EBioMedicine 72 (2021) 103574

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Research Paper

The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data

Aharona Glatman-Freedman[a,b,*], Michal Bromberg[a,b], Rita Dichtiar[a], Yael Hershkovitz[a], Lital Keinan-Boker[a,c]

[a] The Israel Centre for Disease Control, Israel Ministry of Health, Tel Hashomer, Ramat Gan, Israel
[b] Department of Epidemiology and Preventive Medicine, School of Public Health, Tel Aviv University Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] School of Public Health, Haifa University, Haifa, Israel

ARTICLE INFO

Article History:
Received 21 July 2021
Revised 21 August 2021
Accepted 22 August 2021
Available online xxx

Keywords:
Vaccine effectiveness
SARS-CoV-2
COVID-19
Breakthrough cases

ABSTRACT

Background: The rapid vaccination campaign against COVID-19 in Israel relied on the BNT162b2 vaccine. We performed a longitudinal analysis of multiple cohorts, using individual data, to evaluate the effectiveness of the vaccine against new and breakthrough cases.
Methods: We estimated vaccine effectiveness (VE) for 27 consecutive cohorts, each comprised of individuals vaccinated on specific days. VE against new COVID-19 cases was evaluated for five SARS-CoV-2-related outcomes: infection, symptomatic disease, hospitalisation, severe/critical disease and death. For breakthrough cases, rate reduction was evaluated for hospitalisation, severe/critical disease and death. Outcomes were evaluated at predetermined time-periods after vaccination, the last one dedicated to individuals who became SARS-CoV-2-positive 22–28 days after the second dose.
Findings: The highest VE estimates against new cases in ≥16 year old individuals, for all outcomes, were reached at the 15–21 day period after the second dose, ranging between 97.7% (95% CI: 95.9–98.7%) for deaths and 98.6% (95% CI: 97.8–99.1%) for severe/critical disease. VE estimates of the 14–20 day period after the first dose ranged between 54.3% (95% CI: 50.6–57.8%) for infection and 77.3% (95% CI: 71.2–82.1%) for severe/critical disease. VE rose more slowly among ≥80 year old individuals. Rate reductions of breakthrough complications were highest at the 22–28 day period after the second dose, ranging between 47.4% (95% CI: 4.3–71.2%) for death and 66.2% (95% CI: 44.2–79.6%) for severe/critical disease.
Interpretation: The BNT162 vaccine is highly effective in preventing new SARS-CoV-2 cases. Among ≥80 year old individuals, high effectiveness develops more slowly. In breakthrough cases, vaccination reduces complications and death.
Funding: None.

1. Introduction

Several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were granted Emergency Use Authorisation (EUA) by the Food and Drug administration (FDA) and Conditional Marketing Administration (CMA) by the European Medicines Agency (EMA) [1,2].

Israel initiated its public vaccination campaign against SARS-CoV-2 on December 20, 2020, prioritising first health care workers, individuals 60 years old and above, and individuals residing in long-term care facilities. As the vaccination campaign progressed, additional age groups and priority groups were gradually vaccinated as well. The Public vaccination campaign relied on the BNT162b2 vaccine. By May 21, 2021, a total of 5,439,734 individuals received the first dose, and 5,112,516 individuals received the second dose of the BNT162b2 vaccine. These constitute 58.4% and 54.9% of the entire Israeli population and 83.2% and 78.2% of the Israeli population ≥16 years of age, respectively, placing Israel as a leading country in population vaccine coverage [3].

The efficient vaccination rollout in Israel led to rapid changes in vaccine coverage, as well as changes in viral circulation. As such, monitoring vaccine effectiveness (VE) estimates over time, among individuals that were vaccinated on particular dates and were subjected to similar external conditions, such as vaccine coverage and

* Corresponding author at: The Israel Centre for Disease Control, Israel Ministry of Health, Tel Hashomer, Ramat Gan, Israel.
E-mail address: aharona.freedman@moh.gov.il (A. Glatman-Freedman).

https://doi.org/10.1016/j.ebiom.2021.103574

Research in context

Evidence before this study

A rapid BNT162b2 mRNA vaccination campaign started in Israel on December 20, 2021. The vaccine was reported to be highly effective against symptomatic laboratory-confirmed COVID-19 in a randomised controlled trial and was approved initially for use in individuals aged 16 years and older. We searched Pubmed and preprint servers for articles published between December 11, 2020 (date of first Emergency Use Authorisation by the FDA) and July 21, 2021, to identify reports of the effect of the BNT162b2 vaccine in prevention of new COVID-19 cases and on the outcome of disease diagnosed among individuals who had received the BNT162b2 vaccine. While studies estimating the effectiveness of the BNT162b2 vaccine were reported, a nationwide evaluation of the precise dynamics of vaccine effectiveness estimates over time following the administration of one or two vaccine doses, across multiple age groups and multiple outcomes, using multiple cohorts at well-defined one-week evaluation periods was not reported to-date. Furthermore, no studies evaluated the effect of SARS-CoV-2 vaccines on the outcome of disease diagnosed among individuals who were vaccinated.

Added value of this study

Our analysis, which was based on nationwide individualised data recorded in designated national repositories, followed multiple cohorts. It demonstrated modest effectiveness with high variability after the first vaccine dose and high effectiveness with low variability after the second vaccine dose against five SARS-CoV-2-related outcomes: infection, symptomatic disease, hospitalisation secere/critical disease and death. Moreover, our analysis demonstrated for the first time, the reduction in SARS-CoV-2-related hospitalisations, severe/critical disease and death among individuals who became SARS-CoV-2-positive following the receipt of one or two BNT162b2 vaccine doses. Finally, our study demonstrates for the first time, that vaccine effectiveness estimates rise more slowly among individuals 80 years old and above. Each cohort was followed-up for up to 68 days after the second dose.

Implications of all the available evidence

The high effectiveness of the BNT162b2 vaccine against SARS-CoV-2-related outcomes, coupled with the growing number of SARS-CoV-2 hotspots around the world, highlights the urgency of making the COVID-19 vaccines available worldwide. The reduction of severe SARS-CoV-2-related outcomes among breakthrough cases provides further support for the importance of vaccination. The slower rise in vaccine effectiveness among individuals 80 years old and older, suggests considering them fully vaccinated later than younger individuals.

virus circulation, is important. Although a study based on the Israel national database evaluating VE following the administration of two vaccine doses, was recently reported, it was performed using aggregate rather than individual data, and did not evaluate discrete time periods following each vaccine dose [4].

Moreover, a comprehensive analysis of the effect of the vaccine on individuals who became SARS-CoV-2-positive despite being vaccinated (breakthrough cases), in terms of hospitalisations and death reduction, has not been reported to date.

In randomised clinical trials the BNT162b2 vaccine demonstrated 52% and 95% vaccine efficacy after the first and second vaccine doses, respectively, in individuals ≥16 years old [5]. Characterising the effectiveness of the BNT162b2 vaccine is of utmost importance, because it provides information on the performance of the vaccine under real-life circumstances. Multiple factors can potentially affect the performance of the BNT162b2 vaccine, among them, demographics, usage in patients with multiple or unstable chronic medical conditions, inadequate vaccine storage or transport conditions [6], varying degrees of SARS-CoV-2 in the population, variations in vaccine coverage and the appearance of new genomic variants [7–12].

