Effectiveness of BNT162b2 mRNA COVID-19 vaccine against acquisitions of SARS-CoV-2 among health care workers in long-term care facilities: a prospective cohort study

Author List

Khitam Muhsen1*, Nimrod Maimon2*, Ami Mizrahi2*, Omri Bodenneimer2*, Dani Cohen1, Michal Maimon3,4, Itamar Grotto3,5, Ron Dagan3

* Equally contributed

Affiliations

1 Department of Epidemiology and Preventive Medicine, School of Public Health, the Sackler Faculty, Tel Aviv University, Ramat Aviv, Tel Aviv, 6139001, Israel

2 Israel Ministry of Health, "Senior Shield" Project, Israel

3 Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

4 Soroka University Medical Center, Beer-Sheva, Israel.

5 Ministry of Health, Jerusalem, Israel.

Corresponding author: Prof. Khitam Muhsen (PhD)

Department of Epidemiology and Preventive Medicine, School of Public Health, the Sackler Faculty, Tel Aviv University, Tel Aviv, 6139001, Israel.

Email: kmuhsen@tauex.tau.ac.il

Alternate Corresponding author: Prof. Ron Dagan (MD)

Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel

Email: ragan@bgu.ac.il
Summary: In a nationwide prospective study that included routine, weekly SARS-CoV-2 RT-PCR testing from healthcare workers of long-term care facilities in Israel, vaccine effectiveness of two doses of BNT162b2 was 89% against SARS-CoV-2 infection, with lower viral load among vaccinated persons.

Effectiveness of BNT162b2 vaccine
Abstract

**Objective:** We assessed vaccine effectiveness (VE) of BNT162b2 mRNA COVID-19 vaccine against SARS-CoV-2 acquisition among health care workers (HCWs) of long-term care facilities (LTCFs).

**Methods:** This prospective study, in the framework of "Senior Shield" program in Israel, included routine, weekly nasopharyngeal SARS-CoV-2 RT-PCR testing from all LTCF HCWs since July 2020. All residents and 75% of HCWs were immunized between December 2020 and January 2021. The analysis was limited to HCWs adhering to routine testing. Fully vaccinated (14+ days after second dose; n=6960) and unvaccinated HCWs (n=2202) were simultaneously followed until SARS-CoV-2 acquisition, or end of follow-up, April 11, 2021. Hazard ratios (HRs) for vaccination vs. no vaccination were calculated (Cox proportional hazards regression models, adjusting for socio-demographics and residential-area COVID-19 incidence). VE was calculated as $\[(1-HR)\times100\]$. RT-PCR cycle threshold values (Cts) were compared between vaccinated and unvaccinated HCWs.

**Results:** At >14 days post second dose, 40 vaccinated HCWs acquired SARS-CoV-2 (median follow-up, 66 days; cumulative incidence 0.6%) vs. 84 unvaccinated HCWs (median follow-up 43 days; cumulative incidence, 5.1%); HR=0.11 (95% CI 0.07, 0.17), unadjusted VE=89% (95% CI 83%, 93%). Adjusted VE beyond seven days and >14 days post second dose were similar. The median PCR Cts targeting *ORF1ab* gene among 20 vaccinated and 40 unvaccinated HCWs was 32.0 vs. 26.7, respectively, p=0.008.

**Conclusions:** VE following two doses of BNT162b2 against SARS-CoV-2 acquisition in LTCF HCWs was high. The lower viral loads among SARS-CoV-2 positive HCWs suggests further reduction in transmission.

**Keywords:** Effectiveness; BNT162b2 vaccine; SARS-CoV-2 infection; health care workers; prospective study; long-term care facilities, cycle threshold
Introduction

The BNT162b2 mRNA COVID-19 vaccine was the first vaccine to receive emergency use authorization, with a 95% efficacy against COVID-19 in phase III clinical trial [1, 2].

In December 19, 2020, Israel launched a national vaccination campaign using BNT162b2 vaccine, initially prioritizing health care workers (HCWs) and individuals aged 60 years and older. Gradually COVID-19 immunization was expanded to all individuals aged 16 years or older. By April 11, 2021, nearly 53% of 16 years or older individuals were immunized with two doses. The respective figure was 85% for those aged 60 years or older [3].

