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Pfizer-BioNTech vaccine effectiveness against Sars-Cov-2 infection: Findings from a large observational study in Israel

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ABSTRACT

Development of an effective vaccine against Covid-19 is crucial to reducing infection. mRNA BNT162b2, developed and manufactured by Pfizer-BioNTech, was one of the first FDA-approved vaccinations reporting high efficacy (95%) and minimal side effects. Evaluating effectiveness of BNT162b2 in a general population has been made possible after the implementation of a nation-wide vaccination program in Israel.

This retrospective cohort study was carried out in Maccabi HealthCare services, Israel among 1.6 million members aged 16 and over. The population was divided into those who were at least seven days post- second vaccination and those who had not been vaccinated. Number of days till the end of the study or Covid-19 infection, Covid-19-related hospitalization and mortality was calculated for each participant between 18.1.2021 to 25.4.2021. Participants who had reached day eight after second vaccination during the study period could contribute days to both groups. Vaccine efficacy (VE) was calculated using a conditional Poisson model, controlling for age group, gender, hypertension, diabetes and obesity, fitted within clusters defined by geographical statistical area and calendar week.

BNT162b2 was found effective for the total population group for infection, hospitalization and mortality, with adjusted VE of 93·0% (CI:92·6–93·4%), 93·4% (CI:91·9–94·7%) and 91·1% (CI:86·5–94·1%) respectively. VE for infection was lower for participants aged 75 and over, and for those with hypertension, diabetes and obesity.

This study strengthens the evidence that the Pfizer-BioNTech vaccination is effective in preventing infection, hospitalization and mortality.

1. Introduction

A number of vaccines were authorized for emergency use by the U.S. Food and Drug Administration (FDA), after reporting high efficacy and safety results in their respective randomized control trials (RCT) (Fu et al., 2020). Pfizer-BioNTech reported 95% efficacy (CI: 90.3%–97.6%) for their vaccine, with low serious adverse event rates in both the vaccinated and control groups (Polack et al., 2020). The vaccine was initially FDA-approved for ages 16 and over, requiring two doses at a recommended interval of 21 days. After two doses, RCT results indicated a significant divergence in infection rates between the intervention and control group after day seven (FDA, 2020). With an average of two months follow-up from day seven after the second vaccination, only eight new cases of 18,198 infection naïve participants developed symptoms in the intervention group, compared with 162 new cases in a similar population group that received the placebo (Polack et al., 2020).

Israel was among the first countries to implement a national drive to vaccinate its population, employing the mRNA BNT162b2 vaccine, as recommended. All four health maintenance organizations (HMOs) that provide health coverage for all 9.3 million of the population, offered the vaccine free of charge. From 20.12.2020, the vaccine was offered initially to healthcare workers and members aged 60 and over (Rosen et al., 2021), with the target population progressively broadened to include all citizens aged 16 and over by 4.2.2021 (Rossman et al., 2021). At the same time, Israel – like many of the European countries – was experiencing its third wave of the epidemic (Rosen et al., 2021). This

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wave was more severe than previous waves, secondary to the introduction of the B.1.1.7 variant of the SARS-CoV-2 virus into the country (Israel Ministry of Health, 2021), that had a much higher transmissibility than earlier viral forms (Leung et al., 2021; Galloway et al., 2021). The early introduction of the national campaign, combined with the speed with which the majority of the population was vaccinated (end of March), affords Israel the opportunity to evaluate effectiveness of the vaccine for a longer follow-up period than in other countries.

Clalit, the largest HMO in Israel, was the first to report vaccine effectiveness (92%), but with a very short follow-up period (15 days) (Dagan et al., 2021). National population-based data reported 94% vaccine effectiveness for infection with a 45-day follow-up period (Haas et al., 2021). The current study, carried out at Maccabi HealthCare Services (MHC), followed up the vaccine target population for a maximum 98 days. MHC is the second largest HMO in Israel and responsible for the care of over 2.5 million residents. MHC operated 95 vaccination sites across the country, including mobile sites and ambulance transport for homebound patients to reach vaccination sites.