The purpose of this study was to evaluate the effectiveness of the BNT162b2 vaccine against new cases and against complications of breakthrough SARS-CoV-2 cases by performing a retrospective longitudinal multiple cohort study, using national data of the mass BNT162b2 vaccination campaign. We analysed the dynamics of vaccine effectiveness against multiple outcomes over time, for ≥16 year old individuals and by age groups.

2. Methods

2.1. Study setting

Israel is a country with a population of 9.3 million [13]. It has universal health coverage provided to all residents by four Health Maintenance Organisations (HMOs). The BNT162b2 vaccine has been administered in Israel by these four HMOs, by medical centres, long-term care facilities, emergency medical services and the armed forces. Individuals who had a documented positive SARS-CoV-2 test or an MOH-approved SARS-CoV-2 serology test confirming past infection, were not eligible to receive the vaccine initially. Each SARS-CoV-2 vaccine administration and all SARS-CoV-2 Polymerase Chain Reaction (PCR) test results have been registered electronically into two separate designated national databases. Both SARS-CoV-2 PCR testing and vaccines have been provided free of charge.

2.2. Study design

We performed a retrospective longitudinal cohort study, using two MOH national databases: the SARS-CoV-2 vaccine database and the SARS-CoV2 tests database. The national SARS-CoV-2 vaccine database includes the name and lot number of the vaccine administered and the date of administration for each individual. The national SARS-CoV2 PCR tests database includes the results of each test performed, the date of testing, and the date of results for each individual. It also included the presence or absence of symptoms, date of hospitalisation, severity of illness and date of death, if applicable.

Each resident in Israel has a unique personal identity number (UPIN), which was used in both databases. Data retrieved from both databases, were cross-referenced by using individuals' twice-encrypted UPINs; thus, the study database was fully-de-identified to the researchers.

The analyses of this study were performed on 27 consecutive cohorts. Analyses for the first vaccine dose were performed for cohorts that received the first vaccine dose from 21 December 2020 to 16 January 2021 (Fig. 1A). Analyses for the second vaccine dose were performed for individuals who received the second dose from January 11 to February 6, 2021 (Fig. 1A).

Our analysis included two main steps. The first step consisted of determining VE against specific outcomes for 27 cohorts, during specific time-periods following the receipt of the first and second doses. The second step included analysis of rate reductions of specific outcomes for cohort individuals who became SARS-CoV-2-positive following the first or second vaccine dose (breakthrough cases).

Vaccine effectiveness estimation. Individuals included in the analysis were Israeli residents without a documented PCR-confirmed

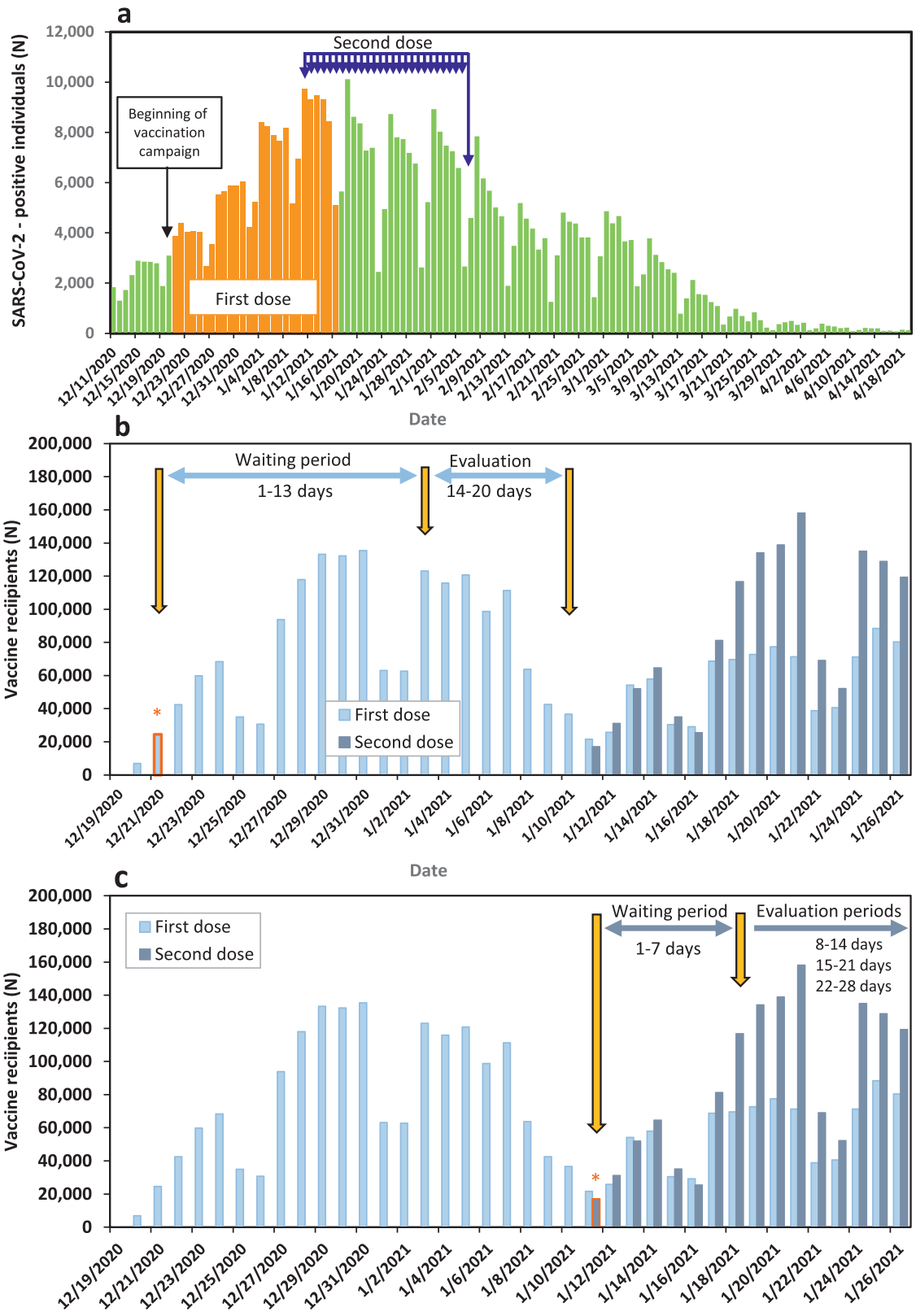

Fig. 1. **a.** Epidemic curve of SARS-CoV-2 cases in Israel, with highlights of vaccination dates for the 27 cohorts of our study. **b.** Graphic representation of the first vaccine dose VE evaluation process for an individual cohort. The panel presents cohort No. 1 that received the first dose on 21 December 2020. Light blue bars represent the number of individuals who received the first vaccine dose each day; Orange asterix represents the date the first-dose cohort No. 1 received the first vaccine dose. C. Graphic representation of second dose VE evaluation process of an individual cohort. The panel presents cohort No. 1 that received the second dose on January 11, 2020. Dark blue bars represent the number of individuals who received the second vaccine dose each day; Orange asterix represents the date the second-dose cohort No. 1 received the second vaccine dose (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

SARS-CoV-2 test prior to the evaluation periods. VE was determined for ≥16 year old individuals and for pre-determined age group (16–39, 40–59, 60–79 and ≥80 years old).

