BNT162b2 vaccine effectiveness in preventing asymptomatic infection with SARS-CoV-2 virus: a nationwide historical cohort study

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Summary

An 89% reduction in SARS-CoV-2 infection incidence rate was observed among vaccinated compared with unvaccinated in a cohort of individuals, who were frequently screened by PCR tests.
Abstract

Background

There is strong evidence regarding the efficacy and effectiveness of BNT162b2 vaccine in preventing symptomatic infection with SARS-CoV-2 virus.

There is a relative paucity of data regarding effectiveness in prevention of asymptomatic infection.

Methods

In this real-world observational study, we identified a sub-population of individuals in a large health maintenance organization who were repeatedly tested for SARS-CoV-2 infection by PCR. We included these individuals in the study cohort, and compared those who were vaccinated with BNT162b2 mRNA vaccine to the unvaccinated ones. A positive SARS-CoV-2 PCR test result was used as the outcome. Follow-up period was from January 1, 2021 until February 11, 2021.

Findings

6,286 individuals were included in the cohort. Seven days following the second vaccine dose, a rate of six positive PCR tests per 10,000 person-days was recorded, compared with a rate of 53 positive tests per 10,000 person-days for the unvaccinated group. The estimated vaccine effectiveness against infection with SARS-CoV-2 virus after two vaccine doses was 89% (95% confidence interval 82%-94%). The estimated effectiveness two weeks following the first vaccine dose was 61% (95% confidence interval 49%-71%).
Interpretation

In this study, vaccination with BNT162b2 reduced infection rates among individuals who underwent screening by frequent SARS-CoV-2 PCR testing. Using a cohort of frequently tested individuals reduced the indication bias for the PCR testing, which enabled estimation of infection rates.

Funding

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Keywords:

Covid-19, SARS-CoV-2, vaccine effectiveness, asymptomatic infection, observational study
Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has afflicted more than 129 million persons worldwide and caused more than 2.8 million deaths as of the end of March 2021. The Pfizer BNT162b2 mRNA vaccine was the first to receive emergency authorization, first in the UK, then in the US and globally at the beginning of December 2020. Since then, more than 100 million doses of this vaccine have been administered worldwide.

BNT162b2 vaccine efficacy was demonstrated in a large phase III randomized controlled clinical trial showing 95% protection against confirmed symptomatic disease seven days after the second dose and 52.4% before receiving the second dose. Several observational real-world clinical studies later demonstrated similar vaccine effectiveness. However, these studies lacked active laboratory surveillance among both vaccinated and unvaccinated individuals, missing diagnoses of asymptomatic cases, possibly overestimating the protection conferred by the vaccine.

The proportion of individuals with asymptomatic SARS-CoV-2 is hard to estimate and best requires prospective, regular screening of a defined population. In a systematic review that summarized 79 reports, the proportion of people who were infected with SARS-CoV-2 and remained asymptomatic throughout infection was 20% (95% CI 17–25), while the proportion was 31% (95% CI 26–37) in seven studies in which active screening for SARS-CoV-2 was performed. While evidence suggests that the risk for transmission of SARS-CoV-2 from asymptomatic individual is significantly lower compared to pre-symptomatic or symptomatic case, understanding vaccine effectiveness on asymptomatic infection is important for public health policy development.

Vaccine protection against asymptomatic SARS-CoV-2 has been estimated in several few studies. In the Moderna mRNA vaccine clinical study, participants underwent nasopharyngeal polymerase-chain-reaction (PCR) testing prior to each dose and were shown to have a 67% decrease in asymptomatic infection following the first dose (0.1% versus 0.3%). In a large study from Israel, in which almost 600,000 vaccinated individuals were compared to a matched group of unvaccinated
individuals, vaccine effectiveness was 92% at seven days following the second vaccine dose for all documented symptomatic and asymptomatic infections\textsuperscript{4}. In this study, the proxy for an asymptomatic infection was a positive PCR without documented symptoms; however, this methodology does not overcome bias of different test-seeking behaviors. In addition, the Israeli public health policy exempts fully vaccinated individuals from undergoing PCR tests after being exposed to an individual with a confirmed SARS-CoV-2 infection or when entering the country, which may further bias the results of observational studies that uses the entire population as their cohort. This may result in overestimation of vaccine effectiveness, due to under-diagnosis of asymptomatic infections among the vaccinated individuals. A recent study from England, that followed a cohort of healthcare workers who underwent regular screening\textsuperscript{14}, demonstrated vaccine effectiveness of 85% seven days after the second vaccine dose, for both symptomatic and asymptomatic infections.