MHC maintains a comprehensive database allowing the HMO to measure vaccine effectiveness in a broad range of population groups. The database includes demographic data, laboratory results, vaccination and hospitalization data of all members, including services not provided directly by the MHC (such as hospitalizations and vaccinations carried out by the ambulance service among nursing home residents). The database also maintains a number of chronic illness registries, based on algorithms incorporating data from multiple sources (medications, tests, diagnoses and procedures), as well as an obesity registry based on routinely recorded height and weight measurements. Persons suffering from chronic illnesses, such as hypertension, diabetes and obesity are at increased risk of Covid-19 infection (Tadic et al., 2020; Peric and Stulnig, 2020; Zhou et al., 2021) and little is known regarding their response to the vaccine.

The main objective of the study was to measure vaccine effectiveness regarding infection, hospitalization and mortality from Sars-Cov-2 virus after adjusting for both person-specific risk variables and virus exposure. The current study provides initial data comparing CoVid-19 incidence rates over a maximum potential 98-day follow-up period.

2. Methods

We conducted a retrospective cohort study based on vaccination, laboratory records and hospital data extracted from the MHC database. The study was approved by the MHC internal review board and by the Helsinki committee (#0178–20-MHS) and exempted from informed consent, after meeting guidelines for the protection of human subjects concerning safety and privacy.

2.1. Study population

The study population included all active HMO members (as of 18.1.2021) aged 16 and over that did not leave the HMO during the study period and had no evidence of prior infection (positive PCR or serology). The study population was divided into two dynamic groups: those who were at least seven days post- second vaccination between 18.1.2021 and 25.04.2021 (herein referred to as the 'vaccinated group'), and those who were not vaccinated (herein referred to as the 'unvaccinated group'). The groups were dynamic, such that people who were initially unvaccinated exited the 'unvaccinated group' on receipt of their first dose and entered the 'vaccinated group' eight days after receiving their second dose, provided that they had not been infected or died in the intervening period. Prior infection was defined for each group as follows: a positive PCR or IgG serology result prior to day eight after second dose of vaccination for the 'vaccinated group' and prior to 18.1.2021 for the 'unvaccinated group'.

Members who had vaccinated with one dose only before the 18.1.2021 and did not receive a second dose by the end of the study period (25.04.2021), and those who had died within seven days of receiving their second dose were excluded from the study.

2.2. Sars-Cov-2 testing

Polymerase chain reaction (PCR) testing is carried out for all HMO members presenting with symptoms or reporting exposure to a confirmed case, free of charge. PCR testing is required for all returning travelers from overseas, anyone who has been in contact with an infected person, or anyone presenting with flu-like symptoms. PCR testing does not require a physician's referral and is carried out upon member request. Serology testing in the general population and among health workers was carried out among sample populations at discrete points in time to assess infection rates (including those asymptomatic) and is carried out in the HMO using a nucleoprotein-based antigen with follow-up chemo-luminescence immunoassay.

2.3. Outcome measures

Outcome measures included Covid-19 infection, hospitalization and mortality. For each group, new PCR positive cases (based on test date), Covid-19-related hospitalizations and deaths were identified. Number of days each member contributed was calculated as follows for each of the outcome variables: for the 'vaccinated group', from day 8 after vaccination to end of study period (25.4.2021) or till date of outcome (positive PCR/hospitalization/death); for the 'unvaccinated group', from 18.1.2021 to end of study period, date of first vaccination or date of outcome.

2.4. Statistical analysis

Crude vaccine effectiveness (VE) rates were calculated as: 1 – (incidence rate in vaccinated/incidence rate in unvaccinated). Incidence rates were calculated as number of outcome events (first positive PCR results/first Covid-19-related hospitalization/Covid-19-related death) per 1000 person-days. Crude outcome VE rates were calculated for each age group, gender, socio-economic status (based on census and national survey classifications applied to home address), presence of hypertension and diabetes (based on registry data) and obesity (BMI $\geq$ 30). To account for risk according to exposure and individuals' characteristics, outcome rates were compared between the two groups within geographical statistical area (GSA) and calendar week using conditional Poisson regression analysis (Armstrong et al., 2014), adjusting for subject-specific variables: age group, gender, presence of hypertension, diabetes and obesity. GSAs (a smaller area unit, as defined by the Central Bureau of Statistics) and calendar week were selected as conditional variables as they reflect risk of infection for a particular neighborhood/area over time. The number of days contributed was calculated for each week and GSA. Adjusted VE rates were calculated as follows: one minus the exponent of the point estimates for vaccine status. Analyses were carried out using R software, version 3.6.2. Packages "gnm" was used to run conditional Poisson models (Turner and Firth, 2020). Confidence intervals (CIs) were calculated using 95% confidence levels.

