

THE EFFECTIVENESS OF THE TWO-DOSE BNT162b2 VACCINE: ANALYSIS OF REAL-WORLD DATA

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Key Points

We assessed the effectiveness of the BNT162b2 COVID-19 vaccine among 1.2M vaccinees. We found a 90% reduction in all confirmed infections and 94% in symptomatic cases starting from 7 days after the second dose. A lower effectiveness was found in immunocompromised elderly.

Abstract

Background COVID-19 mRNA vaccines were shown to be highly efficacious in preventing the disease in randomized controlled trials; nonetheless, evidence on the real-world effectiveness of this vaccine is limited. Study objective was to evaluate the effectiveness of BNT162b2 vaccine in preventing SARS-CoV-2 infection and COVID-19-related hospitalization and mortality.

Methods This historical cohort study included members of a large health provider in Israel that were vaccinated with at least one dose of BNT162b2. The primary outcome was incidence rate of a SARS-CoV-2 infection confirmed with rt-PCR, between 7 to 27 days after second dose (protection-period), as compared to days 1 to 7 after the first dose, where no protection by the vaccine is assumed (reference-period).

Results Data of 1,178,597 individuals vaccinated with BNT162b2 were analyzed (mean age 47.7 years [SD=18.1], 48.4% males) of whom 872,454 (74.0%) reached the protection period. Overall, 4514 infections occurred during the reference period compared to 728 during the protection period, yielding a weighted mean daily incidence of 54.8 per 100,000 (95% CI: 26.1-115.0 per 100,000) and 5.4 per 100,000 (95% CI: 3.5-8.4 per 100,000), respectively. The vaccine effectiveness in preventing infection was 90% (95% CI: 79% - 95%) and 94% (95% CI: 88%-97%) against COVID-19. Among immunosuppressed patients, vaccine effectiveness against infection was 71% (95% CI: 37%-87%). The adjusted hazard ratios for

hospitalization in those infected were 0.82 (95%CI:0.36-1.88), 0.45 (95%CI:0.23-0.90), and 0.56 (95%CI:0.36-0.89) in the age groups 16-44, 45-64 and 75 and above, respectively.

Conclusions The effectiveness of the BNT162b2 vaccine is comparable to the one reported in the phase III clinical trial.

Keywords: COVID-19, BNT162b2, Vaccine, Effectiveness, Real-world data

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Introduction

The recently authorized BNT162b2 mRNA COVID-19 vaccine has demonstrated 95% efficacy in preventing COVID-19 with the two-dose regimen in phase III placebo-controlled randomized clinical trial (RCT).¹ Observational studies using real-world data are important for providing a robust assessment and external validity on vaccine safety and effectiveness in the general population and across diverse populations, including in those that are often excluded from the RCTs such as patients with unstable comorbid conditions.^{1,2} Additionally, large observational studies using real world data with longer follow-up time may allow the assessment of low-probability effects that may not be detected in RCTs.

In Israel, COVID-19 vaccination using BNT162b2 mRNA vaccine started on December 19, 2020, with priority given initially to individuals aged 60 and above, healthcare workers and high-risk groups with chronic conditions. By comparing vaccinated with unvaccinated Israelis, a recent real-world data analysis^{3,4} estimated the vaccine effectiveness (VE) of two doses of BNT162b2 in reducing COVID-19 risk at 91%. Comparisons of vaccinated and unvaccinated individuals might be challenging given inherited unmeasured characteristics that may differ between the groups such as perceived infection risk, poorer compliance with COVID-19 preventive measure which might result in biases.⁵ This challenge is amplified when vaccine uptake is rapid. We propose an alternative design that overcomes this pitfall with a cohort study of vaccinated individuals only comparing the incidence of the infection during the first few days after immunization with first vaccine dose to at-least one-week post second dose. This design allows a valid estimation of the VE given that COVID-19 incidence was similar in the vaccine and placebo arms during the first week after immunization in the RCT.⁶

As of February 25 2021, Israel ranks first in vaccine coverage with 75% of the individuals aged 16 or above vaccinated with at least one dose of BNT162b2 vaccine. The aim of the

current study was to expand our previous research on first dose⁷ and assess the effectiveness of two-dose BNT162b2 vaccine in reducing the risk of SARS-CoV-2 infection in a large cohort of immunized individuals, employing a vaccine-only study design.

