THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Effectiveness of a Third Dose of the BNT162b2 mRNA COVID-19 Vaccine

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Study protocol

ORIGINAL PROTOCOL

BACKGROUND AND STUDY RATIONALE

Clinical/Public health significance of research question

Following successful vaccination campaigns and a period of low pandemic activity, Israel and other countries are experiencing renewed outbursts of Covid-19. This has been attributed to waning immunity of the SARS-CoV-2 mRNA vaccines and/or to a higher infectiousness/virulence of the now-dominant B.1.617.2 (Delta) variant.

Under the assumption that waning immunity is (at least partially) responsible for this resurgence, the Israeli ministry of health has launched a nation-wide campaign to administer a third vaccine dose to individuals previously vaccinated with two doses at least 5 months prior. This was done despite little data existing on the effectiveness (or safety) of such a booster dose from RCTs. Real-world studies can then be used to answer these questions about effectiveness of the third booster dose.

How this research fills gaps/adds new evidence to the literature

This study will allow us to estimate the effectiveness of a third "booster" dose of the BNT162b2 mRNA Covid-19 Vaccine

Study objectives

Assess effectiveness of a third "booster" dose of the BNT162b2 mRNA Covid-19 Vaccine

METHODS

Context and Data

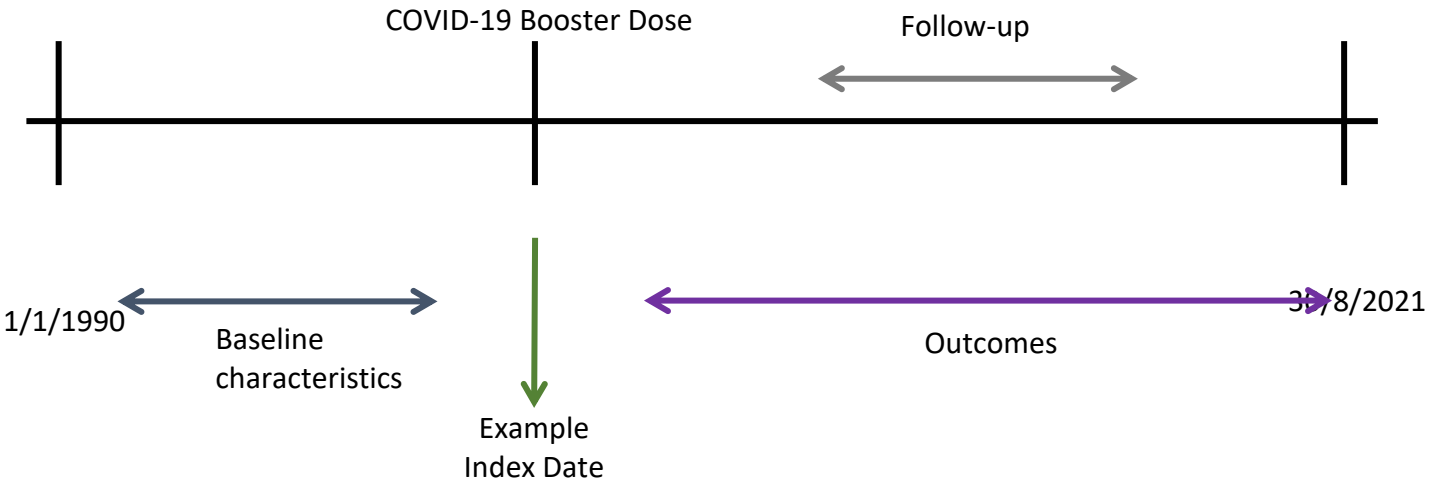
Clalit Health Services (CHS), the largest integrated health care service provider and payer system in Israel, has over 4.7 million active members. CHS has a comprehensive health care data warehouse which combines hospital and community medical records, laboratory and imaging information, pharmaceutical records, health care costs, and Ministry of the Interior vital statistics of all the members. Membership turnover within Clalit is 1-2% annually, facilitating the study of population trends over time.

Study Design and data time period

- This is a retrospective study employing a cohort design.
- This study has two arms: (1) patients vaccinated with the third "booster" dose and (2) patients eligible for the third booster dose who have not received it.
- Unexposed patients will be individually matched to exposed patients.
- Exposed are indexed on the exposure, unexposed are indexed as per their matched exposed participant.
- Exclusion of patients who have experienced COVID-19 prior to the index date or matched index date.