Real-life observational studies from Israel have demonstrated effectiveness of ≥95% against COVID-19 after immunization with two doses [4, 5], consistent with studies in other countries [6, 7]. However, vaccine effectiveness against disease does not predict necessarily the full potential impact of a vaccine, since it does not measure its ability to reduce transmission, an important factor in public health policy. Asymptomatically infected individuals are important in the transmission of SARS-CoV-2, contributing to the evolution of the pandemic [8]. Estimating SARS-CoV-2 acquisition (encompassing both symptomatic and asymptomatic infections) is problematic, mainly due to differences in demographics and other personal characteristics, incentives to be tested, and risk-associated behavior between vaccinated and unvaccinated individuals, resulting in potential confounding and selection bias [9]. Thus, the effectiveness of BNT162b2 vaccine on SARS-CoV-2 transmission and the resulting indirect (herd) protection has not yet been fully elucidated.

HCWs are at risk for SARS-CoV-2 infection [10], and they might transmit the virus to their patients, often a high-risk population of severe COVID-19. Therefore, determining the risk of SARS-CoV-2 acquisition is of utmost importance among HCWs. It was shown that BNT162b2 administered to HCWs was inversely associated with SARS-CoV-2 infection risk
The vaccine effectiveness (VE) of two doses was assessed in four studies, ranging from 85% to 97%, and mostly did not determine VE against asymptomatic infections separately [11, 16, 17, 19, 20], except of one showing lower VE against asymptomatic SARS-CoV-2 infection than symptomatic infection [21].

Since the residents of long-term care facilities (LTCF) are a vulnerable population, a national LTCF protection program, "Senior Shield", was initiated on April 2020 in Israel [22]. In this program, routine, government-funded, weekly screening of SARS-CoV-2 infection by RT-PCR testing of nasopharyngeal swabs from all LTCF HCWs has been implemented since July 2020. Starting on December 22, 2020, BNT162b2 vaccine was offered to all LTCFs HCWs and residents. This task was completed by the end of January 2021, after having enrolled all institutions in Israel. Among HCWs, approximately 75% were vaccinated and 16% were known convalescent. Weekly nasopharyngeal testing of SARS-CoV-2 detection has been ongoing without interruption. We took advantage of the active weekly surveillance of PCR testing, with the primary objective to assess the effectiveness of the BNT162b2 vaccine in preventing the acquisition of SARS-CoV-2 in fully vaccinated HCWs.

Since SARS-CoV-2-neutralizing antibody titers were shown to be highest after seven and 14 days following immunization with the second BNT162b2 dose [23] and following evidence from previous studies [2, 4, 5], we hypothesized that the risk of SARS-CoV-2 infection seven or 14 days following immunization will be lower among vaccinated compared to unvaccinated HCWs.

**Methods**

**Study design and population**

A prospective cohort study was conducted among HCWs aged 16-65 years who took part in "Senior Shield" program [22, 24]. Since July 2020, all HCWs of all LTCFs in Israel have been required to undergo weekly screening for the detection of asymptomatic SARS-CoV-2
infection via nasopharyngeal RT-PCR testing. Those found positive were provided with the recommended care and requested to be quarantined for 10-14-days. All HCWs and tenants at the LTCFs with confirmed cases were repeatedly screened by RT-PCR until all three consecutive negative results. The program was active in 1078 LTCFs, both public and private institutions, with 46,024 HCWs (Supplementary material 1).

**Inclusion criteria of the primary analysis were:**

1) Adherence to routine screening for SARS-CoV-2 infection by RT-PCR testing. Specifically, HCWs who had ≥12 out of the 20 of the planned screening tests for the period September 2020 through January 2021; the rationale by utilizing this criterion was that we considered adherence to testing as a health behaviour, a main confounder in vaccine effectiveness studies, and to better identify current/active HCWs.

2) Working in LTCFs that vaccinated ≥75% of their employees collectively during three consecutive days.

3) Being RT-PCR negative for SARS-CoV-2 infection by the date of immunization with the second vaccine dose.