3. Results

Of all HMO members aged 16 and over with no prior infection as of 18.1.2021 (N = 1,658,604), 7719 members were excluded: 7670 that had only one vaccination dose and 49 who died within seven days of the second dose. Due to the dynamic nature of the study population, participants could contribute to both the 'vaccinated' and 'unvaccinated' groups. Demographic characteristics of the study population (presented in Table 1) have therefore been split into three groups: 'only vaccinated' - those who were already seven days post- second vaccination at the beginning of the study period and therefore contributed all their days to this group, 'became vaccinated' – those who contributed days to both

Table 1
Demographic characteristics of study population by vaccination status, Maccabi HealthCare Services, Israel.

Characteristic	Only vaccinated*	Became vaccinated*	Only unvaccinated*
	N = 575,259	N = 772,717	N = 302,909
Gender			
Female	302,693 (52.62%)	399,047(51.64%)	160,371(52.94%)
Male	272,566 (47.38%)	373,670(48.36%)	142,538(47.06%)
Age Group (years)			
16–44	101,686 (17.68%)	550,538(71.25%)	195,313(64.48%)
45–59	190,838 (33.17%)	175,277(22.68%)	61,007(20.14%)
60–74	208,725 (36.28%)	35,568(4.6%)	31,603(10.43%)
75+	74,010(12.87%)	11,334(1.47%)	14,986(4.95%)
SES			
Low	68,710(11.94%)	146,347(18.94%)	97,674(32.25%)
Middle	280,615 (48.78%)	390,498(50.54%)	152,572(50.37%)
High	225,934 (39.28%)	235,872(30.53%)	52,663(17.39%)
Health Status			
Hypertension	201,292 (34.99%)	64,134(8.3%)	37,984(12.54%)
Diabetes	92,369(16.06%)	27,846(3.6%)	16,562(5.47%)
Obese	135,486 (23.55%)	109,120(14.12%)	45,692(15.08%)

* Population group to which the individual member contributed to, wherein the 'only vaccinated' contributed only to the vaccinated population, the 'became vaccinated' contributed days to both the unvaccinated and vaccinated group and the 'only unvaccinated' contributed only to the unvaccinated group.

the 'unvaccinated' and 'vaccinated' groups (presented for vaccination later and therefore reached day eight post-second vaccination during the study period), and 'only unvaccinated' – those who had not vaccinated (no dose) by the end of the study period.

Of the 1,650,885 study participants, 34.9% were in the 'only vaccinated' group, 46.8% 'became vaccinated' during the study period and 18.3% were in the 'only unvaccinated' group. The 'only vaccinated' participants were more likely to be older than those in the other two groups, and thus also more likely to have hypertension, diabetes and suffer from obesity. Though somewhat younger, the demographic and health characteristics of the 'became vaccinated' group were more analogous to the 'only vaccinated' than the 'only unvaccinated' groups. The 'only unvaccinated' group were more likely to come from a lower socioeconomic bracket than those vaccinated (either group).

Of the total study population, 1.7% (N = 28,042) became PCR positive during the study period, of whom 3.7% were hospitalized (N = 1047) and 0.5% died (N = 164). Infection, hospitalization and mortality incidence rates between the 'vaccinated' and 'unvaccinated' groups are presented in Table 2. Incidence rates for all three outcomes were much lower for the 'vaccinated group' than the 'unvaccinated group'. The 'vaccinated group' had on average 23 days more follow-up than the 'unvaccinated group' (Table 2). This is attributed to the relatively short number of days that those who 'became vaccinated' during the study period contributed to the 'unvaccinated group' before getting their first vaccination.

Crude vaccine effectiveness rates for all three outcome measures are presented in Table 3 and adjusted coefficient estimates presented in Table 4. Adjusted VE rates for infection, Covid-19-related hospitalization and Covid-19-related mortality were 93.0% (CI: 92.6–93.4), 93.4% (CI: 91.9%–94.7%) and 91.1% (CI: 87%–94%) respectively. Incidence of infection decreased with increasing age, but was higher for people suffering from diabetes and obesity. Crude VE for infection decreased by increasing age, but remained above 90% for those under the age of 75

Table 2
Covid-19 infection, hospitalization and mortality rates in study population by vaccination status, 18.1.2021–25.4.2021, Maccabi HealthCare Services, Israel.