Methods

Study design and data sources

The data used for this retrospective cohort study were obtained from Maccabi Healthcare Services (MHS), a state-mandated sick fund, covering 2.6 million-member or 25% of residents in Israel. According to the National Health Insurance Law, membership in sick funds is free and open to all Israeli citizens. MHS database includes extensive demographic data, anthropometric measurements, diagnoses from community clinics and hospitals, medication dispensing information, and comprehensive laboratory data from a single central laboratory.

Study population and design

The study population consisted of all MHS members aged 16 and above who were vaccinated with at least one dose of the BNT162b2 vaccine during a mass immunization program from December 19, 2020 to February 20, 2021. Excluded from analysis were patients who had a documented positive SARS-CoV-2 prior to vaccination date (n=13,656) and individuals who joined MHS after February 2020 and therefore had an incomplete medical history (n=33,666).

The results of the phase III trial⁶ provide experimental evidence that the BNT162b2 vaccine confers no or little protection against SARS-CoV-2 infection during the first seven days post vaccination with the first dose. This is also supported by a recent analysis of the infection cycle threshold (Ct) over time among infected vaccinees in MHS, where viral load substantially decreased only after 12 days after first dose⁸. Therefore, we used the incidence

of infection in day 1 to 7 after first dose as a reference period to assess the effectiveness of the vaccine compared to days 7 to 27 after the second dose, which was defined as the *protection period* based on the phase III trial data¹. We limit to 27 days to allow sufficient time for post infection follow-up.

Study endpoints

COVID-19 infection was defined as having at least one record of primary positive SARS-CoV-2 real-time polymerase chain reaction (rt-PCR) test obtained from nasopharyngeal swabs⁹. The tests are offered to all Israeli citizens free of charge and without a need for referral, regardless of having symptoms.

We also collected information regarding hospitalizations due to COVID-19 among infected patients and subsequent mortality. Follow-up for COVID-19-related hospitalizations and deaths started from day after first date of positive rt-PCR tests and lasted until date of hospitalization/death, leaving MHS, March 3, 2021, or 21 days of follow-up whichever occurred first. Data of symptoms among infected individuals was documented by primary care physicians at the time of referral to rt-PCR test.

Additional variables

Demographic and clinical data were collected from MHS's central databases. This included age at immunization with the first dose of BNT162b2, sex, body mass index (BMI) and coexisting comorbidities including cancer, immunocompromised conditions (e.g. recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome), hypertension, diabetes,¹⁰ and cardiovascular diseases.¹¹ Data on member's enumeration area of residence as reported by the Israeli Central Bureau of Statistic and Points Business Mapping Ltd ©¹² were used to assess socioeconomic status (SES) and belonging to

ultraorthodox Jewish and Israeli Arab communities was collected given epidemiological data supporting different health-related COVID-19 behavior patterns.¹³

Statistical analysis

Continuous variables were expressed as means (standards deviations [SD]) and medians (interquartile range, IQR). Categorical variables were summarized as counts and percentages. Cumulative incidence plots of SARS-CoV-2 infection were created using Kaplan-Meier survival analysis and compared with the log-rank test. The comparison of the incidence rate of rt-PCR-confirmed SARS-CoV-2 infection between the two study periods was performed using generalized linear models, applying a negative-binomial distribution with a log-link and log-daily number of individuals-at-risk as an offset. The offset was used to scale the counts of SARS-CoV-2 infections to daily incidence, expressed as cases per 100,000. The dependent variable was the number of positive PCR per day during each study period. VE was defined as infection relative risk reduction and calculated as: $(1 - \text{relative risk}) \times 100$. Analyses were stratified by age group, sex, patients residing in ultraorthodox Jewish or Israeli Arab sector, and chronic illness. We also stratified the analysis by calendar period to assess the potential effect of new SARS-CoV-2 variants that were spread during the study period (eFigure 1).¹⁴ Binary logistic regression models were used to estimate odds ratios (ORs), adjusted odds ratios (aORs) and 95% CIs for COVID-19 symptoms among infected patients. All binary logistic regression models estimating the aORs simultaneously controlled for age, sex, sector, SES, and chronic conditions. Adjusted hazard ratios (aHRs) for COVID-19-related hospitalization or death among infected patients were calculated using Cox proportional hazards model adjusting for age, sex, calendar period of immunization, sector, and clinical characteristics. The corresponding adjusted survival curves were drawn. Proportional hazards assumption was confirmed according to Schoenfeld residuals tests and graphical evaluations. To assess potential “healthy vaccinee” bias where incidence in the first days after first dose