Unvaccinated HCWs at baseline, who were vaccinated later, were censored upon receiving their first vaccination dose in the primary analysis. Excluded from the primary analysis were HCWs working at institutions that did not have a collective immunization period, partially vaccinated HCWs at baseline (i.e. received one vaccine dose), and those who had a RT-PCR-confirmed SARS-CoV-2 infection before immunization, or between immunization with the second dose until day seven or 14 days post immunization.

A secondary approach was implemented in which data of all vaccinated HCWs were analyzed regardless of whether they worked at an institution with collective immunization period, to increase the generalizability of the study findings and reduce potential selection
bias. In this analysis, HCWs (n=1130) who were initially unvaccinated but received the vaccine later, contributed follow-up time to both the vaccinated and unvaccinated groups.

**Definition of the study variables**

Data were obtained through Senior Shield program on demographics, results of the RT-PCR tests, and COVID-19 immunization.

**Follow-up:** The follow-up starting dates were more than seven and >14 days post vaccination with the second BNT162b2 dose. Since for each LTCF, vaccination was done within three consecutive days, the second of the three consecutive days was defined at the "index" day for unvaccinated HCWs and events were counted after seven and >14 days after this date. By this, we created a matched (common) calendar baseline for the vaccinated and unvaccinated groups at the institution level (mostly calendar weeks 4-5 in 2021), which was important due to substantial changes in COVID-19 incidence during the study period. Both groups were followed until the earliest of the following events: acquisition of SARS-CoV-2 infection, or end of follow-up on April 11, 2021. For the unvaccinated individuals who opted to be vaccinated after the index date, the follow-up ended on the date of the first dose administration. We also tested an alternative approach, in which vaccinated and unvaccinated HCWs were not matched by baseline calendar time and were followed until the earliest of the mentioned above events. The start follow-up date for unvaccinated group in this analysis was determined as the average date of vaccination with the second vaccine dose January 30 2021.

**Effectiveness endpoints - the acquisition of SARS-CoV-2 infection:** a dichotomous variable (yes or no) was defined based on RT-PCR test results. The primary endpoint was the acquisition of SARS-CoV-2 infection >14 days after the second dose administration. To determine acquisition, we included only HCWs who had three or more RT-PCR tests during February 2021, three or more RT-PCR tests during March 2021 and one or more RT-PCR test during April 2021. By this, we created a homogenous cohort in terms of adherence to
RT-PCR screening, eliminating potential effect of immunization on testing. HCWs who tested positive between the first and the second dose administration and up to day 14 after the second dose administration were excluded from the primary analysis. RT-PCR screening policy for SARS-CoV-2 detection in the framework of the Senior Shield program was unchanged throughout the study. A secondary endpoint was SARS-CoV-2 acquisition more than seven days after the second dose administration.

The independent variable: COVID-19 vaccination status (a dichotomous variable). Fully vaccinated HCWs were defined as more than 14 days post two doses of BNT162b2 vaccine given three weeks apart (± 4 days). HCWs who did not receive any dose were classified as unvaccinated.

Covariates: The following variables were considered as confounders: age (years), gender, population group (general Jewish population, ultraorthodox Jewish population or Arab population), residential socioeconomic status (SES) [25] and residential area incidence rates of COVID-19. The residential area incidence rates (per 10,000) was categorized by as low (<15), intermediate (15-24) and high (25-457). We also assessed the level of vaccination uptake among all employees per each institution.

Cycle threshold (Ct) of SARS-CoV-2 RT-PCR testing: Ct of RT-PCR results can be used as surrogate of viral load, and inversely correlates with COVID-19 severity [26]. Increased Ct values of SARS-CoV-2 RT-PCR results were shown among vaccinated vs. unvaccinated HCWs [21]. Accordingly, we explored differences in Ct values between vaccinated and unvaccinated HCWs. Nasopharyngeal swabs were collected on a weekly basis using a standardized protocol. The majority of samples were tested at MyHeritage laboratory that processed daily between 10,000 and 20,000 samples. The detection of SARS-CoV-2 at MyHeritage laboratory was based on a single assay that detects the Orf1_ab gene, the BGI
SARS-CoV-2 RT-PCR testing kit [27]. The laboratories did not have information on the vaccination status of the HCWs or other background information.