VE was evaluated against the following in laboratory-confirmed SARS-CoV-2 outcomes: infection, symptomatic disease, hospitalisations, severe/critical disease severity and death. This analysis was performed on each of the selected 27 cohorts and for all of them combined (combined VE). VE against laboratory-confirmed SARS-CoV-2 related outcomes were estimated for individuals who became SARS-CoV-2-positive during the following four evaluation periods: days 14-20 after receipt of the first dose (first dose evaluation period) (Fig. 1B) and days 8–14, 15–21 and 22–28 after receipt of the second dose (second dose evaluation periods) (Fig. 1C). Days 1-13 after the first dose and 1-7 after the second dose were designated 'waiting periods' (Fig. 1B, 1C).

For VE estimation against hospitalisations, severe/critical disease and death, the time-period allotted for their occurrence following the first positive PCR test were determined based on frequency histograms (Fig. S4).

Disease severity was determined based on the National Institutes of Health guidelines [14].

The number of individuals in the 'unvaccinated group' for each cohort was derived by omitting the following individuals from the total number of Israeli residents [15]: individuals who had a documented PCR-confirmed SARS-CoV-2 test prior to the evaluation period, individuals who were vaccinated before and on the relevant vaccination date, and during the relevant waiting period. Individuals who were vaccinated on a cohort vaccination date, during the cohort waiting period and the cohort evaluation period were moved to the 'vaccinated group' of another cohort based on their vaccination date.

The number of Israeli residents (total, by age, by sex) was based on the 2020 Central Bureau of Statistics (CBS) statistical abstract [15].

Inclusion and criteria for VE analysis are summerised in Tables S1-S4 of the supplementary index.

Hospitalisations, severe/critical disease and death among SARS-CoV-2-positive vaccinated individuals. Rates of SARS-CoV-2-related hospitalisations, severe/critical disease and death were determined for vaccinated individuals belonging to the 27 cohorts of the first vaccine dose and the second vaccine dose who became SARS-CoV-2-positive by PCR during the evaluation periods detailed above (breakthrough cases), and were compared to those of unvaccinated individuals. The time-periods allotted for the appearance of these outcome following the first positive PCR test were based on frequency histograms (Fig. S4) as described above, and adjusted rate reductions (1-RR) were calculated for each.

2.3. Statistics

VE and 95% confidence interval was estimated using (1-IRR)x100 where IRR, the Incidence Rate Ratio, represents the ratio of PCR-confirmed SARS-CoV-2 cases rate in the vaccinated group to the equivalent rate in the unvaccinated control group.

For individuals with more than one positive SARS-CoV2 test during the evaluation period, only the first one was considered in the analysis.

Individuals who had a positive SARS-CoV-2 PCR test prior to the evaluation periods were excluded from analysis, irrespective of whether or not they were vaccinated with the BNT162b2 vaccine or not. The number of unvaccinated controls for each cohort was calculated by omitting the number of Israeli residents who received the relevant BNT162b2 vaccine dose on the cohort vaccination date from the total number of Israeli residents that did not have a documented positive SARS-CoV-2 test by that date. In addition, the number of person-days each individual contributed as unvaccinated during each evaluation period was calculated. Thus, individuals who belonged to the 'unvaccinated' group on the cohort vaccination date, but received the BNT162b2 vaccine during the evaluation period, were transferred to the 'vaccinated group' of a new cohort based on their vaccination date. The person-days they contributed to the evaluation period prior to their vaccination date were included in those of the unvaccinated group.

The number of Israeli residents (total, by age, by gender) was based on the 2020 Central Bureau of Statistics (CBS) statistical abstract [15].

The VE was calculated for each cohort for the evaluation periods determined in the study design.

To calculate combined VE, the following steps were taken: A. The number of vaccinated/unvaccinated SARS-CoV-2 positive cases for each outcome of each evaluation period was summed. B. The number of person-days each individual was vaccinated/unvaccinated, without becoming SARS-CoV-2-positive, were counted once for all 27 cohorts. The number of days in which each individual was vaccinated/unvaccinated without becoming SARS-CoV-2-positive for each cohort during an evaluation period were summed to give the number of person-days in the vaccinated/unvaccinated status of individuals included in all 27 cohorts.

IRR was then determined for the 27 cohorts combined.

Reduction in SARS-CoV2 hospitalisations, illness severity during hospitalisations and mortality in individuals who received the BNT162b2 vaccine were evaluated using 1- IRR.

IRR and 95% confidence interval (95% CI) were adjusted for age-group (16–19, 20–29, 30–39,40–49,50–59, 60–69, 70–79 and ≥80 years old), sex, and calendar week of vaccination by using Poisson regression. The offset of the Poisson regression was the number of vaccinated individuals for the SARS-CoV-2 positive vaccinated cases, and number of unvaccinated individuals for the SARS-CoV-2-positive unvaccinated individuals, included in the analysis. In cases of over dispersion, negative binomial regression was used. Adjustment for fewer variables was performed as required by the data size.

Statistical analysis was performed using SAS Enterprise Guide 7.1 (SAS Institute Inc.) software.

Our study followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines [16].

2.4. Ethics

The study was approved by the superior ethical committee of the Israel MOH, under Helsinki protocol number CoR-MOH-081-2021, and included exemption from informed consent.

2.5. Role of the funding source

Not relevant.

3. Results

3.1. Vaccination campaign

The progress of two-dose vaccine coverage by age group is demonstrated in Fig. S1. It is consistent with age prioritisation by the MOH, with individuals ≥60 years old being the first to reach and surpass vaccine coverage of ≥60 %.

Fig. 1A demonstrates the epidemic curve of SARS-CoV-2- positive cases in Israel, highlighting the dates for the first vaccine dose and the dates of the second vaccine dose for the cohorts evaluated.

3.2. Vaccine effectiveness for ≥16 year old individuals

VE against laboratory-confirmed SARS-CoV-2-related outcomes were determined for ≥16 year old individuals. Based on frequency histograms (Figs. S4. A and S4. B), hospital admissions and severe/critical disease among SARS-CoV-2 cases were counted for up to