are lower than general population due to selection of COVID-19-free patients, we performed a sensitivity analysis limiting the reference-period to days 5 to 7 after first dose (N=1,175,741). Analyses were done using IBM-SPSS Version 27 (Armonk, NY: IBM Corp) and R packages magrittr, readtext, dplyr, ggplot2, tidyverse, survival, forestplot, and survminer.

Ethics approval

The study protocol was approved by the MHS Ethics Committee.

Results

Overall data of 1,178,597 individuals vaccinated with BNT162b2 were analyzed (mean age 47.7 years [SD=18.1], 48.4% males) of whom 872,454 (74.0%) had more than one week of follow-up after the second dose (Table 1). Study population accounts for approximately 80% of the total number of members eligible for vaccination in MHS.

SARS-CoV-2 PCR test was performed by 60,931 individuals (5.2%) during the reference period compared to 27,456 (3.1%) individuals during protection period. The proportion of patients tested with rt-PCR SARS-CoV-2 during the reference and protection periods was 5.2% (n=60931) and 3.1% (n=27456), respectively. The respective number of individuals who tested positive was 4514 (7.4% test positive rate) and 728 (2.7%), representing a weighted mean incidence rate of 54.8 per 100,000 persons (95% CI: 26.1-115.0) and 5.4 per 100,000 (95% CI: 3.5-8.4). Lower incidence of SARS-CoV-2 PCR-confirmed infection rate between reference period and protection period was found across all age groups (Figure 1). The overall VE was estimated at 90% (95% CI: 79%-95%), which was materially unchanged when limiting reference-period to days 5 to 7 after first dose, VE against infection was 92% (95%CI, 75%-97%) (Supplementary Table 1).

VE estimates were 92% (95% CI: 83%-96%) and 90% (95% CI: 80%-95%) in the age groups 16-44 and 45-64 years respectively, 82% (95% CI: 63%-92%) in the age groups 65-74 and 82% in those aged 75 and above (95% CI: 61%-91%). In patients with diabetes and patients with cardiovascular diseases, the estimated VE was 82% (95%CI: 62% to 92%). Somewhat lower VE (71%; 95%CI: 37%-87%) was calculated among immunosuppressed patients, approaching 52% (95%CI: -26% to 82%) in those who were 65 and older (Figure 2). In stratified analysis among immunosuppressed patients during the first month of the vaccination campaign, VE was 70% (95%CI: 35% to 86%) compared to 84% (60%-94%) in the second month (Supplementary Table 2). The overall estimated VE in preventing COVID-19 was 94% (95%CI: 87%-97%), and 75% (95% CI: 44%-88%) among immunosuppressed patients (Figure 2).

Among patients infected with SARS-CoV-2 in the reference period, 70.1% (n=3179) were symptomatic vs. 38.6% (n=281) among those infected during the protection period (aOR= 0.32; 95%CI: 0.27-0.39, P<0.001) (Table 2). The largest difference in proportion of symptomatic cases was evident among patients aged 16-44y (69.9% vs. 30.7% respectively, P<0.001).

Overall, 513 (43.6 per 100,000 persons) and 144 (16.5 per 100,000 persons) deaths occurred among vaccinated individuals during the reference vs. protection periods, respectively. Of these, 39 and 11 occurred among patients with COVID-19, respectively. Fatality cases and rates (% of infected) during protection period vs. reference period in patients aged 45-64, 65-74, and 75y and above were: none vs. 3 (0.2%), 1 (0.7%) vs. 8 (2.4%), and 10 (9.0%) vs. 28 (11.7%), respectively. There were no recorded deaths among infected patients under age 45.