To further estimate vaccine protection against any SARS-CoV-2 infection, we conducted this observational study using a historical cohort of individuals repeatedly tested for SARS-CoV-2 before and after receiving the BNT162b2 vaccine.

Methods

Setting and data source

Meuhedet health maintenance organization (MHMO) serves 1.2 million members in Israel. The Israeli National Health Insurance Act of 1994 requires that all citizens be registered with one of four HMOs, which in turn are obliged to insure every citizen wishing to join, irrespective of sex, age, physical condition or any other criterion. Citizens can move freely among the HMOs, which operate in every region.

MHMO’s comprehensive database stores members’ medical data from all healthcare providers, including dates of vaccination with the BNT162b2 vaccine and all Covid-19 PCR test results that were undertaken since the beginning of the pandemic.
We identified a sub-population of MHMO members who were repeatedly tested for SARS-CoV-2 infection using PCR tests. We used these individuals as the cohort for the study, using BNT162b2 mRNA vaccine as the exposure and a positive SARS-CoV-2 PCR test result as the outcome.

The follow-up period started on January 1, 2021 and ended on February 11, 2021 (six weeks long). Data were extracted on February 17, 2021.

This study was approved by MHMO’s institutional review board number 03-17-02-21, and investigators were exempt from requesting informed consent. One author, DS has a potential conflict of interest.

Study participants

We extracted all SARS-CoV-2 PCR tests and SARS-CoV-2 serological assays that were undertaken by MHMO’s members since the beginning of the pandemic.

Inclusion criteria: Individuals aged 16 or older, who had at least two PCR tests during November, at least two PCR tests during December and at least one PCR test during January.

Exclusion criteria: Individuals who tested positive by either a PCR test or a serological assay before the beginning of the follow-up period (January 1, 2021). We also excluded individuals who tested positive by a serological assay during the follow-up period, since we could not determine their exact infection date. 13 individuals had a positive serological assay during the study period. One of them was vaccinated twice before the positive serology test, two were vaccinated once before the test, and ten were not vaccinated. The following serological assays were used: LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy or SARS-CoV-2 IgG II Quant, Abott Illinois, United States. Both assays identify antibodies against the spike protein, and cannot distinguish prior vaccination from past infection. In general, physicians in MHMO were discouraged from ordering serology tests for vaccinated individuals.

The participants were included in the analysis until the date of their first positive SARS-CoV-2 PCR test or the last negative test within the follow-up period. The outcome was the result of this test.
For each patient we collected the BNT162b2 vaccination dates, SARS-CoV-2 PCR tests that were undertaken during the follow-up period, and demographic data: sex, age, population sector by place of residence (general Jewish, Arab, or ultra-orthodox Jewish), given that in Israel different ethnocultural groups tend to reside in different, usually clearly defined, areas.

**Exposure periods**

In order to estimate vaccine effectiveness during different post-vaccination periods, we calculated infection rates separately for the following:

1. Before the first vaccination (including vaccination day).
2. From fourteen days after the first vaccine dose until the day of the second vaccine dose.
3. One to six days following the second vaccine dose.
4. Seven days and above following the second vaccine dose.

The participants were included in the analysis of the different periods according to the timing of their vaccination within the study period. The days before the first vaccine dose of an individual were added to the first period, from fourteen days after the first vaccine until the second vaccine was the second period, the first six days following the second vaccine dose were added to the third period, and the remaining days in the cohort of this individual were added to the fourth period. An individual could contribute days to one period or more.

**Statistical methods**

For each period, we summarized exposure days of all individuals in each of the four periods, and we counted individuals with a positive PCR test as cases. We calculated infection rates per 10,000 person-days (PD) for each period, and then calculated risk ratios for vaccinated individuals compared with unvaccinated. We estimated the vaccine effectiveness as one minus the risk ratio.

