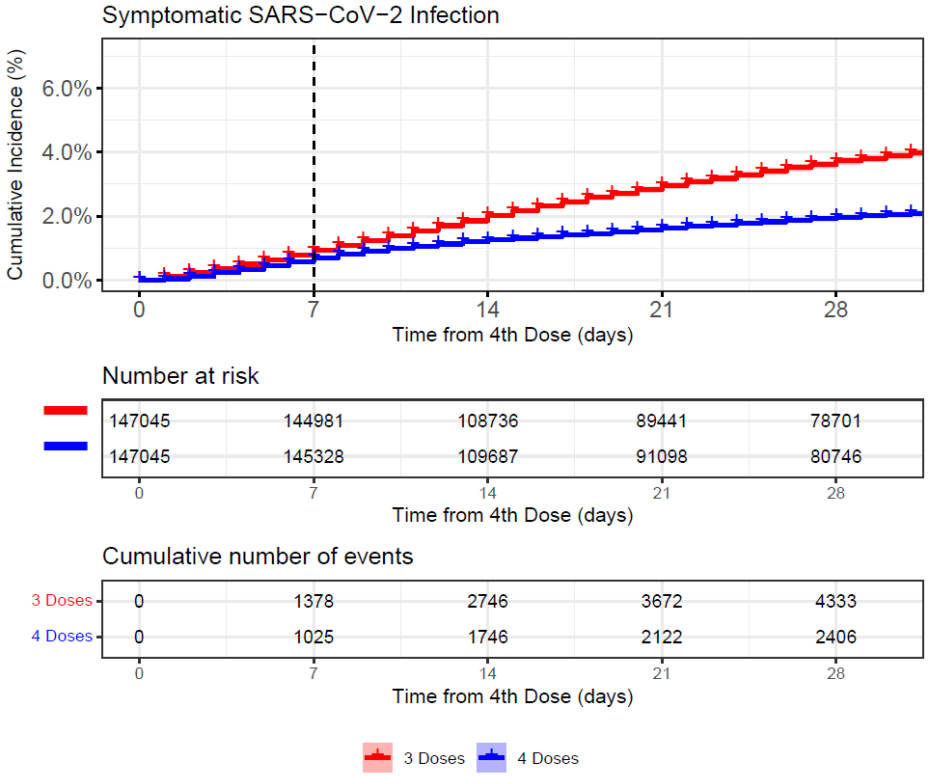
A graph demonstrating the number of SARS-CoV-2 PCR tests performed in the 3rd vaccine dose group (red) and the 4th vaccine dose group (blue) over the study period (January 3rd, 2022 – February 18th, 2022) in the PCR-confirmed documented SARS-CoV-2 infection cohort.

Figure S2 – Sensitivity analysis in which censoring of matched pairs is delayed by 7 days following receipt of a fourth vaccine by the control group individual