Figure 2

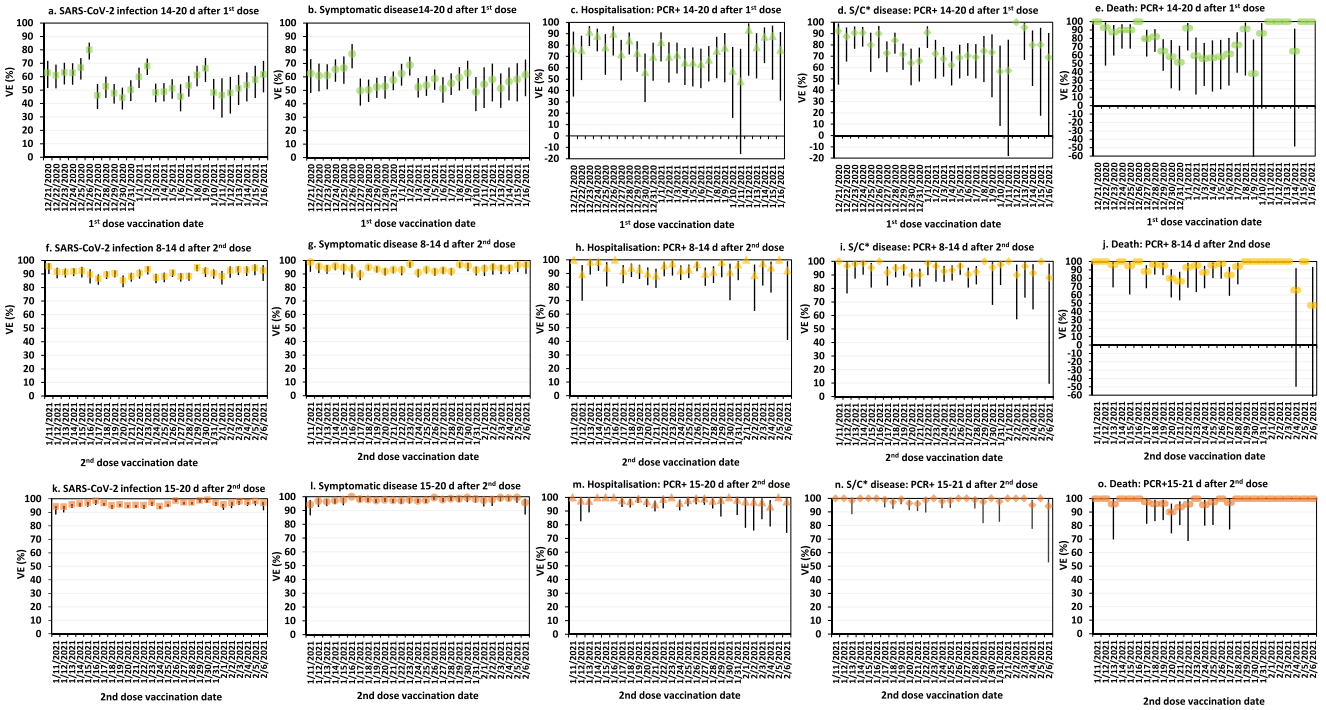

Fig. 2. Adjusted vaccine effectiveness and 95% CI of 27 cohorts against SARS-CoV-2-associated infection (panels a, f, k), symptomatic disease (panels b, g, l), hospitalisations (panels c, h, m), severe/critical disease (panels d, i, n) and death (panels e, j, o). Panels a-e represent outcomes that occurrred on days 14–20 after the first vaccine dose; panels f–j represent outcomes that occurred 8–14 after the second dose; panels k–o represent outcomes that occurred 15–21 after the second vaccine dose dose. Statistical adjustment was performed for age and sex. Asterix (*) represents abrreviation for severe/critical disease.

14 days after individuals' first positive SARS-CoV-2 PCR test, with the last date being March 21, 2021; deaths were counted for up to 40 days after individuals' first positive SARS-CoV-2 PCR test (Fig. S4. C), with the last date being April 16, 2021.

Fig. 2 demonstrates the adjusted VE against outcomes of interest for each of the 27 cohorts for the first three pre-determined evaluation periods. The highest VE estimates with the lowest variability were reached 15–21 days after the second dose. Similarly high VE estimates were observed 22–28 days after the second dose (data not shown). The greatest variability in VE estimates was observed on days 14–20 after the first vaccine dose.

Tables 1–4 demonstrate the adjusted VE against outcomes of interest of all 27 cohorts combined, for the four evaluation periods. The highest combined VE estimates for all outcomes of ≥16 year old individuals were reached 15–21 days after the second dose (Table 3), and were maintained at similar levels 22–28 days after the second dose (Table 4). The largest change in VE against all outcomes was observed between days 14–20 after the first dose and days 8–14 after the second dose, for all age groups (Tables 1–4). The VE differences between days 14–20 after the first dose and days 8–14 after the second dose, and the VE differences between days 8–14 and 15–21 after the second dose were statistically significant (Tables 1–3).

3.3. Vaccine effectiveness by age groups

The combined adjusted VE by age group for all 27 cohorts against the five outcomes are demonstrated in Tables 1–4. VE estimates against laboratory-confirmed SARS-CoV2–related outcomes for age groups 16–39, 40–59 and 60 to 79 years old reached or surpassed 90%, 8–14 days following the second vaccine dose (Table 2). The highest VE estimates for the above age groups were observed on days 15 to 21 (Table 3), and were maintained at similar levels on days 22–28 (Table 4) following the second vaccine dose.

For ≥80 year old individuals, VE estimates were lower than those of other age groups, for the first three evaluation periods (Tables 1–3). These differences were statistically significant for most estimates of the 8–14 and 15–21 days evaluation periods (Tables 2 and 3). VE estimates against laboratory-confirmed SARS-CoV2–related outcomes for ≥80 year old individuals reached or surpassed 90% 15–21 days following the second vaccine dose (Table 3). The highest VE estimates of ≥80 year old individuals were observed 22–28 days after the second dose (Table 4) and were then closest to VE estimates of the other age group (Table 4).

The VE differences between days 14-20 after the first dose and days 8–14 after the second dose, and the VE differences between days 8-14 and 15–21 after the second doses were statistically significant for most age groups and for most outcomes (Tables 1–3).

3.4. Hospitalisations and deaths among vaccinated SARS-CoV-2-positive individuals

Table 5 demonstrates the results of hospitalisations, severe/critical disease and death among vaccinated SARS-CoV-2-positive individuals.

A total of 7,166 individuals from the first dose 27 cohorts turned SARS-CoV-2-positive 14–20 days after receipt of the first dose. A total of 1,639, 542 and 430 from the second dose 27 cohorts became positive on days 8–14, 15–21 and 22–18 after the receipt of the second dose (Table 5).

Due to the relatively small number of individuals who became SARS-CoV-2-positive, the analysis was performed for three age groups only: ≥16 years old, ≥60 years old and ≥80 years old.

The rate reductions for hospitalisations, severe/critical disease and deaths for ≥16 year old individuals who became SARS-CoV-2-positive on days 14–20 after the first vaccine dose were 44.2% (95% CI: 27.3–57.3%), 46.8% (95% CI: 32.9–57.9%) and 36.4% (95% CI: 18.6–50.4%), respectively (Table 5).

Table 1
BNT162B2 vaccine effectiveness against SARS-CoV-2-PCR confirmed outcome of interest, 14-20 days after the first vaccine dose.