Risk for hospitalization among patients infected in protection period and reference period are shown in Figure 3, with aHRs of 0.82 (95% CI: 0.36-1.88), 0.45 (95% CI: 0.23-0.90), and

0.56 (95% CI, 0.36-0.89) in persons aged 45-64, 65-74 and 75 years and above, respectively. Reduced risk of hospitalization was calculated among patients with obesity (aHR=0.40; 95% CI: 0.22-0.73), hypertension (aHR=0.56; 95% CI: 0.36-0.86), and diabetes (aHR=0.46; 95% CI: 0.25-0.86). We found little difference in hospitalization rates in patients with immunosuppression (aHR=1.38; 95% CI: 0.51-3.72) or cancer (aHR=1.04; 95% CI: 0.49-2.23) that were infected with SARS-CoV-2.

Discussion

Our analysis of vaccinated individuals indicates 90% effectiveness of the BNT162b2 mRNA vaccine in preventing rt-PCR-confirmed SARS-CoV-2 infection and 94% against COVID-19, with lower effectiveness among those with immunosuppression. Our findings are in line with the estimated 95% vaccine efficacy for COVID-19 reported in the phase III RCT⁶, as well as 86% to 94% effectiveness against SARS-CoV-2 infection in recent observational studies.^{3,15,16}

To our knowledge, this is the largest cohort of vaccinated persons that assessed VE. With this sizable sample and 728 incident PCR-confirmed SARS-CoV-2 infections starting at 7 days after second dose, we were able to estimate VE among different subpopulations. VE in patients with underlying chronic conditions including diabetes, hypertension, cardiovascular diseases or cancer was somewhat lower (approximately 82%) compared to the population average of 90%. In a previous observational study from a large health provider in Israel³, VE in persons with diabetes or hypertension was similar to the general population, although patients with over three major chronic morbidities had diminished effectiveness. A more substantial difference was found among immunosuppressed patients who had an average VE of 70%, which was further reduced among the elderly. Current data on the risk of COVID-19 morbidity patients with immunosuppression are limited¹⁷ as these patients more strongly adhere to exposure- limiting precautions compared to the general population. Thus, more

research is required to characterize the immunologic profile of these groups to ensure optimal protection.¹⁸

In addition to estimating VE, our analysis evaluated the potential benefit of the vaccine in reducing the risk of COVID-19 hospitalizations and death among patients with vaccine failure in preventing infection. Individuals who were infected starting at day 7 after the second dose were substantially less likely to present symptoms and to be hospitalized compared to those who were infected in the reference period. A comparable reduction of 60% in hospital admissions after vaccination was observed in a previous observational study.¹⁶ Similarly, our results indicate a lower case-fatality of COVID-19 cases infected during protection period compared to the reference period as was previously observed³. However, it can be argued that a hospitalization rate of 6.9% and case-fatality rate of 1.5% in those after the second dose are not negligible, especially not in patients with immunosuppression. It is therefore might be important to retain awareness among vaccinated patients and their caregivers to possible severe COVID-19 when breakthrough infection occurs.

Previous observational studies compared vaccinated and matched unvaccinated patients, which could introduce selection bias due to unmeasured confounders such as health literacy, perceived feelings of vulnerability to COVID-19, and differences in health seeking behavior.^{5,19} Moreover, these comparative studies are also susceptible to a healthy vaccine bias, as immunized individuals are more likely to feel well on the vaccination date while patients with symptoms or suspected contacts are discouraged from immunization.²⁰

Rigorous matching in these studies was employed to make the vaccinated and unvaccinated populations comparable, but is done at the cost of excluding many vaccinated individuals for whom a match cannot be found. For example, in the study by Dagan et al³, more than half of the vaccinated persons were excluded and only 16,180 (24%) out of 67,492 patients with immunosuppression who were vaccinated could be matched. This potentially might limit the

generalizability of findings, especially among persons with more complex medical conditions. The current study design was based upon internal comparisons among vaccinated individuals to avoid such bias.

This study has some limitations. Although 74% of the study participants were included in both periods, follow-up distributed differently over calendar time. However, when analyses were stratified by calendar week, results remained materially unchanged. In addition, we assessed COVID-19 symptoms from physician reports at patient's visits. Thus, symptoms that developed after that visit were not captured in our data. Additional limitation is change in health seeking behavior between the periods where patients after two doses may have a lower test rate, leaving more asymptomatic infections undocumented. Nevertheless, this potential information bias is likely insignificant, as VE calculated for all infections was similar or lower to the one calculated for symptomatic cases. Finally, the “healthy vaccinee” effect should also be considered when using the incidence in the first days after first dose as a reference period, although sensitivity analysis suggested that the attenuation in the estimated VE is relatively small.