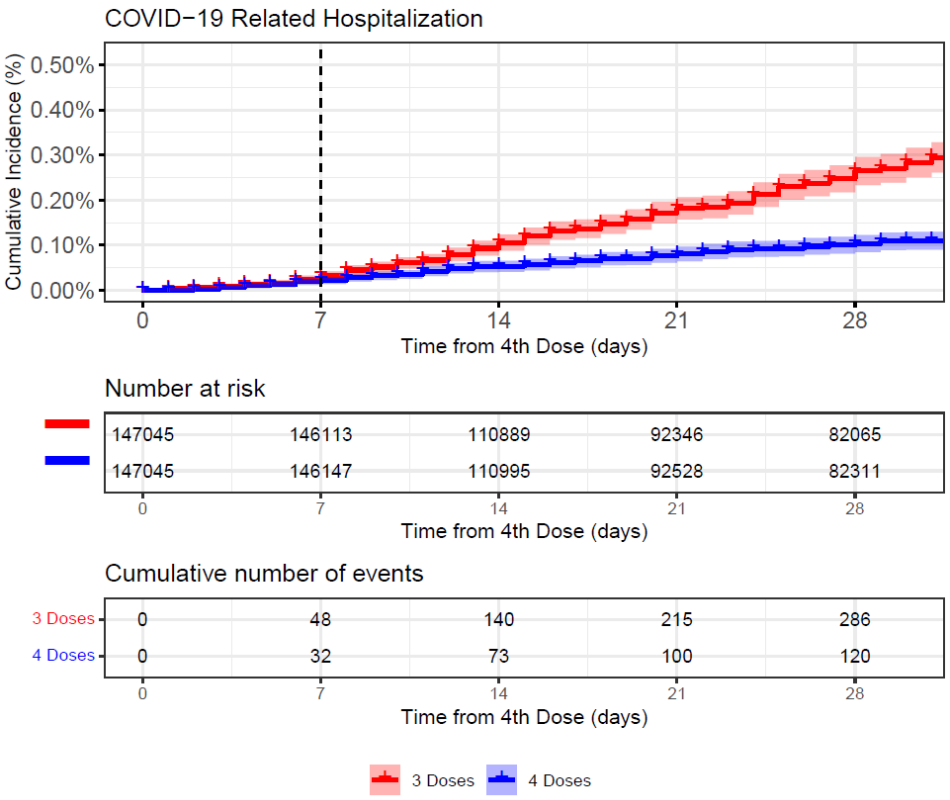
A



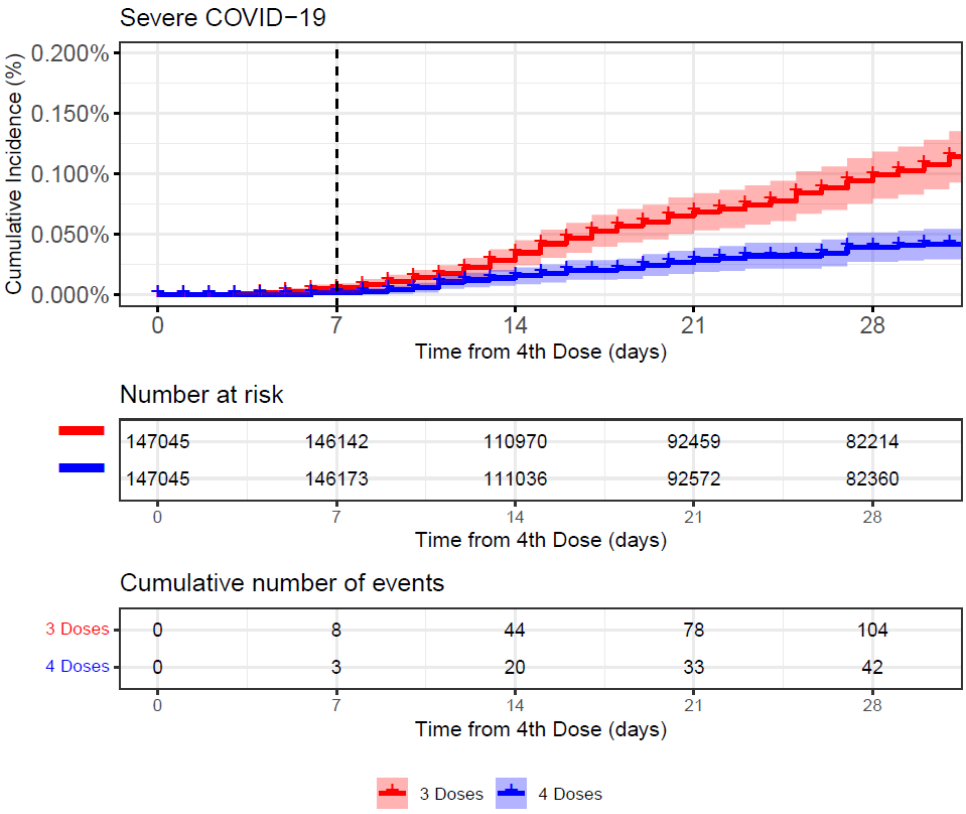
B



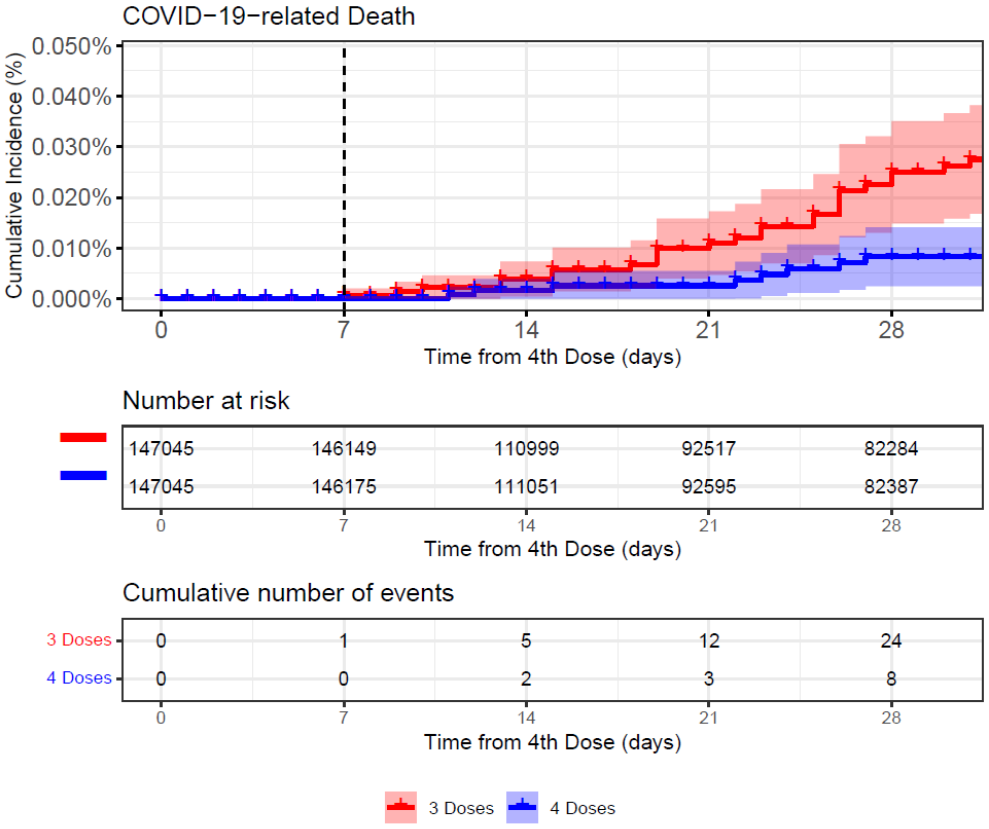
C


COVID−19 Related Hospitalization
Cumulative Incidence (%)
0.50%
0.40%
0.30%
0.20%
0.10%
0.00%
0
7
14
21
28
Time from 4th Dose (days)
Number at risk
147045 146113 110889 92346 82065
147045 146147 110995 92528 82311
Time from 4th Dose (days)
Cumulative number of events
3 Doses 0 48 140 215 286
4 Doses 0 32 73 100 120
Time from 4th Dose (days)
3 Doses
4 Doses

D


Severe COVID−19
Cumulative Incidence (%)
0.200%
0.150%
0.100%
0.050%
0.000%
0
7
14
21
28
Time from 4th Dose (days)
Number at risk
147045 146142 110970 92459 82214
147045 146173 111036 92572 82360
Time from 4th Dose (days)
Cumulative number of events
3 Doses 0 8 44 78 104
4 Doses 0 3 20 33 42
Time from 4th Dose (days)
3 Doses
4 Doses

E



Cumulative incidence curves, calculated using the Kaplan-Meier estimator (1 – the Kaplan-Meier risk) for individuals in the study group and the control group across all five COVID-19-related outcomes (A: infection, B: symptomatic COVID-19, C: COVID-19-related hospitalization, D: severe COVID-19 illness, E: COVID-19-related death). The dashed vertical line marks day 7 – the day the primary analysis begins.