- Overall study period is 1/1/1990 – 30/8/2021
  - Patients will be recruited into the study starting from the first day the third dose was generally available (30/7/2021)
  - Data will be extracted continuously until 30/8/2021
  - Background information, e.g. regarding risk factors, will be extracted from the period before the index date.
- Exposed will be matched to unexposed on
  - Age
  - Sex
  - Place of residence (at city/town level)
  - Number of CDC risk comorbidities
  - Calendar month in which the second dose was received
  - Number of PCR tests in the 9 months before enrollment
- Unexposed who receive the booster dose will be censored, together with their matched exposed, and then re-enrolled as vaccinated exposed with a new control if a compatible match can be found.

Figure 1: Example Study Design Chart



Study population

- Inclusion criteria
  - Clalit membership
  - Eligibility for the booster dose (second dose received at least 5 months prior with the age threshold determined by exact date)
- Exclusion criteria
  - Previous Positive SARS-CoV-2 PCR
  - Being health care workers
  - Residence in a long-term care facility
  - Being confined to their home
  - Missing data in BMI or smoking status
  - Unmapped place of residence
  - Interaction with the healthcare system in the days before matching
- Estimated sample size is no more than 2 million patients.

- ❖ Special population (e.g. pregnant women) will be included as per the above-mentioned inclusion and exclusion criteria.

Variables

Data will be taken from the inpatient and outpatient Clalit data warehouses. For all variables:

Outcomes

- ❖ Primary
  - Documented SARS-CoV-2 Infection (per PCR)
  - Symptomatic SARS-CoV-2 Infection
  - COVID-19 hospitalization
  - Defined severe due to COVID-19 infection
  - COVID-19 mortality
- ❖ All outcomes will be measured in days 7-30 following receipt of the third "booster" dose in the vaccinated

Exposures

- ❖ Receipt of third "booster" dose as per MoH/CHS vaccination records

Covariates

- Covariates used for exclusion:
  a. As per list above
- Covariates to be Matched on:
  a. List of variables above to be matched on

Statistical analysis plan

- Starting from 30/7/2021 and advancing daily, eligible individuals who received the booster on that day will be matched to eligible individuals who haven't and have not been previously recruited.
- Matching will be performed on variables predicting vaccination, the risk of infection, the risk of severe disease and health-seeking behavior.
- Matching will be exact, using narrow bins for continuous variables.
- Cumulative incidence curves comparing the risk of infection between the two curves will be drawn using the Kaplan-Meyer method.
- Survival analysis will be performed using the Kaplan-Meier estimator.
  a. Patients selected as matched controls (unexposed) who will then receive the vaccine will be censored at the date of vaccination, and their matched exposed patients will be censored at the same date.
  b. Analysis will contain only pairs of exposed and unexposed who both "survived" (not censored and did not experience an event) until start of the analysis period (day 7).

Privacy

Data extraction and analyses will be conducted at the Clalit Research Institute (CRI) by employees of the CRI. The raw data extracted are coded, viewed and stored only within the CRI.

Once data are analyzed and leave the CRI they are de-identified aggregated and do not contain any identifiable information.

FINAL PROTOCOL

BACKGROUND AND STUDY RATIONALE

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- Exposed are indexed on the exposure, unexposed are indexed as per their matched exposed participant.
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- Overall study period is 1/1/1990 – 30/8/2021
    - Patients will be recruited into the study starting from the first day the third dose was generally available (30/7/2021)

- Data will be extracted continuously until 30/8/2021
- Background information, e.g. regarding risk factors, will be extracted from the period before the index date.

- Exposed will be matched to unexposed on
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  - Sex
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  - Calendar month in which the second dose was received
  - Number of PCR tests in the 9 months before enrollment
- Unexposed who receive the booster dose will be censored, together with their matched exposed, and then re-enrolled as vaccinated exposed with a new control if a compatible match can be found.