Data analysis

Baseline characteristics of the study groups were described using means and standard deviations (SD) for continuous variables and counts, and percentages for categorical variables.

Curves of cumulative incidence of SARS-CoV-2 infection among vaccinated and unvaccinated groups were created using Kaplan-Meier survival analysis and compared with the log-rank test. Cox proportional hazards regression models [28] with follow-up time (days) as the time scale were constructed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SARS-CoV-2 acquisition. The "facilities" were included in the analysis as strata; i.e. the variable "facility" was treated as a "matching" variable. Independent variables were COVID-19 vaccination, gender, age, residential SES and the cumulative incidence of SARS-CoV-2 infection by residential area. We repeated the analysis while including the variable "level of vaccine uptake" in the model, to assess potential indirect (herd) protection. The variables "population group" and "residential SES" were significantly correlated (lower residential SES among Arabs than Jews, Spearman's rank correlation coefficient -0.59, p<0.0001), therefore only residential SES was included in the multivariable model. We calculated HR for vaccination compared with no vaccination. VE was calculated as: (1–HR)×100 and it was calculated from both >14 and more than seven days after the second vaccine dose until the end of the follow-up. The proportional hazards assumption was tested using the Schoenfeld residuals, with no violations found.

Sensitivity analysis was undertaken, in which the analyses were repeated following our secondary approach that included all vaccinated HCWs, regardless of whether their institution had collective vaccination period. We did not have the exact reasons for non-
adherence or low adherence of HCWs to RT-PCR testing, but mostly it was attributed to logistic reasons. Thus, we reanalyzed the data while considering various levels of adherence to testing to explore possible impact of potential selection bias. Differences in the median Ct values from RT-PCR test between fully vaccinated and unvaccinated HCWs were assessed using Mann-Whitney U test. Two-sided p value <0.05 was considered statistically significant. Analyses were done using R software, version 4.0.4.

Ethics
The study protocol was approved by the institutional review board of the Soroka University Medical Center, Beer-Sheva, Israel.

Results
Among 46,024 HCWs, 15,535 were adherent to routine screening for SARS-CoV-2 infection by RT-PCR testing; of these, 9162 (n=6960 vaccinated and n=2202 unvaccinated) worked in LTCFs in which employees were vaccinated within three consecutive days, and included in the main (calendar-matched) analysis (Figure 1). The mean age of the study sample was 46.2 years and most (79.5%) participants were females. The vaccinated group was older, included more males and individuals who lived in towns/communities of high SES rank and low COVID-19 incidence rates than the unvaccinated group. Vaccinated and unvaccinated HWCs were distributed across all levels of vaccine uptake, although slightly more unvaccinated HCWs worked in institutions with lower uptake (Table 1). Accordingly, we adjusted for these variables in multivariable models.

Vaccine effectiveness
Among the vaccinated group, 40 HCWs acquired SARS-CoV-2 infection >14 days post second dose (median follow-up, 66 days; cumulative incidence 0.6%). Among the unvaccinated group, 84 HCWs acquired SARS-CoV-2 (median follow-up 43 days;
cumulative incidence, 5.1%) (Figure 2). Significantly lower risk of acquisition of SARS-CoV-2 was found among vaccinated than unvaccinated HCWs (HR 0.11 [95% CI 0.07, 0.17]), yielding unadjusted VE of 89% (95% CI 83%, 93%). Multivariable Cox proportional hazards regression model that controlled for potential confounders showed an adjusted VE of 89% (95% CI 83%, 93%) >14 days after immunization with the second dose (Table 2). The level of vaccine uptake by the employees in each institution was inversely related SARS-CoV-2 infection incidence, but it did not affect the VE estimates (Supplementary Table 1). The results were similar when considering the period of more than seven days after the second dose (Supplementary Table 2, Supplementary Table 3, and Supplementary Figure 1).