Table S1 –Variables Used to Define Exposures, Outcomes, Eligibility and Adjustment

Names, potential values, definitions and time periods for all variables used in the study to define exposure, eligibility and perform adjustment. Variables were defined using internal CHS registries, ICD-9 codes, and ATC codes. PCR: Polymerase Chain Reaction; CHS: Clalit Health Services; ICD: International Classification of Disease; ATC: Anatomic therapeutic chemical; COPD: Chronic Obstructive Pulmonary Disease.

Variable	Definitions[1]	Timing[2]	Values	
			Main analysis	Poisson
Exposure				
Individuals 60 years of age and older, vaccinated with a fourth dose of the BNT162b2 mRNA vaccine	Four doses of BNT162b2 mRNA COVID-19 Vaccine	Administration of the fourth dose on or after January 3rd 2022	0/1	0/1
Individuals 60 years of age and older, eligible to receive a fourth dose, who have not yet received a fourth dose as of the matching date	Three doses of BNT162b2 mRNA COVID-19 Vaccine at least 4 months earlier	Administration of the third dose at least 4 months prior to the index date	0/1	0/1
Outcome				
PCR-confirmed COVID-19 infection	A PCR confirmed infection.	The date of a specimen collection that was found to be positive in a PCR test.	0/1	0/1
Symptomatic COVID-19	A PCR-confirmed infection with report of symptoms during the PCR referral / during the follow-up in the community setting / COVID-19 related hospitalization / COVID-19 related death. Existing symptoms were considered when the physician or nurse checked the "symptomatic" option in the EMR, or when the following specific symptoms were recorded: fever or chills, cough, shortness of breath or difficulty breathing, sore throat, headache, weakness, congestion or runny nose, myalgia, nausea or vomiting, diarrhea, abdominal pain,	The date set for the SARS-CoV-2 infection outcome.	0/1	0/1

	loss of taste or smell, inability to eat or drink.			
COVID-19 related hospitalization	A hospitalization that was reported to the Israeli MOH as a hospitalization of a SARS-CoV-2 infected individual.	The start date of the hospitalization	0/1	0/1
Severe COVID-19 illness	As defined by the hospitalizing institution per the Israeli MOH guidelines, consistent with the NIH criteria for severe illness or critical illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency > 30 breaths/min, or lung infiltrates >50%. Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.	The first date during the hospitalization in which the individual was flagged as being In a severe or critical state.	0/1	0/1
COVID-19 related Death	A death of a SARS-CoV-2 infected individual reported to the Israeli MOH.	The reported date of death.	0/1	0/1
Eligibility & Adjustment				
Age	Age in whole years	Current	Integer	Integer
Sex	As defined in CHS files	Current	Male/ Female	Male/ Female
Long-term care facility resident	Is patient a long-term care facility resident per CHS files	Current	0/1	0/1
Confined to Home	Is patient confined to their home per CHS files	Current	0/1	0/1
Health-care worker	Is patient a health-care worker per CHS files	Current	0/1	0/1
Continuous Membership in the Health Organization	Was patient a member of CHS for a full year before the index date	Last Year	0/1	0/1

Place of Residence	Residency code in which the patient resides per CHS files	Current	List of places	-
Infection positivity rate per place of residence	Number of positive results divided by number of tests per area	Current	-	5 bins: 0-20% / 21-40% / 41-60% / 61-80% / 81%-100%
Population Sector	As defined in CHS files	Current	General Jewish / Arab / Ultra-orthodox Jewish	General Jewish / Arab / Ultra-orthodox Jewish
Third vaccination month	The month of the third vaccination	Last year	01-12	01-12
Calendar day	The specific calendar day during the study period (the analysis is run through all calendar days)	Current	-	Dates between January 3rd 2022 and February 8th 2022
Number of hospital admissions	Number of hospital admissions in the past 3 years	Last 3 years	0/1/2/ 3-4/5+	Integer
CDC Risk Factors Count (count of pre-existing conditions considered by the CDC as risk criteria)	Summation of 1 point for each of the following: • Cancer • CKD • Heart Disease • Sickle Cell Disease • Asthma • Cerebrovascular Disease • Hypertension • Neurological Disease • Liver Disease • Thalassemia • COPD or other respiratory disease • Type 1 or 2 Diabetes Mellitus • Solid organ transplant recipient or immunodeficiency • Obesity or severe obesity	Based on the variables below	0/1/2/3+	Integer
	Other covariates used for population description			