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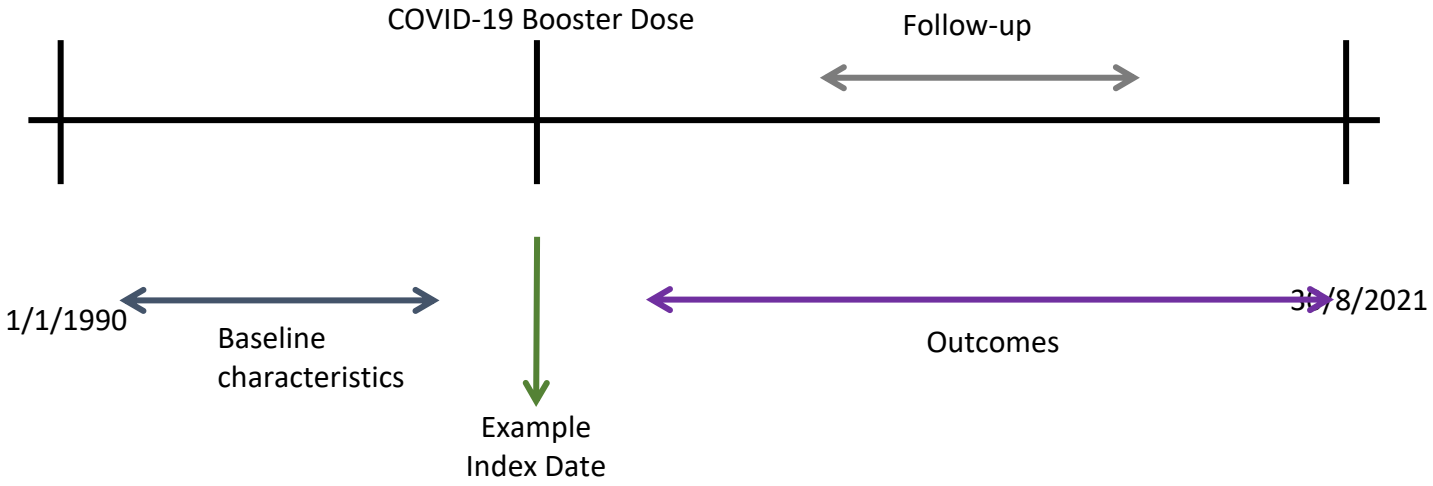

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  - Being confined to their home
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  - Interaction with the healthcare system in the days before matching
- Estimated sample size is no more than 2 million patients.
- Special population (e.g. pregnant women) will be included as per the above-mentioned inclusion and exclusion criteria.

Variables

Data will be taken from the inpatient and outpatient Clalit data warehouses. For all variables:

Outcomes

- Primary
  - COVID-19 hospitalization
  - Defined severe due to COVID-19 infection
  - COVID-19 mortality
- Secondary
  - Documented SARS-CoV-2 Infection (per PCR)
  - Symptomatic SARS-CoV-2 Infection
- All outcomes will be measured in days 7+ following receipt of the third "booster" dose in the vaccinated
- Outcomes will be assessed in the full population and in subpopulations defined by age, sex and comorbidity counts.

Exposures

- Receipt of third "booster" dose as per MoH/CHS vaccination records

Covariates

- Covariates used for exclusion:
  a. As per list above
- Covariates to be Matched on:
  a. List of variables above to be matched on

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- Starting from 30/7/2021 and advancing daily, eligible individuals who received the booster on that day will be matched to eligible individuals who haven't and have not been previously recruited.
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- Matching will be exact, using narrow bins for continuous variables.
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- Survival analysis will be performed using the Kaplan-Meier estimator.
  a. Patients selected as matched controls (unexposed) who will then receive the vaccine will be censored at the date of vaccination, and their matched exposed patients will be censored at the same date.
  b. Analysis will contain only pairs of exposed and unexposed who both "survived" (not censored and did not experience an event) until start of the analysis period (day 7).
- Two additional analyses will be performed:
  a. An analysis of the same dataset will be performed using Poisson regression, using incidence rate ratio as the effect measure.
  b. An ecological analysis showing daily incidence proportions among different age groups around the time of booster initiation for each age group.

Privacy

Data extraction and analyses will be conducted at the Clalit Research Institute (CRI) by employees of the CRI. The raw data extracted are coded, viewed and stored only within the CRI. Once data are analyzed and leave the CRI they are de-identified aggregated and do not contain any identifiable information.

Summary of changes

- The outcomes "**documented SARS-CoV-2 Infection (per PCR)**" and "**Symptomatic SARS-CoV-2 Infection**" were shifted to be a secondary analysis. This was done because the count of PCR tests performed showed a large difference between the two study groups.
- Subgroup analysis was added, given the availability of data.
- The analysis period was changed from 7-30 to 7+, given the availability of data.
- An additional analysis was added using IRRs as the effect measure at the request of a reviewer.
- An additional analysis was added using an ecological analysis of each age group around the time of booster initiation.

Table S1 – Variable definitions

Names, possible values, definitions and time periods for all variables used in the study.Variables were defined using internal CHS registries, ICD9 codes and ATC codes. MOH: Ministry of Heath; CHS: Clalit Health Services; ICD: International Classification of Disease; ATC: Anatomic therapeutic chemical; NDC: National drug code.