Measure	Vaccinated population	Unvaccinated population
	N = 1,347,976	N = 1,075,626
Mean follow-up days (SD)*	63.3 (22.15)	40.5 (33.95)
Median follow-up days (min, max)*	64 (1,98)	28 (1,98)
Number infected (PCR positive)	1410	26,632
Proportion infected / 1000 persons	1.05	24.76
Incidence infection rate (cases/1000 person-days)	0.017	0.61
Number hospitalized	105	942
Proportion hospitalized / 1000 persons	0.078	0.876
Incidence hospitalization rate (hospitalized/1000 person-days)	0.001	0.018
Number deaths	33	131
Proportion died / 1000 persons	0.02	0.12
Mortality incidence rate (deaths/1000 person-days)	0.0004	0.0025

* For infection rate analysis.

(crude and adjusted rates). Adjusted VE for infection was 94.7% for the 16–44 age group and dropped to 84.0% for the 75+ age group. Adjusted VE for infection for the 70+ age group was calculated as 89.1% (CI:83%–93%). From the results of the conditional Poisson model, when the interaction of age with vaccine status was included (Table 4) vaccine effectiveness was 11% lower for those aged 75 and above compared to the youngest age group (16–44). For both hospitalization and mortality, the variation in vaccine effectiveness by age group was not significant, but this may be attributed to the small number of cases (Tables 3 & 4). For all three outcomes, males had consistently lower VE rates (crude and adjusted) than females, however, these differences were not significant (Table 4).

Adjusted VE rates for infection were lower for study participants with hypertension (89.7%, CI:88.6–91.7), diabetes (88.9%, CI: 87.3–90.2) and obesity (89.7%, 88.6–90.7) than total population VE for infection (93%, CI: 92.6–93.4). VE point estimates for hospitalization and mortality among those with hypertension, diabetes or obesity were not appreciably different from total population VE.

4. Discussion

In this study of over 1.6 million participants, Pfizer-BioNTech VE for infection adjusted for gender, age, hypertension, diabetes and obesity and conditioned on GSA and calendar week was 93% (CI:92.6–93.4). Based on an average follow-up period of 63 days for the two-dose vaccinated population and 40 days for those not vaccinated, the infection rates found here are slightly lower than those reported in the original Pfizer RCT (95% (CI: 90.3–97.6) with an average of 2 months follow-up) (Polack et al., 2020) but comparable with those of Clalit, another HMO in Israel (92% (CI: 88–95) with a maximum 15 day follow-up) (Dagan et al., 2021) and national data (94.1%, CI: 93.4–94.7) (Haas et al., 2021).

Adjusted VE for hospitalization in this study was 93.4% (CI:91.9%–94.7%). The Clalit study (Dagan et al., 2021) reported lower adjusted VE point estimates for hospitalization (87%, CI: 55%–100%). We suggest that the Clalit data under-estimate VE for hospitalization as a result of the small number of cases in the short time period available for analysis. National data (Haas et al., 2021), adjusted for age, gender and calendar week with a maximum follow-up period of 41 days reported a higher VE for hospitalization (96.2%, CI: 95.5–96.8) than the present study. We suggest that the inclusion of GSA in our model for adjustment of exposure, controlling for chronic illness conditions and the longer follow-up period, provides a more accurate estimate of VE for hospitalization.

Adjusted VE for mortality in this study was 91.1% (CI: 86.5%–94.1%). The initial Pfizer RCT (Polack et al., 2020) reported six deaths

Table 3
Crude incidence rates by selected demographic and crude vaccine effectiveness (VE) in study population by vaccination status, 18.1.2021–25.4.2021, Maccabi HealthCare Services, Israel.