Cancer	ICD9 Code 174* ICD9 Code 175* ICD9 Code 233.0 ICD9 Code V10.3 ICD9 Proc Code 85.4* ICD9 Code 153* ICD9 Code 154* ICD9 Code V10.5* ICD9 Code V10.6* ICD9 Code 185 ICD9 Code V10.46 ICD9 Code 162* ICD9 Code V10.1* ICD9 Code 188* ICD9 Code V10.51 ICD9 Code 183* ICD9 Code V10.43 ICD9 Code 179 ICD9 Code 182* ICD9 Code V10.42 ICD9 Code 157* ICD9 Code 191* ICD9 Code 192* ICD9 Code V10.85 ICD9 Code 151* ICD9 Code V10.04 ICD9 Code 172* ICD9 Code V10.82 ICD9 Code 201* ICD9 Code 200* ICD9 Code 202.4* ICD9 Code 204* ICD9 Code 205* ICD9 Code 206* ICD9 Code 207.1* ICD9 Code 208.1* ICD9 Code 189* ICD9 Code V10.52 ICD9 Code 160* ICD9 Code 161* ICD9 Code 164.0 ICD9 Code 195.0 ICD9 Code V10.21 ICD9 Code V10.22 ICD9 Code 180* ICD9 Code V10.41 ICD9 Code 140* ICD9 Code 141* ICD9 Code 142* ICD9 Code 143* ICD9 Code 144* ICD9 Code 145* ICD9 Code 150* ICD9 Code V10.03 ICD9 Code 155* ICD9 Code 156* ICD9 Code V10.07 ICD9 Code 170* ICD9 Code V10.81 ICD9 Code 193 ICD9 Code V10.87	Ever	-	-

Chronic Kidney Disease	ICD Proc Code 39.95 ICD Proc Code 54.98 ICD9 Code 996.81 ICD9 Code V42.0 ICD Proc Code 55.6* ICD9 Code 403._1 ICD9 Code 404._2 ICD9 Code 404._3 ICD9 Code 585* ICD9 Code 586 ICD9 Code 250.4* ICD9 Code 274.1* ICD9 Code 440.1 ICD9 Code 581* ICD9 Code 582* ICD9 Code 583* ICD9 Code 587 ICD9 Code 588* ICD9 Code 589*	Ever	-	-
Chronic Obstructive Pulmonary Disease	ICD9 Code 491* ICD9 Code 492* ICD9 Code 496	Ever	-	-
Heart Conditions	ICD9 Code 410* ICD9 Code 411* ICD9 Code 412 ICD9 Code 413* ICD9 Code 414* ICD9 Code 429.2, 429.7* ICD9 Code V45.81, V45.82 ICD9 Proc Code 36.0* ICD9 Proc Code 36.1* ICD9 Code 428* ICD9 Code 398.91 ICD9 Code 402._1 ICD9 Code 404._1, ICD9 Code 404._3 ICD9 Code 416.9 ICD9 Code 514 ICD9 Code 425* ICD9 Code 416*	Ever	-	-
Solid Organ Transplant Recipient	ICD9 Code 996.81 ICD9 Code V42.0 ICD Proc Code 55.6* ICD9 Code V42.7 ICD Proc Code 50.5* ICD9 Code V42.1 ICD9 Code V43.2 ICD Proc Code 37.5 ICD9 Code V42.83 ICD Proc Code 52.8* ICD9 Code V42.6 ICD Proc Code 33.5* ICD Proc Code 33.6	Ever	-	-
Obesity	Body Mass Index (BMI) 30-40	Latest measurement in last 5 years not taken during pregnancy	-	-