Variable	Values	Definitions[1]	Timing[2]
Population Definition			
Eligible for 3rd Dose	0/1	150 days or more following receipt of two doses of the BNT162b2 mRNA Covid-19 Vaccine, aged 60+ (starting at July 30, 2021), 50+ (starting at August 12, 2021), 40+ (starting at August 19, 2021), 30+ (starting at August 24, 2021), or 16+ (starting at August 30, 2021)	Current
Outcomes			
Documented SARS-CoV-2 Infection	0/1	A PCR-confirmed infection.	The date of specimen collection that resulted in a positive PCR test for SARS-CoV-2. If the PCR test was performed after the beginning of a hospitalization flagged as a COVID-19 hospitalization, the infection date was set to the beginning of the hospitalization.
COVID-19 (symptomatic SARS-CoV-2 Infection)	0/1	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,	The date set for the SARS-CoV-2 infection outcome.

		weakness, congestion or runny nose, myalgia, nausea or vomiting, diarrhea, abdominal pain, loss of taste or smell, inability to eat or drink.	
COVID-19 related hospitalization	0/1	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
COVID-19 related severe state	0/1	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 SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, 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.
COVID-19 related death	0/1	Death of a SARS-CoV-2-infected individual reported to the Israeli MOH	The reported date of death
Vaccination Period			
Days 7+ after the 3rd dose	0/1	From day 7 after receipt of the third vaccine onwards	After the index date
Covariates			
Age	Integer	Age in complete years	Current
Sex	Male/Female	As defined in CHS' files	Current
Geo-statistical Area	List of places	City or town in which the patient resides per CHS' files	Current
Health-care worker	0/1	Is patient a health-care worker per CHS' files	Current
Long-term care facility resident	0/1	Is patient a long-term care facility resident per CHS' files	Current
Confined to Home	0/1	Is patient confined to his home per CHS' files	Current
Influenza vaccinations	0/1	Did patient receive an influenza vaccine in the last 5 years	Last 5 Years
Cancer	0/1	ICD9 Code 174* ICD9 Code 175* ICD9 Code 233.0 ICD9 Code V10.3 ICD9 Proc Code 85.4*	Last 5 years

		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 ICD9 Code 171* ICD9 Code 176* ICD9 Code 184* ICD9 Code 186* ICD9 Code 187* ICD9 Code V10.4* ICD9 Code 203* ICD9 Code 273.3 ICD9 Code 152* ICD9 Code 158* ICD9 Code 159* ICD9 Code 163* ICD9 Code 164* ICD9 Code 165* ICD9 Code 181 ICD9 Code 190* ICD9 Code 192.8 ICD9 Code 196* ICD9 Code 197* ICD9 Code 198* ICD9 Code 199*	
Chronic Kidney Disease	0/1	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	0/1	ICD9 Code 491* ICD9 Code 492* ICD9 Code 496	Ever
Heart Conditions	0/1	ICD9 Code 410* ICD9 Code 411* ICD9 Code 412	Ever

		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*	
Solid Organ Transplant Recipient	0/1	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	0/1	Body Mass Index (BMI) 30-40	Latest measurement in last 5 years not taken during pregnancy
Severe Obesity	0/1	Body Mass Index (BMI) 40+	Latest measurement in last 5 years not taken during pregnancy
Pregnancy	0/1	Internal Clalit Registry	Current
Sickle Cell Disease	0/1	ICD9 Code 282.6*	Ever
Smoking	0/1	Internal Clalit Registry	Last recorded value
Type 2 Diabetes Mellitus	0/1	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	0/1	ICD9 Code 493*	Ever
Cerebrovascular Disease	0/1	ICD9 Code 362.34 ICD9 Code 430 ICD9 Code 431	Ever

		ICD9 Code 432* ICD9 Code 433* ICD9 Code 434* ICD9 Code 435* ICD9 Code 436* ICD9 Code 438*	
Other Respiratory Disease	0/1	ICD9 Code 277.0* ICD9 Code 494* ICD9 Code 515	Ever
Hypertension	0/1	ICD9 Code 401* ICD9 Code 402* ICD9 Code 403* ICD9 Code 404* ICD9 Code 405*	Ever
Immunocompromised State	0/1	**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	0/1	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] 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	For diagnosis codes, Ever For drugs, 4 or more dispensed in last 12 months

		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	0/1	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	0/1	Body Mass Index (BMI) 25-30	Latest measurement in last 5 years not taken during pregnancy
Thalassemia	0/1	ICD9 Code 282.4*	Ever
Type 1 Diabetes Mellitus	0/1	ICD9 Code 250._1, 250._3	Ever
CDC Risk Factor Count	Integer	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	Based on the variables above

		• Type 1 or 2 Diabetes Mellitus • Solid organ transplant recipient or immunodeficiency • Obesity or severe obesity	

[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 – Baseline characteristics of the eligible and matched study vaccinated populations

Comparison of the eligible vaccinated population and the eventual matched study population. (CDC: Centers for disease control and prevention; BMI: Body mass index.)