Outcome	Population	Vaccinated group		Unvaccinated group		VE (CI)
		Cases / N (%)	Incidence rate/1000 person-days	Cases / N (%)	Incidence rate/1000 person-days	
Covid-19 infection	Total population	1410/1347974 (0·1%)	0·017(85367633)	26,632/1074275 (2·48%)	0·612(43548556)	0·972(0·971, 0·974)
	Females	723/701738(0·1%)	0·016(44301847)	14,543/558661 (2·6%)	0·631(23036470)	0·975(0·973, 0·976)
	Males	687/646236 (0·11%)	0·017(41065786)	12,089/515620 (2·34%)	0·589(20512086)	0·971(0·969, 0·973)
	16–44 years	378/650004 (0·06%)	0·011(33396806)	20,160/744834 (2·71%)	0·673(29952051)	0·984(0·982, 0·985)
	45–59 years	435/367678 (0·12%)	0·017(25077190)	4610/236005(1·95%)	0·564(8177652)	0·97(0·967, 0·973)
	60–74 years	393/244744 (0·16%)	0·02(19943541)	1388/67130(2·07%)	0·369(3766187)	0·946(0·939, 0·952)
	75+ years	204/85549(0·24%)	0·029(6950096)	474/26311(1·8%)	0·287(1652666)	0·899(0·881, 0·914)
	Hypertension	294/120575 (0·24%)	0·032(9329714)	1102/44404(2·48%)	0·533(2066733)	0·94(0·932, 0·947)
	Diabetes	512/266417 (0·19%)	0·025(20525175)	2156/102108(2·11%)	0·451(4779689)	0·945(0·939, 0·95)
	Obesity	405/244837 (0·17%)	0·024(16795802)	4369/154789(2·82%)	0·694(6294289)	0·965(0·962, 0·969)
Covid-19 hospitalization	Total population	105/1353847 (0·01%)	0·001(85846734)	942/1162033(0·08%)	0·018(52753054)	0·944(0·932, 0·955)
	Females	43/704587(0·01%)	0·001(44537129)	478/601350(0·08%)	0·017(27675270)	0·941(0·92, 0·957)
	Males	62/649260(0·01%)	0·002(41309605)	464/560689(0·08%)	0·019(25077784)	0·895(0·863, 0·919)
	16–44 years	6/652429(0%)	0(33563279)	312/803504(0·04%)	0·009(36431271)	–
	45–59 years	15/369323(0%)	0·001(25216862)	261/256605(0·1%)	0·026(10155430)	0·962(0·935, 0·977)
	60–74 years	28/245923(0·01%)	0·001(20058792)	200/74179(0·27%)	0·046(4383957)	0·978(0·968, 0·985)
	75+ years	56/86172(0·06%)	0·008(7007801)	169/27750(0·61%)	0·095(1782396)	0·916(0·886, 0·938)
	Hypertension	20/463454(0%)	0·001(31348964)	66/302181(0·02%)	0·006(10482442)	0·953(0·935, 0·967)
	Diabetes	60/673900(0·01%)	0·001(42356338)	472/580830(0·08%)	0·018(26284928)	0·951(0·937, 0·962)
	Obesity	25/216494(0·01%)	0·002(12141432)	404/279205(0·14%)	0·025(15985684)	0·976(0·962, 0·984)
Covid-19 mortality	Total population	33/1354444(0%)	0·0004(85894784)	131/1166487(0·01%)	0·0025(53150685)	0·84(0·766, 0·891)
	Females	23/649557(0%)	0·0002(44561168)	75/562886(0·01%)	0·0020(27881504)	0·9(0·804, 0·949)
	Males	10/704887(0%)	0·0006(41333616)	56/603607(0·01%)	0·0030(25269181)	0·8(0·681, 0·875)
	16–44 years	0/652535(0%)	0(33570019)	5/805124(0%)	0(36582830)	–
	45–59 years	0/369422(0%)	0(25224360)	15/257786(0·01%)	0·001(10263103)	–
	60–74 years	8/246077(0%)	0·0004(20071813)	40/75249(0·05%)	0·0089(4473540)	0·955(0·904, 0·979)
	75+ years	25/86410(0·03%)	0·0036(7028592)	71/28333(0·25%)	0·0388(1831212)	0·907(0·854, 0·941)
	Hypertension	18/121521(0·01%)	0·0019(9419554)	59/50100(0·12%)	0·0228(2581586)	0·917(0·859, 0·951)
	Diabetes	26/268205(0·01%)	0·0013(20691931)	90/112791(0·08%)	0·0156(5755391)	0·917(0·871, 0·946)
	Obesity	2/246346(0%)	0·0001(16929075)	5/172373(0%)	0·0006(8047035)	0·833(0·141, 0·968)

(two in the intervention group and four in the control group) but deemed all deaths to be unrelated to the vaccine. We have been able to present here mortality data that is illness-specific that perhaps reflects a more realistic assessment of mortality risk. In the national study (Haas et al., 2021), VE rates reported for mortality were slightly higher (93.3%, CI: 91.5–94.8) than those reported here. Clalit reported adjusted VE for severe disease (defined as severe disease or death) as 92%(CI:75%–100%) (Dagan et al., 2021).