Severe Obesity	Body Mass Index (BMI) 40+	Latest measurement in last 5 years not taken during pregnancy	-	-
Sickle Cell Disease	ICD9 Code 282.6*	Ever	-	-
Smoking	Internal Clalit Registry	Last recorded value	-	-
Type 2 Diabetes Mellitus	HbA1C > 6.5 ATC Codes A10[A,B] ICD9 Code 250* ICD9 Code 357.2 ICD9 Code 362.0* **And not:** ICD9 Code 250._1, 250._3	For diagnosis codes, Ever; For drugs, 4 or more dispensed in last 12 months	-	-
Asthma	ICD9 Code 493*	Ever	-	-
Cerebrovascular Disease	ICD9 Code 362.34 ICD9 Code 430 ICD9 Code 431 ICD9 Code 432* ICD9 Code 433* ICD9 Code 434* ICD9 Code 435* ICD9 Code 436* ICD9 Code 438*	Ever	-	-
Other Respiratory Disease	ICD9 Code 277.0* ICD9 Code 494* ICD9 Code 515	Ever	-	-
Hypertension	ICD9 Code 401* ICD9 Code 402* ICD9 Code 403* ICD9 Code 404* ICD9 Code 405*	Ever	-	-
Immunocompromised State	**Any of:** ICD9 Code 042* ICD9 Code 043* ICD9 Code 044* ICD9 Code 795.71 ICD9 Code V08 ICD9 Code V42.8* ICD9 Proc Code 41.0* **Or at least 2 of:** ATC4 Code H02AB ATC4 Code H02BX ATC4 Code M01BA **Or at least 2 of:** ATC2 Code L04	For diagnosis codes, Ever; For drugs, 4 or more dispensed in last 12 months	-	-
Neurologic Conditions	ICD9 Code 290.* ICD9 Code 294* ICD9 Code 310.1 ICD9 Code 331* ATC Codes N06DA02, N06DA03 ICD9 Code 358* ICD9 Code 332.[0,1]	For diagnosis codes, Ever; For drugs, 4 or more dispensed in last 12 months	-	-

	ICD9 Code 345* ICD9 Code 340 ATC Codes L03AB07, L03AB08, L04AA07 ICD9 Code 343* ICD9 Code 333.4 ICD9 Code 334* ICD9 Code 356* ICD9 Code 138 ICD9 Code 335* ICD9 Code 730.7* ICD9 V12.02 ICD9 Code 228.02 ICD9 Code 307.23 ICD9 Code 330.9 ICD9 Code 331.3* ICD9 Code 331.4 ICD9 Code 333* ICD9 Code 334* ICD9 Code 336* ICD9 Code 337 ICD9 Code 335.1* ICD9 Code 359.0 ICD9 Code 359.21 ICD9 Code 357.0 ICD9 Code 237.7* ICD9 Code 742.8[1,2]			
Liver Disease	ICD9 Code 070.22 ICD9 Code 070.23 ICD9 Code 070.32 ICD9 Code 070.33 ICD9 Code 070.44 ICD9 Code 070.54 ICD9 Code V02.61 ICD9 Code V02.62 ICD9 Code 571* ICD9 Code 275.1 ICD9 Code 277.4 ICD9 Code 452 ICD9 Code 453.0 ICD9 Code 571.8 ICD9 Code 571.9 ICD9 Code 572*	Ever	-	-
Overweight	Body Mass Index (BMI) 25-30	Latest measurement in last 5 years not taken during pregnancy	-	-
Thalassemia	ICD9 Code 282.4*	Ever	-	-
Type 1 Diabetes Mellitus	ICD9 Code 250._1, 250._3	Ever	-	-

[1]Additional confirmation of the diagnostic codes was done by checking the matching of the free text within the diagnosis description field.

[2]Covariates were extracted at the beginning of the calendar month in which the index date occurred.