In order to overcome possible variation of infection rates across the different population sectors, we calculated separately infection rates for each sector.
The incidence infection rates in Israel increased at the beginning of the follow-up period from a moving-seven-days-average of 4,728 new cases per day on January 1, 2021, reaching a peak of more than 8,000 new cases per day from January 14 to January 20. The rate slowly subsided while remaining above 6,500 new cases per day until February 7, reaching a rate of 5,822 new cases per day at the end of the follow-up period on February 11, 2021. In view of this variation, we performed a sensitivity analysis and calculated the rates in two-weeks long intervals: January 1-14, January 15-28, and January 29 – February 11.

We used chi-square test to examine the association between categorical variables and analysis of variance (ANOVA) to analyze the differences among means. Analyses were conducted with IBM SPSS v27. Two-tailed p-values are reported, and α=0·05 for confidence interval (CI) calculations.

Results

The participants

6,286 individuals met the inclusion criteria and were eligible for the study. During the study period 2,941 of them received two doses of BNT162b2 vaccine, 1,445 received only one dose and 1,900 were not vaccinated at all (table 1). Mean age of the two-dose vaccinated group was significantly higher than mean age of individuals who received a single vaccine dose or none (52 ± 17 years vs 41 ± 21 years and 36 ± 19 years respectively, p-value<0.001). 1,055 individuals (17%) were 65 years old or older. Significantly more PCR tests were performed from November 1, 2020 until the end of the follow-up period for the fully vaccinated group compared with individuals who were vaccinated with a single dose or none (13 tests vs 9 tests and 10 tests respectively, p-value<0.001). 53% of the women (1,961 of 3,685) were vaccinated with two doses compared with 38% of the men (980 of 2,601) (p-value<0.001). Vaccination rates also significantly varied between the different sectors in our cohort (p-value<0.001).
Exposure days and outcome

There were 190,084 exposure days for the study cohort with mean exposure days for individual: 30 (standard deviation 11.5). Table 2 summarizes the exposure days for each of the vaccination periods.

There were 382 positive SARS-CoV-2 PCR tests in the first period (unvaccinated individuals), with a calculated rate of 53 cases per 10,000 PD. 14 days and more after the first vaccine dose there were 59 cases, a rate of 21 cases per 10,000 PD, effectiveness 61% (CI 49%-71%). During the first six days following the second dose only 16 cases were recorded, a rate of nine cases per 10,000 PD, effectiveness 82% (CI 71%-89%). In the period that started a week after the second vaccine dose, 15 cases were recorded, with a rate of six cases per 10,000 PD, effectiveness 89% (CI 82%-94%) (Table 2).

Effectiveness across different sub-populations and time periods

Infection rates varied significantly across the different populations. The Arab and general Jewish population had similar infection rate for the unvaccinated group (35 and 36 cases per 10,000 PD, respectively), compared with 112 cases per 10,000 PD for the unvaccinated group of ultra-orthodox Jewish population. Table 3 summarizes the infection rate ratios and effectiveness separately for the ultra-orthodox Jewish population and the rest of the cohort. Vaccine effectiveness seven days post second vaccine dose was 90% for the ultra-orthodox Jewish (CI 68%-97%, n=1,177), and 86% for the rest of the cohort (CI 75%-92%, n=5,109).

A sensitivity analysis for three two-week periods was performed in order to overcome a possible bias from temporal trends. This analysis was limited due to low number of cases and exposure days for some of the analyzed periods. However, the effectiveness trend was clear for all three periods.

Figure 1 presents the daily incidence rates of positive PCR tests in Israel (per 100,000 people) and in the study cohort (per 10,000 people).
Discussion

In a cohort of individuals who underwent frequent SARS-CoV-2 PCR testing we found that the rate of positive SARS-CoV-2 PCR tests in the vaccinated group was reduced by 61% from 14 days after the first vaccination and by 89% from seven days after the second vaccination. The frequent PCR testing in our cohort enabled estimation of infections, whether symptomatic or asymptomatic. The reduction ratio remained constant between the individuals in ultra-orthodox Jewish towns, which had higher incidence of COVID-19 infection, and the other cohort participants. The large cohort with its large age variance suggests that these results may be applicable in different population groups.