Outcome of interest	Age groups (Years)	UnvaccinatedSARS-CoV-2-positive cases	Unvaccinated person-days	VaccinatedSARS-CoV-2-positive cases	Vaccinatedperson-days	Adjusted VE* (95% CI)
SARS-CoV-2 infection						
	≥16	133,994	119,701,675	7,166	14,289,253	54.3 (50.6-57.8)
	16−39	89,755	76,128,060	1,099	2,243,247	57.2 (51.2-62.5)
	40−59	33,687	33,229,472	2,432	4,574,236	47.1 (42.1-51.7)
	60−79	8,528	8,272,226	2,850	6,107,505	60.2 (54.1-65.6)
	≥80	2,024	2,071,917	785	1,364,265	47.2 (33.8-57.9)[@]
Symptomatic disease						
	≥16	88,320	119,019,006	4,156	14,278,200	58.3 (54.7-61.6)
	16−39	58,725	75,645,370	568	2,241,466	66.4 (62.5-69.8)
	40−59	23,370	33,083,651	1,553	4,570,986	52.3 (48.6-55.6)
	60−79	5,303	8,230,370	1,719	6,103,198	60.5 (54.3-65.9)
	≥80	922	2,059,615	316	1,362,550	49.5 (42.6-55.6)[@]
Hospitalisation						
	≥16	4,709	119,701,675	571	14,289,253	74.5 (69.1-79.0)
	16−39	1,187	76,128,060	10	2,243,247	73.7 (50.7-85.9)
	40−59	1,377	33,229,472	52	4,574,236	77.9 (70.6-83.4)
	60−79	1,342	8,272,226	282	6,107,505	77.0 (73.0-80.5)
	≥80	803	2,071,917	227	1,364,265	59.1 (52.5-64.7)[&]
Severe/Critical disease						
	≥16	2,635	119,701,675	393	14,289,253	77.3 (71.2-82.1)
	16−39	253	76,128,060	2	2,243,247	78.5 (10.5-94.8)[#]
	40−59	792	33,229,472	27	4,574,236	81.7 (71.1-88.4)[#]
	60−79	963	8,272,226	194	6,107,505	78.4 (74.1-82.1)
	≥80	627	2,071,917	170	1,364,265	62.8 (49.7-72.5)[^]
Death						
	≥16	819	119,701,675	178	14,289,253	71.7 (64.1-77.7)
	16-39	16	76,128,060	1	2,243,247	-25.8 (-851.8-83.4)[#]
	40-59	82	33,229,472	3	4,574,236	81.9 (42.5-94.3)
	60-79	327	8,272,226	79	6,107,505	77.4 (70.7-82.7)
	≥80	394	2,071,917	95	1,364,265	65.4 (56.4-72.6)[@]

* Adjusted for age, sex and epidemiological week;
[@] Adjusted for sex and epidemiological week
[#] Adjusted for sex and age;
[&] Adjusted for sex;
[^] No adjustment

Table 2
BNT162B2 vaccine effectiveness against SARS-CoV-2-PCR confirmed cases by outcome of interest, 8-14 days after the second vaccine dose.

Outcome of interest	Age groups (Years)	UnvaccinatedSARS-CoV-2-positive cases	Unvaccinated person-days	VaccinatedSARS-CoV-2-positive cases	Vaccinatedperson-days	Adjusted VE* (95% CI)
SARS-CoV-2 infection						
	≥16	95,655	89,535,711	1,639	14,060,250	89.9 (88.6-91.1)
	16-39	66,648	60,032,245	156	2,186,209	93.2 (91.9-94.2)
	40-59	22,066	22,243,132	493	4,451,669	89.0 (87.6-90.2)
	60−79	5,679	5,718,267	687	6,069,089	90.8 (89.2-92.3)
	≥80	1,262	1,542,067	303	1,353,283	73.9 (69.0-78.0)[@]
Symptomatic disease						
	≥16	65,032	89,104,030	652	14,056,907	93.6 (92.7-94.3)
	16-39	45,004	59,727,620	62	2,185,925	96.1 (94.9-96.9)
	40-59	15,658	22,152,821	211	4,450,755	93.3 (92.3-94.2)
	60-79	3,690	5,689,388	270	6,067,631	94.0 (92.8-94.9)
	≥80	680	1,534,201	109	1,352,596	82.6 (78.2-86.1)[@]
Hospitalisation						
	≥16	3,869	89,535,711	166	14,060,250	93.8 (91.9-95.2)
	16-39	1,138	60,032,245	1	2,186,209	97.8 (84.4−99.7)
	40-59	1,187	22,243,132	13	4,451,669	95.5 (92.1-97.4)
	60-79	1,001	5,718,267	68	6,069,089	95.7 (94.2-96.8)
	≥80	543	1,542,067	84	1,353,283	83.4 (78.8-87.0)[@]
Severe/Critical disease						
	≥16	2,231	89,535,711	111	14,060,250	94.4 (92.6-95.8)
	16-39	308	60,032,245	1	2,186,209	93.1 (50.6-99.0)
	40-59	719	22,243,132	7	4,451,669	96.2 (92.0-98.2)
	60-79	759	5,718,267	42	6,069,089	96.6 (95.2-97.6)
	≥80	445	1,542,067	61	1,353,283	85.5 (79.6-89.6)[^]
Death						
	≥16	567	89,535,711	61	14,060,250	91.3 (87.4-94.0)
	16-39	17	60,032,245	0	2,186,209	100.0
	40-59	63	22,243,132	1	4,451,669	94.3 (57.5-99.2)
	60-79	225	5,718,267	20	6,069,089	95.3 (92.5-97.1)
	≥80	262	1,542,067	40	1,353,283	83.6 (77.1-88.2)[@]

* Adjusted for age, sex and epidemiological week;
[@] Adjusted for sex and epidemiological week; [#]Adjusted for sex and age; [&]Adjusted for sex;
[^] No adjustment.

Table 3
BNT162B2 vaccine effectiveness against SARS-CoV-2-PCR confirmed cases by outcome of interest, 15−21 days after the second vaccine dose.

Outcome of interest	Age groups (Years)	UnvaccinatedSARS-CoV-2-positive cases	Unvaccinated person-days	VaccinatedSARS-CoV-2-positive cases	Vaccinatedperson-days	Adjusted VE* (95% CI)
SARS-CoV-2 infection						
	≥16	80,857	75,237,221	542	14,053,144	96.8 (96.1-97.4)
	16-39	56,520	50,701,680	75	2,185,505	96.7 (95.8-97.4)
	40-59	18,394	18,306,473	146	4,449,679	96.7 (96.1-97.2)
	60-79	4,868	4,851,486	224	6,066,052	97.7 (96.8-98.3)
	≥80	1,075	1,377,582	97	1,351,908	91.1 (88.7-93.1)[@]
Symptomatic disease						
	≥16	55,352	74,888,353	206	14,051,978	98.1 (97.7-98.5)
	16-39	38,529	50,459,628	27	2,185,323	98.3 (97.5-98.8)
	40-59	13,080	18,232,593	57	4,449,376	98.2 (97.7-98.6)
	60-79	3,149	4,826,269	93	6,065,601	98.3 (97.6-98.9)
	≥80	593	1,370,805	29	1,351,678	95.1 (92.9-96.7)[@]
Hospitalisation						
	≥16	3,607	75,237,221	57	14,053,144	98.0 (97.1-98.6)
	16-39	1,099	50,701,680	3	2,185,505	94.3 (82.2-98.2)
	40-59	1,116	18,306,473	8	4,449,679	97.6 (95.1-98.8)
	60-79	924	4,851,486	17	6,066,052	99.3 (98.7-99.6)
	≥80	468	1,377,582	29	1,351,908	94.1 (91.3-95.9)[@]
Severe/Critical disease						
	≥16	2,052	75,237,221	32	14,053,144	98.6 (97.8-99.1)
	16-39	309	50,701,680	1	2,185,505	93.4 (51.2-99.1)[^]
	40-59	679	18,306,473	3	4,449,679	98.6 (95.6-99.6)
	60-79	693	4,851,486	11	6,066,052	99.4 (98.8-99.7)
	≥80	371	1,377,582	17	1,351,908	95.6 (92.5-97.4)[^]
Death						
	≥16	495	75,237,221	21	14,053,144	97.7 (95.9-98.7)
	16-39	17	50,701,680	0	2,185,505	100.0
	40-59	60	18,306,473	0	4,449,679	100.0
	60-79	203	4,851,486	5	6,066,052	99.2 (97.9-99.7)
	≥80	215	1,377,582	16	1,351,908	92.9 (88.2-95.7)[&]

* Adjusted for age, sex and epidemiological week;
[@] Adjusted for sex and epidemiological week; [#]Adjusted for sex and age; [b]Adjusted for sex;
[^] No adjustment.