Variable	Eligible, N = 1,158,269	Matched, N = 728,321
Age	55 (39, 69)	52 (37, 68)
Sex		
Female	583,400 (50%)	371,435 (51%)
Male	574,869 (50%)	356,886 (49%)
Population Sector		
General Jewish	988,844 (85%)	612,006 (84%)
Arab	133,814 (12%)	92,656 (13%)
Ultra-Orthodox Jewish	35,611 (3.1%)	23,659 (3.2%)
CDC Risk Factor Count		
0	499,073 (43%)	340,607 (47%)
1	288,707 (25%)	175,738 (24%)
2	164,861 (14%)	90,704 (12%)
3+	205,628 (18%)	121,272 (17%)
SARS-CoV-2 PCR Tests in the Last 9 Months		
0	591,901 (51%)	407,815 (56%)
1	217,775 (19%)	134,016 (18%)
2	145,936 (13%)	84,832 (12%)
3	81,125 (7.0%)	41,962 (5.8%)
4	47,481 (4.1%)	21,553 (3.0%)
5+	74,051 (6.4%)	38,143 (5.2%)
CDC “Certain” Risk Criteria		
Cancer	34,803 (3.0%)	19,773 (2.7%)
Chronic Kidney Disease	116,515 (10%)	66,886 (9.2%)

Chronic Obstructive Pulmonary Disease	35,484 (3.1%)	20,669 (2.8%)
Heart Disease	122,087 (11%)	71,428 (9.8%)
Solid Organ Transplant	1,313 (0.1%)	431 (<0.1%)
Obesity (BMI 30-40)	249,699 (22%)	147,399 (20%)
Severe Obesity (BMI 40+)	22,377 (1.9%)	13,438 (1.8%)
Pregnancy	6,675 (0.6%)	4,588 (0.6%)
Sickle Cell Disease	156 (<0.1%)	65 (<0.1%)
Smoking	181,062 (16%)	115,250 (16%)
Type 2 Diabetes Mellitus	194,234 (17%)	115,451 (16%)
CDC “Possible” Risk Criteria		
Asthma	81,945 (7.1%)	47,187 (6.5%)
Cerebrovascular Disease	57,767 (5.0%)	32,822 (4.5%)
Other Respiratory Disease	6,494 (0.6%)	3,771 (0.5%)
Hypertension	313,670 (27%)	184,317 (25%)
Immunosuppression	46,718 (4.0%)	26,471 (3.6%)
Neurological Disease	79,611 (6.9%)	45,483 (6.2%)
Liver Disease	27,419 (2.4%)	16,074 (2.2%)
Overweight (BMI 25-30)	416,696 (36%)	260,353 (36%)
Thalassemia	7,208 (0.6%)	4,085 (0.6%)
Type 1 Diabetes Mellitus	7,638 (0.7%)	4,339 (0.6%)

Table S3 – Effectiveness of the third vaccine dose compared to two vaccine doses of the BNT162b2 mRNA COVID-19 vaccine estimated using incidence rates

Estimates were obtained starting from day 7 after receipt of the third dose in those who received it. RR: Risk Ratio; RD: Risk Difference.

	Vaccinated with 2 Doses		Vaccinated with 3 Doses		
Outcome	**Events**	**Person-Days**	**Events**	**Person-Days**	**1-IRR (95-CI)**
Documented Infection	6,131	6,311,181	1,135	6,398,540	82% (81%-83%)
Symptomatic Infection	3,345	6,383,764	514	6,440,115	85% (83%-86%)
Hospitalization	231	6,494,642	29	6,503,731	87% (82%-92%)
Severe Disease	157	6,498,692	17	6,506,353	89% (83%-94%)
Death	44	6,501,661	7	6,506,787	84% (67%-93%)

Figure S1 – Population Flow Chart

Size and percent change of study population resulting from each inclusion and exclusion criteria. The table focuses on the vaccinated population.