With more than 86% of adults in MHS are currently covered with at least one dose of BNT162B2, COVID-19 morbidity is still significant. Although the relative importance of children and young adolescents in SARS-CoV-2 transmission is still unclear, their vaccination seems to be essential to support herd immunity. This underlines the importance of several COVID-19 pediatric vaccines trials that are underway.²¹

We report a high effectiveness of the BNT162b2 vaccine for preventing documented SARS-CoV-2 infection in real-world setting, corroborating estimates reported in previous randomized trial and observational analyses. Our study also suggests that second dose of the vaccine reduced, but not nullified, the risk of hospitalization among infected patients. The relationship between immunosuppression and BNT162b2 VE should be further explored.

Although this early evidence is highly encouraging, new challenges are imposed with the emergence of the new SARS CoV 2 variants. It is necessary therefore to reassess the effectiveness of the vaccine periodically in the general population and in various subpopulations.

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Notes

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Table 1: Characteristics of study population by period of follow-up

	Days 1-7 after 1st dose (reference period)		Days 7-27 after 2nd dose (protection period)	
	N	%	N	%
N	1,178,597	(100)	872,454	(100)
Sex				
	Males	569,392 (48.4)	420,010 (48.1)	
	Females	608,277 (51.6)	452,444 (51.9)	
Age y , mean ±SD	47.7	±18.1	52.3	±17.1
BMI kg/m², mean SD	26.4	±5.3	26.8	±5.2
SES level, median(IQR)	7	(5, 8)	7	(6,8)
Ultraorthodox	41,947	(3.6)	27,668	(3.2)
Arabs	44,474	(3.8)	26,672	(3.1)
Immunosuppression	27,822	(2.4)	25,459	(2.9)
Diabetes mellitus	113,769	(9.7)	104,152	(11.9)
Cardiovascular diseases	70,716	(6.0)	66,252	(7.6)
Hypertension	251,323	(21.3)	229,892	(26.4)
Cancer	95,935	(8.1)	90,512	(10.4)

BMI: Body mass index; kg: kilogram; m: meters SD: standard deviation; SES: residential socioeconomic status rank

Table 2: Proportion of Symptomatic COVID-19 infection among patients with positive SARS-CoV-2 PCR

		Total number of infected cases		Symptomatic COVID-19 infection				OR*	95% CI	
		Reference period (N)	Protection period (N)	Reference period		Protection period				
				n	%	n	%			
Total		4514	728	3163	70.1%	281	38.6%	0.32	0.27	0.39
Sex	Male	2289	356	1552	67.8%	124	34.8%	0.28	0.22	0.37
	Female	2225	372	1611	72.4%	157	42.2%	0.35	0.27	0.45
Age	16-44y	2323	163	1624	69.9%	50	30.7%	0.16	0.11	0.24
	45-64y	1617	308	1250	77.3%	133	43.2%	0.25	0.19	0.33
	65-74y	337	146	204	60.5%	59	40.4%	0.50	0.33	0.76
	≥75y	237	111	85	35.9%	39	35.1%	1.15	0.68	1.93
Jewish Ultra-orthodox		701	49	540	77.0%	25	51.0%	0.34	0.17	0.65
Arabs		242	25	157	64.9%	12	48.0%	0.54	0.22	1.33
Obesity		1107	245	833	75.2%	108	44.1%	0.33	0.24	0.45
Immunosuppression		79	56	54	68.4%	32	57.1%	0.81	0.35	1.89
Diabetes		411	170	265	64.5%	73	42.9%	0.48	0.32	0.73
Cardiovascular disease		212	92	125	59.0%	38	41.3%	0.56	0.32	0.98
Hypertension		798	297	530	66.4%	135	45.5%	0.56	0.41	0.75
Cancer		230	90	143	62.2%	35	38.9%	0.56	0.32	0.98

*Mutually adjusted for all listed variables and calendar epidemiologic week

Figure legends:

Figure 1: Age-specific daily incidence of PCR-confirmed SARS-CoV-2 infection (7-day moving average) after immunization with first and second doses of BNT162b2 vaccine

Figure 2: Estimated BNT162b2 mRNA vaccine effectiveness and 95% confidence intervals against PCR-confirmed SARS-CoV-2 infection by age, sector and comorbidity