A study that assessed the effectiveness of BNT162b2 vaccine among 600,000 individuals showed 92% reduction in positive PCR test. Another study which monitored daily symptom reporting with an immediate same-day testing allowed for prompt (<24h) detection and investigation of exposed or symptomatic health care workers, and showed that among 4,081 vaccinated healthcare workers in Israel, 22 (0.54%) developed COVID-19 1-10 days (median 3.5 days) after the vaccine first dose. Additional analysis estimated vaccine effectiveness of 51% of BNT162b2 vaccine in reducing positive PCR rates, 13-24 days following vaccination with the first dose. These studies were limited in their ability to assess asymptomatic SARS-CoV-2 infection rates, due to different test-seeking behaviors that results in different rates of PCR testing by vaccinated and unvaccinated individuals. A study of healthcare workers from California, half of whom had mandatory weekly PCR screening after the first and second vaccination, showed that the absolute risk of testing positive for SARS-CoV-2 after vaccination was 1.19% among health care workers who had mandatory screening. However, among healthcare workers who received the second dose two or more weeks previously there was a positivity rate of 0.05%. Another study of healthcare workers, undergoing weekly PCR testing showed a 90% effectiveness two weeks after the second vaccination and 80% 14 days after the first vaccination. A recent study that followed healthcare workers who underwent routine fortnight PCR screening demonstrated 85% effectiveness seven days after the second vaccine dose.
This compares with 89% seven days after the second vaccination and 61% after the first vaccination in our study.

The temporal trend of daily infection incidence rate of the unvaccinated group mirrors the pattern of the incidence rate of the total Israeli population (figure 1). Fewer tests were performed during weekends, causing weekly fluctuations. The rates in the unvaccinated group in our cohort were ten times higher compared with the total population, which suggests that the study cohort was a high-risk group. This assumption is supported by the cohort demographics: 17.7% of our cohort was from the ultra-orthodox population who had a higher incidence of SARS-CoV2 than the general population. In addition, the frequent PCR testing in this cohort may partially explain the higher incidence rate of SARS-CoV-2 compared with the total population of Israel, since it has been shown that 20-31% of SARS-CoV-2 infection are asymptomatic.

The strengths of this study are full data collection and the comprehensive countrywide assessment in different population groups. The entry criteria required at least two PCR tests in November, two tests in December and one in January ensuring that the cohort was composed mainly of frequently screened individuals. The repeated testing reduces the false negative rate of a single test, thus decreasing the likelihood of missing an asymptomatic infection. Misclassification into the vaccinated or unvaccinated groups is unlikely since all interactions were recorded in our electronic medical record (EMR), at the time of vaccination regardless of the vaccination location. The EMR also ensured full data collection of PCR test results from all laboratories.

The limitations of this study include the observational nature of the study design. We do not know the reason why individuals within our cohort, chose to be vaccinated or not, or why they had repeated PCR testing. From table 1 we see significant differences between the three groups (unvaccinated, partially vaccinated and fully vaccinated). The age difference between vaccinated and unvaccinated individuals resulted from the fact that the study period overlapped the beginning of the Israeli vaccination campaign, when vaccine availability was initially limited to older citizens. This table also shows that the ultra-orthodox Jewish sector was vaccinated at lower rates; however, the
calculated effectiveness for this sector did not differ from the other sectors (table 3). The number of PCR tests per individual was significantly higher for the fully vaccinated group (table 1). Consequently, there is a lower chance of missing an infection in this group, which could cause a bias reducing the calculated effectiveness. We were unable to validate the reason for the repeated PCR testing, and it is possible that some of the tests were performed by symptomatic individuals. During the study period PCR tests were free and widely available in Israel and did not require a physician’s referral. In the ultra-orthodox community, young adults continued to study in high schools and religious institutions during the outbreak; the repeated testing in this group could be related to outbreak investigation or symptomatic infection. Thus, the increased effectiveness of the vaccine seen in the ultra-orthodox population might be an artifact. The cohort’s limited size and short follow-up period did not allow for a multivariate analysis and estimation of vaccination effectiveness in reducing infection in different age groups. In addition, due to the high uptake of the second vaccination, we could not assess the long-term effectiveness of a single dose.

Conclusions: In this real world setting, vaccination greatly reduced infection rates among individuals who underwent screening by frequent SARS-CoV-2 PCR testing.

Recommended further research: a prospective clinical trial needs to be undertaken in order to confirm this finding and to establish the long-term protection from asymptomatic infection following the first and second vaccine dose.
Patient Consent Statement

This database study was approved by the local ethical committee that decided that patient consent was not required.