Sensitivity analysis

Sensitivity analysis that included all vaccinated HCWs (n=11,496) who received two vaccine doses and unvaccinated HCWs (n=3151) (Supplementary Figure 2), showed comparable characteristics between these groups and those who were included in the primary analysis (Supplementary Table 4). During a median follow-up of 65 and 41 days of vaccinated and unvaccinated HCWs, respectively, the cumulative incidence of SARS-CoV-2 infection more than 14 days post second dose was 1.2% (n=131 events) and 7.9% (n=182 events), respectively (Supplementary Figure 3). The adjusted HR for the COVID-19 immunization was 0.15 (95% CI 0.11, 0.19) (Supplementary Table 5), yielding VE of 85% (95% CI 81%, 89%).

Considering different levels of adherence to routine RT-PCR testing by HCWs, showed 85%-90% VE against SARS-CoV-2 infection more than 14 days post second dose (Supplementary table 6).
SARS-CoV-2 RT-PCR Ct values and BNT162b2 immunization

Information on Ct values from RT-PCR test was available for 64 HCWs (20 were vaccinated and 44 were unvaccinated) (Figure 3). The median Ct value was significantly higher among fully vaccinated individuals than unvaccinated ones 32.0 (IQR=14.5) vs. 26.7 (IQR=8.8), p=0.008.

Discussion

In this study among HCWs in LTCFs, BNT162b2 VE against SARS-CoV-2 acquisition was 89% after 14 days post vaccination with the second dose. This finding was consistent after adjustment for confounders, and when considering the period of more than seven days after second dose. Our results were obtained in a "well-controlled" setting, by assessing comparable groups in terms of utilization of SARS-CoV-2 RT-PCR screening tests and follow-up calendar, during a mass deployment of COVID-19 immunization and substantial changes in the disease incidence in Israel [4, 5, 29].

HCWs are at increased risk for SARS-CoV-2 infection [10, 30, 31], additionally, HCWs of LTCFs might play a role in the virus transmission within the institution [32-34]. LTCFs have been the epicenter of COVID-19 outbreaks in many countries with high mortality among residents [32-34], who are highly vulnerable to severe and fatal disease given their usually advanced age, living environments, dependence on staff, functional and comorbid conditions. Accordingly, conferring maximal protection against both asymptomatic infection and disease, to both HCWs and residents of LTCFs was highly pursued in Israel, resulting in "Senior Shield" program [22, 24]. The MOH designated a special taskforce for the deployment of COVID-19 vaccines among LTCFs HCWs and residents, resulting in Israel being the first country to complete vaccination of all LTCFs as early as February 2021.

Our estimate of 89% effectiveness of two-dose BNT162b2 regimen against SARS-CoV-2 acquisition is consistent with findings of a study from England that reported 85% vaccine
effectiveness against any SARS-CoV-2 infection among HCWs [11]. Other studies reported higher effectiveness of >95% [16, 17], a discrepancy that might be due methodological variation.

We found significantly higher Ct values among vaccinated than unvaccinated HCWs. It was proposed that Ct values might represent viral load, and inversely correlates with COVID-19 severity [26] and transmissibility [35, 36]. Other studies from Israel and the United States provided supported findings [20, 21, 37].

Our study has limitations. We did not have data on symptoms, since the main goal of the RT-PCR screening was to detect and quarantine positive workers in order to prevent/stop the virus transmission. Thus, we were not able to produce separate VE estimates for asymptomatic or symptomatic infections as was the case in other studies among HCWs. We included working adults aged 65 years or less, thus severe comorbidities likely are not an issue in this population. Moreover most participants were women, thus direct extrapolation to the general population might be limited. We assessed only short-term protection following vaccination, therefore could not to assess potential waning immunity. Our study was undertaken during a period in which the Alpha variant (B.1.1.7) SARS-CoV-2 variant was predominant [4]. Current evidence showed waning immunity about six months following vaccination [38, 39] with the second BNT162b2 dose, and reduced 40-50% effectiveness against the Delta variant, although effectiveness against COVID-19 hospitalizations was 89% [40]. Most (75%) HCWs in our cohort received BNT162b2 vaccine and 25% were unvaccinated HCWs. Likely these groups differ in health behaviors. To account for these factors, we included in the primary analysis adherent HCWs to routine screening for SARS-CoV-2 infection, prior to and during COVID-19 vaccine deployment, thus creating homogeneous groups in term of RT-PCR testing uptake and minimizing potential effect of immunization on testing.
Information on Ct values was available for ~50% of infected HCWs, this is due differences between the laboratories in reporting format of the RT-PCR test results. The missingness was not related to vaccination status of the HCWs, since the laboratories did not have background information on the HCWs.