The elderly population are at higher risk of morbidity and mortality from Sars-Cov-2 infection (Salzberger et al., 2021) and one of the greatest concerns regarding the vaccine is that it would be less effective in the elderly population (Soiza et al., 2021). We found that adjusted VE for infection was in fact lower in the 75+ age group (81%) than for those under age 75 (90 + %), with a VE for infection of 89% (CI: 83%–93%) for those aged 70 and over. Dagan et al., 2021[9] reported adjusted VE rates for infection of 95% (CI:87%–100%) for the 70+ age group. Their study excluded members from nursing homes, the homebound and those presenting to the healthcare system within three days. These groups were not excluded in this study. Inclusion of these population groups, and the longer follow-up period eight-plus days post- second vaccination may account for the lower VE for infection in this study.

Hypertension (Tadic et al., 2020), diabetes (Peric and Stulnig, 2020) and obesity (Zhou et al., 2021) have all been established as risk factors for Sars-Cov-2 infection. Independent of age, we wished to determine if

Table 4
Exponents of coefficients for infection, hospitalization and mortality, adjusted for sex, age group and morbidity, and conditioned on GSA and calendar week (using Conditional Poisson model) 18.1.2021–25.4.2021, Maccabi HealthCare Services, Israel.

Outcome	Variable	Without interaction	Sex	Age Group	Hypertension	Diabetes	Obesity
Infection	Vaccinated	***0·070	***0·066	***0·053	***0·059	***0·064	***0·066
	Sex(M)	***0·913	***0·908	***0·911	***0·912	***0·912	***0·913
	45–59	***0·910	***0·910	***0·913	***0·919	***0·915	***0·911
	60–74	***0·625	***0·625	***0·595	***0·625	***0·626	***0·625
	75 ≤	***0·577	***0·577	***0·945	***0·576	***0·579	***0·578
	Hypertension	*0·945	*0·945	*0·950	***0·878	*0·945	*0·944
	Diabetes	***1·124	***1·123	***1·125	***1·122	1·027	***1·121
	Obesity	***1·147	***1·147	***1·149	***1·150	***1·149	***1·132
	Vaccinated Male		1·111				
	Vaccinated 45–59			*1·163			
	Vaccinated 60–74			***1·600			
	Vaccinated 75 ≤			***2·996			
	Vaccinated Hypertension				***1·745		
	Vaccinated Diabetes					***1·755	
	Vaccinated Obesity						**1·218
Covid-19-related hospitalization	Vaccinated	***0·068	***0·058	***0·051	***0·050	***0·064	***0·090
	Sex(M)	***1·260	**1·231	***1·252	***1·256	***1·259	***1·263
	45–59	***2·622	***2·621	***2·688	***2·664	***2·627	***2·580
	60–74	***3·605	***3·601	***3·783	***3·675	***3·614	***3·540
	75 ≤	***8·112	***8·100	***7·09	***8·265	***8·134	***7·939
	Hypertension	***1·348	***1·347	***1·351	***1·276	***1·348	***1·717
	Diabetes	***1·715	***1·712	***1·719	***1·717	***1·695	***1·346
	Obesity	***1·347	***1·347	***1·351	***1·350	***1·348	***1·491
	Vaccinated Male		1·254				
	Vaccinated 45–59			0·795			
	Vaccinated 60–74			0·864			
	Vaccinated 75 ≤			2·37			
	Vaccinated Hypertension				*1·550		
	Vaccinated Diabetes					1·086	
	Vaccinated Obesity						***0·354
Covid-19-related mortality	Vaccinated	***0·089	***0·082	0	***0·089	***0·087	***0·087
	Sex(M)	***1·902	***1·852	***1·879	***1·902	***1·901	***1·901
	45–59	***10·062	***10·067	***10·851	***10·062	***10·092	***10·089
	60–74	***49·270	***49·299	***51·024	***49·264	***49·507	***49·417
	75 ≤	***208·388	***208·138	***189·483	***208·381	***209·351	***209·181
	Hypertension	***2·108	***2·104	***2·109	***2·108	***2·110	***2·110
	Diabetes	***2·692	***2·689	***2·687	***2·692	***2·657	***2·694
	Obesity	***0·070	***0·070	***0·070	***0·070	***0·070	***0·060
	Vaccinated Male		1·149				
	Vaccinated 45–59			0·091			
	Vaccinated 60–74			Inf.			
	Vaccinated 75 ≤			Inf.			
	Vaccinated Hypertension				1		
	Vaccinated Diabetes					1·061	
	Vaccinated Obesity						1·926

Si Significance codes: *** < 0·001, ** < 0·001, * < 0·05.