Table 4
BNT162B2 vaccine effectiveness against SARS-CoV-2-PCR confirmed outcome of interest, 22-28 days after the second vaccine dose.

Outcome of interest	Age groups (Years)	UnvaccinatedSARS-CoV-2-positive cases	Unvaccinated person-days	VaccinatedSARS-CoV-2-positive cases	Vaccinatedperson-days	Adjusted VE* (95% CI)
SARS-CoV-2 infection						
	≥16	65,742	62,218,584	430	14,049,905	97.3 (96.7-97.8)
	16-39	45,537	41,758,437	77	2,185,026	96.6 (95.7-97.3)
	40−59	15,110	15,171,804	143	4,448,722	96.7 (96.1-97.3)
	60−79	4,176	4,059,480	149	6,064,782	98.4 (97.6-98.9)
	≥80	919	1,228,863	61	1,351,375	94.1 (92.1-95.6)
Symptomatic disease						
	≥16	45,406	61,942,845	221	14,049,087	97.9 (97.4-98.3)
	16−39	31,396	41,570,364	37	2,184,862	97.7 (96.8-98.3)
	40−59	10,792	15,112,508	81	4,448,465	97.4 (96.8-98.0)
	60−79	2,707	4,038,475	86	6,064,559	98.5 (97.6-99.0)
	≥80	510	1,222,945	17	1,351,201	97.1 (95.2-98.2)
Hospitalisation						
	≥16	3,277	62,218,584	33	14,049,905	99.0 (98.4-99.3)
	16−39	1,010	41,758,437	0	2,185,026	100[#]
	40−59	1012	15,171,804	4	4,448,722	98.9 (97.0-99.6)
	60−79	829	4,059,480	15	6,064,782	99.5 (99.0-99.7)
	≥80	426	1,228,863	14	1,351,375	97.1 (94.8-98.4)[&]
Severe/Critical disease						
	≥16	1,880	62,218,584	20	14,049,905	99.2 (98.6-99.5)
	16−39	287	41,758,437	0	2,185,026	100[^]
	40−59	630	15,171,804	2	4,448,772	99.2 (96.6-99.8)
	60−79	630	4,059,480	9	6,064,782	99.6 (99.1-99.8)
	≥80	333	1,228,863	9	1,351,375	97.7 (95.5-98.8)[^]
Death						
	≥16	440	62,218,584	11	14,049,905	98.6 (97.0-99.3)
	16−39	17	41,758,437	0	2,185,026	100
	40−59	53	15,171,804	1	4,448,722	96.1 (71.7-99.5
	60−79	179	4,059,480	6	6,064,782	99.1 (97.7-99.7)
	≥80	191	1,228,863	4	1,351,375	98.2 (95.2-99.3)[@]

* Adjusted for age, sex and epidemiological week;
[@] Adjusted for sex and epidemiological week;
[#] Adjusted for sex and age;
[&] Adjusted for sex;
[^] No adjustment.

Table 5
Effect of the BNT162b2 vaccine on hospitalisation, severe/critical disease and death among SARS-CoV-2-positive individuals.

Adjusted[#]1-RR (95%CI)	Vaccinated SARS-CoV-2- positive cases		Unvaccinated SARS-CoV-2- positive cases		Age group (Years)	Time of first SARS-CoV-2 PCR test	Outcome of interest
	Total	Outcome	Total	Outcome			
Hospitalisation							
44.2 (27.3-57.3)	7,166	571	133,994	4,709	≥16	14–20 d after 1st dose	
36.5 (27.8–44.2)	3,631	509	10,586	2,145	≥60		
28.9 (3.2–47.8)[&]	785	227	2,024	803	≥80		
49.8 (33.7-62.0)	1,639	166	95,655	3,869	≥16	8–14 d after 2nd dose	
43.3 (32.9–52.1)	987	152	6,974	1,544	≥60		
36.6 (17.2–51.4)[&]	303	84	1,262	543	≥80		
44.6 (22.4-60.5)	542	57	80,857	3,607	≥16	15–21 d after 2nd dose	
52.2 (31.8–66.5)[&]	319	46	5,966	1,392	≥60		
32.1 (-2.2–54.8)[&]	97	29	1,075	468	≥80		
56.1 (35.0-70.4)	430	33	65,742	3,277	≥16	22–28 d after 2nd dose	
52.9 (28.0-69.2)	210	29	5,095	1,255	≥60		
56.1 (35.0-70.4) [&]	61	14	919	426	≥80		
Severe/Critical disease							
46.8 (32.9–57.9)	7,166	393	133,994	2,635	≥16	14–20 d after 1st dose	
38.8 (30.1–46.5)	3,631	364	10,586	1,590	≥60		
32.6 (5.8–51.7) [&]	785	170	2024	627	≥80		
57.9 (42.5–69.2)	1,639	111	95,655	2,231	≥16	8–14 d after 2nd dose	
52.0 (40.8–61.1)	987	103	6,974	1,204	≥60		
43.9 (23.6–58.8)[&]	303	61	1,262	445	≥80		
63.0 (43.5–75.7)	542	32	80,857	2,052	≥16	15-21 d after 2nd dose	
61.4 (43.4–73.7)	319	28	5,966	1,064	≥60		
49.7 (16.6–69.7)	97	17	1,075	371	≥80		
66.2 (44.2–79.6)	430	20	65,742	1,880	≥16	22–28 d after 2nd dose	
62.0 (39.0–76.3)	210	18	5,095	963	≥60		
55.0 (-42.6–85.8) [&]	61	9	919	333	≥80		
Death							
36.4 (18.6–50.4)	7,166	178	133,994	819	≥16	14–20 d after 1st dose	
36.6 (22.4–48.2)	3,631	174	10,586	721	≥60		
41.2 (12.1–60.7)	785	95	2,024	394	≥80		
39.5 (21.0–53.6)	1,639	61	95,655	567	≥16	8–14 d after 2nd dose	
38.6 (19.6–53.1)	987	60	6,974	487	≥60		
37.2 (12.4-55.0)	303	40	1,262	262	≥80		
36.3 (1.31-58.9)	542	21	80,857	495	≥16	15–21 d after 2nd dose	
34.9 (-0.91–58.7)	321	21	5,943	418	≥60		
17.34 (-37.4–50.3)	97	16	1,075	215	≥80		
47.4 (4.3–71.2)	430	11	65,742	440	≥16	22–28 d after 2nd dose	
50.8 (7.7–73.7)	210	10	5,114	370	≥60		
68.7 (15.7–88.4)	61	4	919	191	≥80		

[#] Adjustment for age and sex;
[&] Adjustment for age; [※]Adjustment for sex; ^No adjustment

The rate reductions for hospitalisations, severe/critical disease and deaths for individuals who became SARS-CoV-2-positive on days 22–28 after the first vaccine dose were 56.1% (95% CI: 35.0–70.4%), 66.2% (95% CI: 44.2–79.6%) and 47.4% (95% CI: 4.3–71.2%), respectively (Table 5).