Table S2 – A comparison of the baseline characteristics of the total eligible vaccinated population, the matched vaccinated population and the unmatched (to the exposed group) vaccinated population

Variable	Total Eligible for Inclusion in Exposed Group, N = 258,994	Exposed Group, N = 182,122	Unmatched to Exposed Group, N = 76,872
Age	73 (67, 79)	72 (67, 78)	74 (68, 81)
Age Group			
60-69	90,701 (35%)	67,778 (37%)	22,923 (30%)
70-79	107,620 (42%)	76,630 (42%)	30,990 (40%)
80+	60,673 (23%)	37,714 (21%)	22,959 (30%)
Sex			
F	133,282 (51%)	97,113 (53%)	36,169 (47%)
M	125,712 (49%)	85,009 (47%)	40,703 (53%)
Population Sector			
General Jewish	243,651 (94%)	173,689 (95%)	69,962 (91%)
Arab	9,178 (3.5%)	4,828 (2.7%)	4,350 (5.7%)
Ultra-Orthodox Jewish	6,165 (2.4%)	3,605 (2.0%)	2,560 (3.3%)
Number of hospital admissions (past 3 years)			
0	184,499 (71%)	140,226 (77%)	44,273 (58%)
1	44,502 (17%)	27,612 (15%)	16,890 (22%)
2	16,295 (6.3%)	8,310 (4.6%)	7,985 (10%)
3-4	10,116 (3.9%)	4,692 (2.6%)	5,424 (7.1%)
5+	3,582 (1.4%)	1,282 (0.7%)	2,300 (3.0%)
CDC Risk Factors Count			
0	43,408 (17%)	31,533 (17%)	11,875 (15%)
1	59,304 (23%)	42,236 (23%)	17,068 (22%)
2	58,992 (23%)	40,275 (22%)	18,717 (24%)
3+	97,290 (38%)	68,078 (37%)	29,212 (38%)
CDC Risk Factors			
Cancer	14,123 (5.5%)	9,228 (5.1%)	4,895 (6.4%)
Chronic Kidney Disease	47,529 (18%)	32,343 (18%)	15,186 (20%)
Chronic Obstructive Pulmonary Disease	15,882 (6.1%)	10,919 (6.0%)	4,963 (6.5%)
Heart Disease	61,521 (24%)	41,018 (23%)	20,503 (27%)

Solid Organ Transplant	250 (<0.1%)	171 (<0.1%)	79 (0.1%)
Obesity (BMI 30-40)	68,436 (26%)	48,949 (27%)	19,487 (25%)
Severe Obesity (BMI 40+)	4,911 (1.9%)	3,548 (1.9%)	1,363 (1.8%)
Sickle Cell Disease	14 (<0.1%)	4 (<0.1%)	10 (<0.1%)
Smoking	27,962 (11%)	20,224 (11%)	7,738 (10%)
Type 2 Diabetes Mellitus	84,137 (32%)	59,936 (33%)	24,201 (31%)
Possible CDC Risk Factors			
Asthma	18,193 (7.0%)	12,806 (7.0%)	5,387 (7.0%)
Cerebrovascular Disease	27,902 (11%)	18,319 (10%)	9,583 (12%)
Other Respiratory Disease	3,170 (1.2%)	2,232 (1.2%)	938 (1.2%)
Hypertension	148,096 (57%)	103,260 (57%)	44,836 (58%)
Immunosuppression	16,214 (6.3%)	11,304 (6.2%)	4,910 (6.4%)
Neurological Disease	31,546 (12%)	21,295 (12%)	10,251 (13%)
Liver Disease	8,889 (3.4%)	6,221 (3.4%)	2,668 (3.5%)
Overweight (BMI 25-30)	109,322 (42%)	76,447 (42%)	32,875 (43%)
Thalassemia	1,061 (0.4%)	732 (0.4%)	329 (0.4%)
Type 1 Diabetes Mellitus	2,393 (0.9%)	1,614 (0.9%)	779 (1.0%)

Table S3 - Vaccine effectiveness (1 - Risk Ratio) and Risk Difference for the sensitivity analysis in which censoring of control members who received a fourth vaccine dose is delayed by 7 days