Figure 3: Adjusted cumulative hospitalization rate among individuals with PCR-confirmed SARS-CoV-2 infection according to time of diagnosis, days from BNT162b2 immunization, by age group and comorbidity

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Figure 1

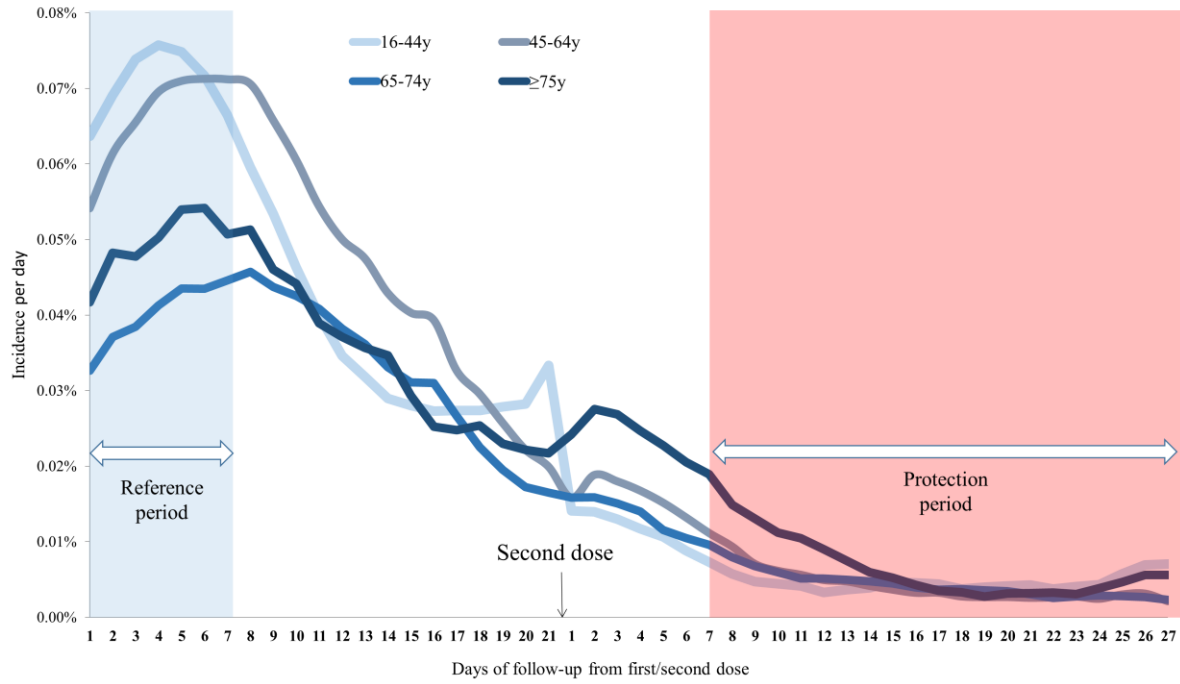


Figure 2

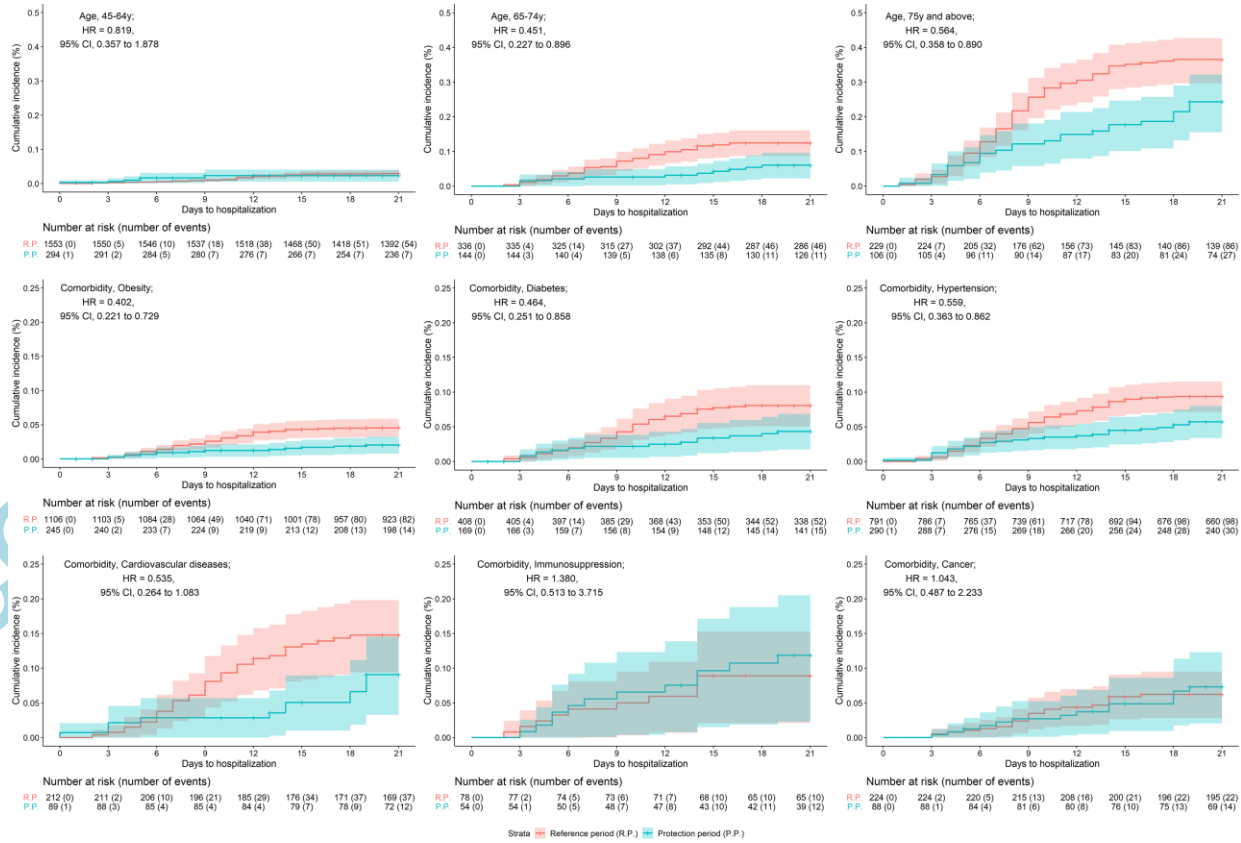
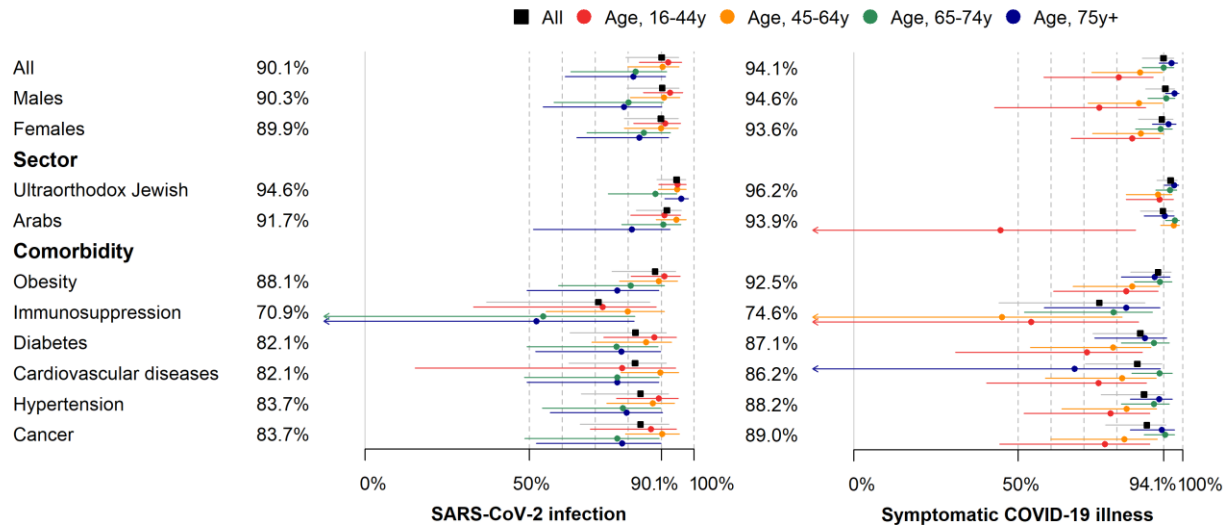


Figure 3



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