Analysis by age groups demonstrated that the rate reductions for hospitalisations and severe/critical disease among ≥80 year old individuals were lower than other age categories during the first three evaluation periods. However, these differences were not statistically significant (Table 5).

4. Discussion

In this study, we evaluated the effect of the BNT162b2 vaccine on both prevention of SARS-CoV-2-related outcomes and on outcomes that occurred despite vaccination.

Individuals that are vaccinated at different times can be subjected to various external factors such as, inadequate vaccine storage or transport conditions [6], varying degrees of SARS-CoV-2 in the population, variations in vaccine coverage and the appearance of new genomic variants [7–12]. Since such external factors cannot be readily adjusted for, we elected to estimate VE against SARS-CoV-2 for multiple cohorts, each representing individuals who were vaccinated on a separate date.

Our findings demonstrated high VE against laboratory-confirmed SARS-CoV-2 infection, symptomatic disease, hospitalisations, severe/critical disease and death after the second BNT162b2 vaccine dose, with the highest VE point estimates reaching well over 90% during the 15–21 and the 22–28 day evaluation periods after the second vaccine dose. VE point estimates on days 14–20 after the first vaccine dose against SARS-CoV-2-related outcomes ranged between 54.3% and 77.3%.

Our results indicate consistently that a high level of protection, with little variability, is provided by the BNT162b2 vaccine against COVID-19 after the second vaccine dose. We also demonstrated that VE estimates achieved after the first vaccine dose were more modest and had substantial variability.

Our VE estimates are consistent with the vaccine efficacy results published by the manufacturer [5]. Several other VE assessments also suggested that the two-dose regimen of the BNT162b2 vaccine is highly effective [17–19] and a single vaccine dose is less effective [18,20,21]. However, none of these assessments relied on national-level data. Although several VE studies from Israel were recently published, few important differences exist between those studies and our study. Two studies relied on a substantially smaller number of individuals as compared to our study, all belonging to specific HMOs [18,19]. These studies demonstrated VE point estimates of 90%-92% against SARS-CoV-2 infection and 94% against symptomatic disease ≥ 7 days after the second vaccine dose [18,19]. Although the HMO studies provided co-morbidity-related VE estimates, they did not provide age group-specific VE estimates against hospitalisations, severe/critical illness or death, nor did they provide VE analysis for specific time-intervals after the second vaccine dose. Another study from Israel relied on the national databases; however, it used aggregated data and assessed VE following the second vaccine dose only. Furthermore, it presented VE results of ≥7 days and ≥14 days after the second dose. As such, VE results of ≥7 days, included also the VE results of ≥14 days and could not present the real difference between VE results of 7-13 days and ≥14 days [4]. Lastly, our study is the first study to assess the effect of the vaccine on breakthrough cases.

The large number of vaccine recipients in our study, the careful determination of the necessary follow up time for each outcome and the ethical approval to examine individualised data, allowed us to perform a detailed analysis of VE in specific cohorts.

Our results demonstrated, for the first time, a delayed rise in VE estimates among ≥80 year old individuals, against all outcomes. Specifically, while VE estimates in <80 years old individuals reached VE of ≥90% on days 8–14 after the second vaccine dose, individuals ≥80 years of age reached that level of VE a week later (days 15–21 after the second dose). In fact, VE estimates among ≥80 year old individuals became closest to those of the other age groups, only for the 22–28 day evaluation period after the second vaccine dose.

This estimation is of particular importance since the oldest age group (≥75 years old), was substantially smaller than other age groups in the vaccine efficacy study conducted by the manufacturer [5]. Furthermore, the ≥80 year old age-group was not compared to other age groups over time in other VE studies [4,18,19,22].

Based on the manufacturer's vaccine efficacy study [5], Israeli individuals have been considered fully vaccinated if seven days passed from the receipt of the second BNT162b2 vaccine dose [23]. However, the U.S. CDC recommends waiting two weeks before full vaccination can be assumed [24]. Our results support the U.S. CDC recommendation, and we suggest that full vaccination is defined once 14 days have passed since the second vaccine dose for all individuals, with special emphasis on ≥80 year old individuals.

Our study demonstrates, for the first time, the beneficial effects of the BNT162b2 vaccine on all relevant outcomes of interest in individuals ≥16 years old who became SARS-CoV-2-positive despite being vaccinated.

The rapid pace of the vaccination campaign in Israel allowed for the analysis of multiple cohorts, each representing a specific vaccination date. This form of analysis demonstrated the consistent nature of protection elicited by the vaccine through the rapidly changing circumstances of vaccine coverage and level of viral circulation that occurred during the vaccination campaign. Furthermore, each cohort is expected to have somewhat different population mix in terms of age, sex and socio-economic status.

Such analysis is of particular importance in view of the penetration of new genomic variants [7–12], their potential for rapid transmission [25], and the concern that some may evade the immunity elicited by existing vaccines and lower VE. In this regard the Alpha variant (B.1.1.7) was the most prevalent genomic variant until May 2021 [4]. Although other variants of concerns (VOCs) were discovered in Israel [26–28] prior to May 2021, they did not spread widely in the population by the end of May 2021 [29]. A wide spread of VOCs in the population will require re-evaluation of VE. The worldwide spread of the highly transmissible Delta variant (B.1.617.2) [30], underscores this issue.

Re-evaluation of VE may also be required because of the concern of waning vaccine-induced immunity. In this regard, waning of spike protein antibody levels was observed over-time following the administration of a second dose of SARS-CoV-2 vaccines [31].

Our study has several limitations. Due to the nature of our research, the size of control unvaccinated population group was computed based on the Israel Bureau of statistics data, which included information regarding population size, age and sex. Specific individual data was available in our databases for unvaccinated individuals who became positive for SARS-CoV-2. Thus, despite the control group size computation, we were able to adjust age, sex and epidemiologic week, and our results are consistent with the manufacturer's vaccine efficacy results [5].

The unavailability of information regarding underlying morbidity presents another limitation. However, the consistent VE results among multiple cohorts and multiple age groups, and the marked decrease in the incidence of SARS-CoV-2 cases in Israel indicate that the vaccine is highly effective for the population at large.

The prevalent SARS-CoV-2 PCR testing in hospitals, could have led to the inclusion of some individuals who were admitted to the hospital due to reasons other than COVID-19, but were found to be asymptomatic carriers of SARS-CoV-2. However, critical/severe disease was registered in our database only for hospitalised COVID-19 patients.

In this study, we used the date of positive SARS-CoV-2 PCR test, rather than the date of symptom onset, due to the fact that it was the most reliable and consistent datum in our database. Using the date of positive PCR test is valuable since a significant subset of individuals are asymptomatic. Furthermore, individuals can become symptomatic at different time-points after they were determined to be SARS-CoV-2-positive, thus their symptom onset date may not be available or could introduce other biases.