VE was lower for these conditions. It has been suggested that both Covid-19 infection and mRNA-based vaccines promote an ACE2 platelet receptor imbalance (Angeli et al., 2021) and poorer sero-conversion in these population groups (Watanabe et al., 2021). We found that presence of any of these conditions is accompanied by a lower adjusted VE for infection. Adjusted VE rates for infection for participants with these conditions in this study were consistently lower here than those reported by Dagan et al. (2021) (Dagan et al., 2021) (hypertension: 89.7% vs 93%, diabetes: 88.9% vs 91%, obesity: 89.7% vs 95%). Again, we suggest that our data reflect general population VE, given the minimal exclusion criteria.

The results presented here measured vaccine effectiveness at a time when the British (alpha) variant was predominant in Israel. After implementing the national vaccination drive, infection rates dropped to very low levels (Leshem and Wilder-Smith, 2021), until the introduction of the delta variant in Israel. Test-negative case-control studies comparing BNT162b2 efficacy by variant have shown comparable (Nasreen et al., 2021) or slightly lower VE rates (Lopez Bernal et al., 2021) against infection among those infected with the delta variant compared to those infected with the British variant.

Mehrota et al. (2021) (Mehrotra et al., 2020) suggest a number of clinical endpoints for evaluating the effectiveness of the Covid-19 vaccines: symptomatic infection, burden of infection (proportion with high morbidity/mortality) and asymptomatic infection. In this study, infection was identified by PCR results, irrespective of reported symptoms. In most cases, it can be assumed that the test was carried out secondary to symptom presentation. However, an unknown number of those tested will have done so for other reasons, such as exposure to an infected individual, prior to medical procedure or travel overseas. Asymptomatic illness has been estimated as 20% (Izda et al., 2021). While the VE for infection in this study may capture a proportion of this population group, it is likely to be small. Length of follow-up period is also an important component of measuring vaccine effectiveness, where the literature ideally recommends two years of follow-up (Mehrotra et al., 2020). IgG antibodies typically drop dramatically after 16 months with non-activated viral vaccines (Izda et al., 2021).

This study provides data on a longer follow-up period but only long-term studies with alternate methodology will be able to shed light on length of protection the mRNA BNT162b2 vaccine provides. As pointed out in other studies where national drives were implemented to vaccinate the population quickly (Dagan et al., 2021), the longer the follow-up period, the greater the difficulty in finding an adequately matched unvaccinated population. Over 86% of the 60+ population in Israel have been fully vaccinated to date (Israel Ministry of Health, 2021). Those

that have not been vaccinated are likely to include those that had been infected with the illness (and therefore not eligible for two dose vaccination according to current protocol), or unwilling to vaccinate. Those unwilling to vaccinate may be different in their use of healthcare and preventive services.

As an observational study, differences between those presenting for vaccination and those that did not, cannot be fully accounted for. Factors not included in the model here may have introduced bias, such as presence of heart disease and other chronic illnesses, and health worker employee status. Furthermore, PCR tests were performed upon request, most commonly because of accompanying symptoms. Asymptomatic members, unaware of their infection status, are less likely to have been tested and thus included in the study. Their inclusion in the seemingly unprotected 'unvaccinated' group would reduce infection incidence for that group, whilst their inclusion in the 'vaccinated group' may inflate VE estimates.

Finally, in our study we included MHC members only, who tend to be younger and come from a higher socioeconomic bracket compared to general population in Israel. However, given the similar findings in Clalit, an HMO with a larger elderly and lower socio-economic bracket population encourages us to assume that the impact on VE may be minimal.

5. Conclusions

This large observational study is based on an HMO population with few exclusion criteria. Our findings showed high vaccine effectiveness rates for the total population, with slightly lower rates for the elderly and those suffering from hypertension, diabetes or obesity. Our findings are slightly lower than those published by the manufacturer of the vaccine (based on a more restricted population group) but comparable with a study from another large HMO and national data. This study confirms earlier findings that the mRNA BNT162b2 vaccine provides high levels of protection to all major segments of the population, including the elderly. Whilst vaccination does not eliminate the risk of hospitalization or death, the risks are significantly reduced. Physicians should encourage vaccination in the general population. Continued follow-up is required to determine long term effectiveness of the vaccine.

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