Acknowledgments:

GZ and DS contributed equally to this research.

De-identified participant data and statistical analysis will be made available via the corresponding author for a year from publication.

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Potential conflict of interest statement: DS reports receiving personal fees from Pfizer, outside the submitted work (advisory board on Trumenba); and Consultation fees from GSK and Gilead. The other authors, GZ, RB, IK, FHS, IK, DM and ADH declare no competing interests.
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|                   | Unvaccinated | Vaccinated with one dose | Vaccinated with two doses | p-value  |
|-------------------|-------------|--------------------------|---------------------------|----------|
| **Overall**       | 1,900       | 1,445                    | 2,941                     |          |
| **Women (%)**     | 1,007 (53%) | 717 (50%)                | 1,961 (67%)               | <0.001   |
| **Mean age, years ± SD** | 36 ± 19     | 41 ± 21                  | 52 ± 17                   | <0.001   |
| **Age >=65 years (%)** | 165 (9%)    | 205 (14%)                | 314 (11%)                 | <0.001   |
| **Sectors (%)**   |             |                          |                           |          |
| General Jewish (n=4,410) | 1,189 (63%) | 966 (67%)                | 2,255 (77%)               |          |
| Ultra-orthodox Jewish (n=1,177) | 314 (11%)   | 314 (11%)                | 685 (23%)                 | <0.001   |
| Arabs (n=699)     | 186 (10%)   | 141 (10%)                | 525 (28%)                 | <0.001   |
| **Mean number of PCR tests* ± SD** | 10 ± 3.7    | 9 ± 3.1                  | 13 ± 3.6                  | <0.001   |

* performed from Nov 1, 2020 to the end of the follow-up period

Table 1: Characteristics of participants according to their vaccination status at the end of the follow-up period.
Table 2: Incidence infection rates of SARS-CoV-2 and BNT162b2 vaccine effectiveness

| Time Period                          | Number of exposure days | PCR positive cases | Incidence rate per 10,000 person-days | Rate reduction compared with unvaccinated (95% CI) |
|-------------------------------------|-------------------------|--------------------|----------------------------------------|-----------------------------------------------|
| before the 1st vaccine (= unvaccinated) | 71,797                  | 382                | 53                                     | NA                                            |
| 14 days and more following the 1st dose | 28,727                  | 59                 | 21                                     | 61% (49%-71%)                                 |
| 1-6 days following the 2nd dose      | 16,921                  | 16                 | 9                                      | 82% (71%-89%)                                 |
| 7 days and more following the 2nd dose | 26,260                  | 15                 | 6                                      | 89% (82%-94%)                                 |
Table 3: Incidence infection rates of SARS-CoV-2 and BNT162b2 vaccine effectiveness according to population sectors

|                          | Number of exposure days | PCR positive cases | Incidence rate per 10,000 person-days | Rate reduction compared with unvaccinated (95% CI) |
|--------------------------|-------------------------|--------------------|---------------------------------------|-----------------------------------------------|
| **Arabs and general Jewish populations (n=5,109)** |                         |                    |                                       |                                               |
| before the 1st vaccine (= unvaccinated) | 55,250                 | 197                | 36                                    | NA                                            |
| 14 days and more following the 1st dose | 25,457                 | 48                 | 19                                    | 47% (28%-61%)                                  |
| 1-6 days following the 2nd dose | 15,153                 | 13                 | 9                                     | 76% (58%-86%)                                  |
| 7 days and more following the 2nd dose | 23,674                 | 12                 | 5                                     | 86% (75%-92%)                                  |
| **Ultra-orthodox Jewish populations (n=1,177)** |                         |                    |                                       |                                               |
| before the 1st vaccine (= | 16,547                 | 185                | 112                                   | NA                                            |
| Unvaccinated | | | |
|----------------|----|----|----|
| 14 days and more following the 1st dose | 3,270 | 11 | 34 | 70% (45%-84%) |
| 1-6 days following the 2nd dose | 1,768 | 3 | 17 | 85% (53%-95%) |
| 7 days and more following the 2nd dose | 2,586 | 3 | 12 | 90% (68%-97%) |
Figure 1: daily incidence rates of positive SARS-CoV-2 PCR tests in Israel compared with the study cohort groups*.

* The last three days of the study period are not presented since the total amount of days at risk in the cohort was lower than 2000 person-days.