Since this is an observational study, PCR testing for SARS-CoV-2 could differ between vaccinated and unvaccinated individuals. Comparing the percent of PCR testing among fully vaccinated individuals and among unvaccinated individuals, demonstrated lower testing frequency among vaccinated individuals (not shown). Such differences can stem from reduced symptomatology among vaccine recipients and/or behavioural changes resulting from confidence in the vaccine. However, since SARS-CoV-2 PCR testing was widely performed among hospitalised individuals, VE against hospitalisations, severe/critical disease and death, were probably not affected by individuals' behaviour.

Cohort studies with active regular PCR testing regardless of the appearance of symptoms can eliminate testing differences. In this regard, a cohort study from Italy demonstrated VE of 93.7% (95%CI: 50.8–99.2%) of the BNT162b2 vaccine against laboratory confirmed SARS-CoV-2 infection ≥7 days after the second vaccine dose among health care workers that were PCR tested regularly [17]. Another study of US healthcare and emergency workers who received one of two mRNA vaccines found VE of 90% (95%CI: 68–97%) ≥14 days after the second vaccine dose against laboratory-confirmed SARS-CoV-2 infection [32]. A study from a large medical centre in Israel found an adjusted incidence rate ratio of 0.02 (95% CI: 0–0.07) for symptomatic disease and 0.09 (95% CI: 0.03–0.25) for asymptomatic infection following full BNT162b2 vaccination [33].

The finding that the BNT162b2 vaccine is beneficial in terms of lowering hospitalisations, severe/critical disease and death among breakthrough SARS-CoV-2 cases, is important. However, a close examination of the breakthrough cases with regard to co-morbidities and genomic SARS-CoV-2 variants is required and should be the subject for future studies. Furthermore, the last evaluation period of our study included individuals who became SARS-CoV-2-positive 22−28 days after the second vaccine dose. Analysis of additional evaluation periods after vaccination is important in order to evaluate the long-term effect of the BNT162b2 vaccine.

Our results of high BNT162b2 VE against new COVID-19 cases and the beneficial effect among breakthrough cases, coupled with the reports of major COVID-19 hotspots around the world, strongly support the need to widen and to intensify vaccination efforts throughout the world in order to control the spread of SARS-CoV-2.

4.1. Contributors

AG-F and LK-B conceived the study. AG-F designed the study, wrote the protocol, led data analysis and wrote the first draft of the manuscript. YH and RD retrieved the data and performed data analysis. AG-F, MB and LK-B interpreted the data and edited the final manuscript. YH and RD verified the underlying data. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest

Data sharing

Individual-level data used in this study cannot be publicly available due to material sensitivity. Requests for data can be made to the Ministry of Health of Israel.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2021.103574.

References

[1] U.S. Food and Drug Administration. COVID-19 vaccines. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. [Accessed 7 February, 2021].

[2] European Medicines Agency. Treatments and vaccines for COVID-19: authorised medicines. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-authorised-medicines#covid-19-vaccines-section. [Accessed 7 February, 2021].

[3] Our World in Data. Coronavirus (COVID-19) vaccination. https://ourworldindata.org/covid-vaccinations. [Accessed 25 May 2021].

[4] Haas E, Mclaughlin JM, Anis E, Singer SR, Khan F, Brooks N, Smaja M, Mircus G, Pan K, Southern J, Swerdlow DL, Jodar L, Levy Y, Alroy-Preis S. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalizations and deaths followin nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397 (online ahead of print).

[5] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383 (27):2603–15.

[6] Centers for Disease Control and Prevention. Pfizer-BioNTech COVID-19 vaccine. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/index.html. [Accessed 7 February, 2021].

[7] Hu J, Li C, Wang S, Li T, Zhang H. Genetic variants are identified to increase risk of COVID-19 related mortality from UK Biobank data. 2021;15(1):10.

[8] Ogawa J., Zhu W., Tonnu N., Singer O., Hunter T., Ryan A.L., et al. The D614G mutation in the SARS-CoV2 Spike protein increases infectivity in an ACE2 receptor dependent manner. bioRxiv: the preprint server for biology. 2020.

[9] Tang JW, Toovey OTR, Harvey KN, Hui DDS. Introduction of the South African SARS-CoV-2 variant 501Y.V2 into the UK. J Infect 2021;82(4):e8–e10.

[10] Toovey OTR, Harvey KN, Bird PW, Tang JWW. Introduction of Brazilian SARS-CoV-2 484K.V2 related variants into the UK. J Infect 2021.

[11] Mascola JR, Graham BS, Fauci AS. SARS-CoV-2 viral variants-tackling a moving target. JAMA 2021;325(13):1261–2.

[12] Washington NL, Gangavarapu K, Zeller M, Bolze A, Cirulli ET, Schiabor Barrett KM, et al. Emergence and rapid transmission of SARS-CoV-2 B.1.1.7 in the United States. Cell 2021.

[13] Central Bureau of Statistics. Population. https://www.cbs.gov.il/EN/pages/default.aspx. [Accessed 20 April, 2021].

[14] National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines: clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov. [Accessed 25 February, 2021].

[15] Central Bureau of Statistics. Population - statistical abstract of Israel - No. 71. https://www.cbs.gov.il/en/publications/Pages/2020/Population-Statistical-Abstract-of-Israel-2020-No-71.aspx. [Accessed 13 February, 2021].

[16] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7.

[17] Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Euro Surveill 2021;26(17).

[18] Dagan N, Barda N. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. 2021;384(15):1412-23.

[19] Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. Clin Infect Dis 2021 an official publication of the Infectious Diseases Society of America.

[20] Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021;397 (10285):1646–57.

[21] Chodick G, Tene L, Patalon T, Gazit S, Ben TA, Cohen D, et al. Assessment of effectiveness of 1 dose of BNT162b2 vaccine for SARS-CoV-2 infection 13 to 24 days after immunization. JAMA Netw Open 2021;4(6):e2115985.

[22] Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021;373:n1088.

[23] Israel Ministry of Health. What is a vaccination certificate? https://corona.health.gov.il/en/directives/vaccination-certificate/2021. [Accessed 25 April 2021]

[24] Centers for Disease Control and Prevention. When you've been fully vaccinated. 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html [Accessed 25 April 2021]

[25] Baden LR, El Sahly HM. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. 2021;384(5):403-16.

[26] Israel Ministry of Health. 44 confirmed cases of the South African variant have been detected so far. https://www.gov.il/en/departments/news/14022021-02. [Accessed 14 February, 2021].

[27] Israel Ministry of Health. 41 Indian variant cases detected, 24 of them among returning international passengers. https://www.gov.il/en/departments/news/29042021-01. [Accessed 29 April, 2021]

[28] Israel Ministry of Health. For the first time: Brazilian and Chilean variants have been detected among returning international passengers https://www.gov.il/en/departments/news/03052021-02. [Accessed 3 May, 2021].

[29] Our World in Data. Share of COVID sequences that are the Delta variant. https://ourworldindata.org/grapher/covid-cases-delta?country=~ISR. [Accessed 20 July 2021]

[30] Del Rio C, Malani PN, Omer SB. Confronting the delta variant of SARS-CoV-2, summer 2021. JAMA 2021.

[31] Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet 2021;398(10298):385–7.

[32] Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70(13):495–500.

[33] Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association between vaccination with BNT162b2 and incidence of symptomatic and asymptomatic SARS-CoV-2 infections among health care workers. JAMA 2021;325 (24):2457–65.