Period	PCR-confirmed SARS-CoV-2 infection		Symptomatic COVID-19		COVID-19-related hospitalization		Severe COVID-19		COVID-19-related death	
	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)
7-30 days after 4th dose	43% (41%-45%)	3,419.9 (3,186.4-3,616.2)	53% (50%-56%)	1,645.3 (1,515.3-1,774.8)	65% (57%-72%)	167.8 (132.0-205.7)	61% (43%-73%)	62.5 (38.1-85.8)	68% (27%-89%)	17.9 (4.9-28.9)
14-30 days after 4th dose	49% (46%-51%)	2,636.7 (2,445.0-2,816.9)	59% (56%-62%)	1,225.7 (1,116.6-1,339.5)	70% (60%-78%)	132.6 (103.8-165.5)	64% (48%-79%)	50.5 (32.0-75.0)	70% (30%-91%)	15.7 (4.5-27.3)

Table S4 - Vaccine effectiveness (VE) estimates for the Poisson Regression days 7+ model

Exposure Period	Adjusted VE (1-IRR)
3rd Vaccine > 4 months prior	Reference
Days 1-4 from 4th vaccine	0.26 (0.24-0.29)
Days 5-6 from 4th vaccine	0.09 (0.03-0.14)
Days 7-30 from 4th vaccine	0.44 (0.43-0.45)

Table S5 - Vaccine effectiveness (VE) estimates for the Poisson Regression days 14+ model

Exposure Period	Adjusted VE (1-IRR)
3rd Vaccine > 4 months prior	Reference
Days 1-4 from 4th vaccine	0.31 (0.28-0.33)
Days 5-6 from 4th vaccine	0.06 (0.02-0.11)
Days 7-13 from 4th vaccine	0.3 (0.28-0.32)
Days 14-30 from 4th vaccine	0.52 (0.51-0.53)

Table S6 - Vaccine effectiveness (VE) estimates for the Poisson Regression daily vaccine effectiveness (1-IRR) model

Exposure Period	Adjusted VE (1-IRR)
3rd Vaccine > 4 months prior	Reference
Day 1 from 4th vaccine	0.55 (0.5-0.59)
Day 2 from 4th vaccine	0.29 (0.24-0.35)
Day 3 from 4th vaccine	0.2 (0.14-0.26)
Day 4 from 4th vaccine	0.2 (0.14-0.25)
Day 5 from 4th vaccine	0.06 (0-0.11)
Day 6 from 4th vaccine	0.07 (0.01-0.12)
Day 7 from 4th vaccine	0.09 (0.04-0.15)
Day 8 from 4th vaccine	0.15 (0.1-0.2)
Day 9 from 4th vaccine	0.26 (0.21-0.31)
Day 10 from 4th vaccine	0.3 (0.25-0.35)
Day 11 from 4th vaccine	0.38 (0.33-0.42)
Day 12 from 4th vaccine	0.45 (0.41-0.49)
Day 13 from 4th vaccine	0.46 (0.41-0.5)
Day 14 from 4th vaccine	0.49 (0.45-0.53)
Day 15 from 4th vaccine	0.53 (0.49-0.57)
Day 16 from 4th vaccine	0.56 (0.52-0.6)
Day 17 from 4th vaccine	0.59 (0.55-0.63)
Day 18 from 4th vaccine	0.57 (0.53-0.61)
Day 19 from 4th vaccine	0.52 (0.47-0.56)
Day 20 from 4th vaccine	0.55 (0.51-0.59)
Day 21 from 4th vaccine	0.47 (0.43-0.52)
Day 22 from 4th vaccine	0.55 (0.51-0.59)
Day 23 from 4th vaccine	0.59 (0.55-0.63)
Day 24 from 4th vaccine	0.53 (0.48-0.57)

Day 25 from 4th vaccine	0.51 (0.46-0.56)
Day 26 from 4th vaccine	0.51 (0.46-0.56)
Day 27 from 4th vaccine	0.46 (0.4-0.51)
Day 28 from 4th vaccine	0.46 (0.4-0.51)
Day 29 from 4th vaccine	0.37 (0.31-0.43)
Day 30 from 4th vaccine	0.48 (0.41-0.54)