Our study has several strengths. We prospectively and systematically collected samples periodically from all our participants, reducing the potential biases in comparing vaccinated to unvaccinated HCWs. Our analytical approach adjusted for potential confounders that might affect both vaccine uptake and COVID-19 incidence, and importantly matching on calendar time, during a period with marked fluctuations in disease incidence. Lastly, we considered multiple sensitivity analyses showing consistent findings comparable with the main analysis.

Conclusions
Vaccination with two doses of BNT162b2 vaccine was highly effective in preventing acquisition of SARS-CoV-2 infection in HCWs of LTCFs, thus reducing the potential for transmission of the virus to the community, and in particular this highly vulnerable population.

Notes:
Author contributions
NM, AM, OB conceived the study, KM, DC, MM, IG, RD contributed to the study design, NM supervised all aspects of the study, AM, OB were responsible for data curation and analysis and verified the underlying data and results. KM, DC, RD contributed to data analysis, KM, RD wrote the first draft of the manuscript. All authors critically reviewed the manuscript and contributed to writing-editing and approved the final version.
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Potential Conflicts

None

Data sharing statement

Data analyzed in this study cannot be made publically available since legal restrictions apply.

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| Table 1: Baseline characteristics of the study sample—primary analysis | Unvaccinated (N=2202) | Vaccinated 2 doses + 14 days (N=6960) | Overall (N=9162) |
|---|---|---|---|
| **Sex** | | | |
| Female | 1827 (83.0%) | 5456 (78.4%) | 7283 (79.5%) |
| Male | 373 (16.9%) | 1476 (21.2%) | 1849 (20.2%) |
| Missing | 2 (0.1%) | 28 (0.4%) | 30 (0.3%) |
| **Age (years)** | | | |
| Mean (standard deviation) | 43.1 (11.7) | 47.2 (11.7) | 46.2 (11.8) |
| Median (interquartile range) | 44.0 (19.0) | 48.0 (19.0) | 47.0 (19.0) |
| (Min, Max) | (16.0, 65.0) | (16.0, 65.0) | (16.0, 65.0) |
| **Residential socioeconomic status** | | | |
| Low | 576 (26.2%) | 1736 (24.9%) | 2312 (25.2%) |
| Intermediate | 682 (31.0%) | 2140 (30.7%) | 2822 (30.8%) |
| High | 605 (27.5%) | 2424 (34.8%) | 3029 (33.1%) |
| Missing | 339 (15.4%) | 660 (9.5%) | 999 (10.9%) |
| **Population group** | | | |
| General Jewish population | 1745 (79.2%) | 5540 (79.6%) | 7285 (79.5%) |
| Ultraorthodox Jewish population | 65 (3.0%) | 107 (1.5%) | 172 (1.9%) |
| Arab population | 392 (17.8%) | 1313 (18.9%) | 1705 (18.6%) |
| **Calendar week of starting the follow-up** | | | |
| 3 | 73 (3.3%) | 384 (5.5%) | 457 (5.0%) |
| 4 | 1227 (55.7%) | 4323 (62.1%) | 5550 (60.6%) |
| 5 | 892 (40.5%) | 2240 (32.2%) | 3132 (32.6%) |
| 6 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 7 | 10 (0.5%) | 2 (0.2%) | 23 (0.1%) |
| **Residential area incidence of SARS-CoV-2 infection** | | | |
| Low (<15 per 10,000 persons) | 524 (23.8%) | 2220 (31.9%) | 2744 (29.9%) |
| Intermediate (15-24 per 10,000 persons) | 632 (28.7%) | 2115 (30.4%) | 2747 (30.0%) |
| High (25-457 per 10,000 persons) | 730 (33.2%) | 2024 (29.1%) | 2754 (30.1%) |
| Missing | 316 (14.4%) | 601 (8.6%) | 917 (10.0%) |
| **COVID-19 vaccination level per** | | | |
| facility | 0-59%  | 60-69% | 70-79% | 80-89% | 90-100% | Missing |
|----------|--------|--------|--------|--------|---------|---------|
|          | 343 (15.6%) | 411 (5.9%) | 754 (8.2%) | 532 (24.2%) | 1232 (17.7%) | 1764 (19.3%) |
|          | 532 (24.2%) | 1232 (17.7%) | 1764 (19.3%) | 831 (37.7%) | 2702 (38.8%) | 3533 (38.6%) |
|          | 831 (37.7%) | 2702 (38.8%) | 3533 (38.6%) | 403 (18.3%) | 2194 (31.5%) | 2597 (28.3%) |
|          | 403 (18.3%) | 2194 (31.5%) | 2597 (28.3%) | 20 (0.9%) | 280 (4.0%) | 300 (3.3%) |
|          | 73 (3.3%) | 141 (2.0%) | 214 (2.3%) |         |         |         |

*a The primary analysis included health care workers (HCWs) who were adherent to RT-PCR testing and worked in long-term care facilities (LTCFs) that vaccinated ≥75% of their employees against COVID-19 during 3 consecutive days. Follow-up starting date was determined by the vaccination time in each LTCF (mostly calendar weeks 4-5 (~end of January) in 2021) +14 days, thus yielding a "matched/common calendar period for the vaccinated and unvaccinated HCWs at the institution level (methods section).

*b Vaccinated with 2 doses of BNT162b2 COVID-19 vaccine, 3 weeks apart, and remained negative to SARS-CoV-2 until 14 day post vaccination.
Table 2: Relationships of COVID-19 immunization and other co-variates with the acquisition of SARS-CoV-2 infection >14 after immunization with 2\textsuperscript{nd} dose of BNT162b2 COVID-19 vaccine

|                                | Unadjusted HR (95% CI) | P value | Adjusted HR \(^a\) (95% CI) | P value |
|--------------------------------|------------------------|---------|----------------------------|---------|
| **COVID-19 vaccination**       |                        |         |                            |         |
| Unvaccinated                   | 1.00                   | <0.0001 | 1.00                       | <0.0001 |
| Vaccinated (2 doses +14 days)  | 0.11 (0.07, 0.17)      |         | 0.11 (0.07, 0.17)          |         |
| **Age, years**                 |                        |         |                            |         |
| <0.0001                        |                        |         |                            |         |
| **Sex**                        |                        |         |                            |         |
| Female                         | 1.00                   |         | 1.00                       |         |
| Male                           | 1.19 (0.74, 1.91)      | 0.0112  | 1.10 (0.90, 1.74)          | 0.650   |
| **Residential area incidence rate of SARS-CoV-2 infection** | | | | |
| Low (<15 per 10,000 persons)  | 1.00                   |         | 1.00                       |         |
| Intermediate (15-24 per 10,000 persons) | 1.33 (0.68, 2.61) | 0.399 | 1.95 (0.51, 3.82) | 0.051 |
| High (25-457 per 10,000 persons) | 3.32 (1.75, 6.31) | 0.0002 | 3.81 (2.00, 7.24) | <0.0001 |
| **Residential socioeconomic status\(^b\)** | | | | |
| Low                            | 1.00                   |         | 1.00                       |         |
| Intermediate                   | 0.67 (0.42, 1.07)      | 0.099   | 0.63 (0.41, 0.96)          | 0.0326  |
| High                           | 0.37 (0.20, 0.69)      | 0.0018  | 0.48 (0.27, 0.84)          | 0.0112  |
| **Population group\(^b\)**    |                        |         |                            |         |
| General Jewish population      | 1.00                   |         |                            |         |
| Ultraorthodox Jewish population | 1.60 (0.54, 4.72)     | 0.389   | Not included               |         |
| Arab population                | 2.16 (1.29, 3.63)      | 0.0032  | Not included               |         |

HR: Hazard ratio; CI: Confidence intervals

\(^a\) Multivariable Cox regression model adjusted for the variables in the table except of "population group", given its high correlation with residential area socioeconomic status (SES).

\(^b\) The variables population group was correlated with residential SES (Spearman’s rank correlation coefficient -0.59, p<0.0001), therefore only the variable residential socioeconomic status was included in the model.
Figure legend

Figure 1: Flow chart of selection the study groups of the primary analysis

COVID-19 vaccination campaign of health care workers (HCWs) of long-term care facilities (LTCFs) in Israel took place between December 22, 2020 and January 29, 2021. The primary analysis included HCWs who worked in LTCFs that vaccinated ≥75% of their employees during three consecutive days. The follow-up starting dates were >7 and >14 days post vaccination with the second BNT162b2 dose. The second of the three consecutive vaccination days defined at the "index" date for starting the follow-up among the unvaccinated HCWs. By this, we created a matched (common) calendar baseline for the vaccinated and unvaccinated groups at the institution level (mostly weeks 4-5 in 2021).

Overall, 4221 HCWs (9.1%) did not work in LTCFs that vaccinated their ≥75% employees within three consecutive days, thus were excluded from the primary analysis. Overall, 6974 vaccinated and 2368 unvaccinated HCWs were included in the primary analysis of vaccine effectiveness against SARS-CoV-2 >7 days post dose 2. The respective numbers were 6960 and 2202 for the effectiveness analysis >14 days post dose 2.

Abbreviations: HCWs: Health care workers; LTCF: long-term care facility

Figure 2: Cumulative incidence of RT-PCR confirmed SARS-CoV-2 infection among health care workers 14 days after vaccination with the second dose of BNT162b2 compared unvaccinated ones

Results of the primary analysis of calendar-matched groups. P value by log-rank test

Shaded lines represent 95% confidence intervals.

Figure 3: Box plots of Cycle threshold (Ct) values from RT-PCR test targeting SARS-CoV-2 ORF1ab gene among BNT162b2 fully vaccinated and unvaccinated individuals
Fully vaccinated: >14 days after second dose

Box plots of Ct values (Y-axis) of SARS-CoV-2 positive RT-PCR results according to COVID-19 vaccination status (X-axis) among health care workers

The line in the mid of the box represents the median level, lower bound of the box represents the 25th percentile, the upper bound of the box represents the 75th percentile, the lowest point of the lower whisker represents the minimum and the highest point of the upper represents the maximum. Each circle represents Ct value of one participant.

P value=0.008 by Mann Whitney U test.
Figure 1

N=46,024 HCWs from 1078 LTCFs

N=38,576 remained uninfected until second dose administration

N=15,525 from 740 LTCFs adherent with routine RT-PCR screening

N=11,314 HCWs from 464 LTCFs vaccinated within 3 consecutive days (index follow-up starting date= mostly weeks 6-12 in 2021)

N=10,235 HCWs adherent with routine RT-PCR screening and remained uninfected until second dose administration

N=9342 remained uninfected until day 7 after second dose administration

N=6974 vaccinated

N=2368 unvaccinated

N=6960 remained uninfected until day 14 after a second dose administration

N=2202 remained uninfected/unvaccinated until day 14 after second dose administration

N=7448 previously infected with SARS-CoV-2

N=23,041 (50.0%) HCWs not fully adherent with routine RT-PCR screening

N=4221 (9.1%) did not work in LTCFs that vaccinated their employees within 3 consecutive days

N=1079 infected before second dose administration

N=893 infected between 1-7 days after second dose administration; or unvaccinated who received first dose

N=180 infected between 8-14 days post second dose administration, or unvaccinated who received first dose
Figure 2

Status
not Vaccinated  Vaccinated

Cumulative Incidence (%)

Time (days)

p < 0.0001

Number at risk

not Vaccinated  2202  2031  1723  1448  1282  1169  1107  1078  1051  751  70  0
Vaccinated  6960  6948  6935  6924  6903  6894  6884  6879  6861  5404  519  0

Cumulative number of events

not Vaccinated  0  30  44  58  67  74  81  82  82  84  84  84
Vaccinated  0  6  11  21  31  34  37  40  40  40  40  40
Figure 3

1 - Not Vaccinated

2 - Fully Vaccinated

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