BNT162b2 mRNA Vaccine Effectiveness Given Confirmed Exposure:

Analysis of Household Members of COVID-19 Patients

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Summary: We evaluated BNT162b2 vaccine effectiveness against infection in high-risk exposure settings, by analyzing vaccinated and unvaccinated household members of individuals with SARS-CoV-2. The vaccine is effective in high-risk real-life exposure scenarios, but not as effective as in the general population.

Abstract

Background:

While BNT162b2 vaccine-efficacy analyses were previously published, the effectiveness of the vaccine in preventing COVID-19 given confirmed exposure has not been previously demonstrated, even though it has policy implications, such as the need for self-quarantine when exposure has occurred or protective measures for vaccinated individuals in high-risk areas.

Methods:

In a retrospective cohort study, we used data collected between 20/12/2020 and 17/03/2021 from the second largest healthcare provider in Israel to analyze the probability of an additional household infection occurring within 10 days after an index infection. In model 1, vaccine effectiveness was described for Fully Vaccinated individuals (7 or more days from second dose) versus either Unvaccinated participants or those Recently Vaccinated Once (0-7 days from the first dose, presumably still unprotected). Secondary analyses included correction for differing testing rates. In model 2, we conducted a separate analysis of households comprised of only adults with the same vaccination status.

Results:

173,569 households were included, of which 6,351 households had an index infection (mean [SD] age, 58.9 [13.5] years; 50% were women).Adjusted vaccine effectiveness of Fully Vaccinated compared to Unvaccinated participants was 80.3% [95% CI, 73.5 to 85.4] and 82.0% [95% CI, 75.6 to 86.8] compared to those Recently Vaccinated Once.

Conclusions:

The BNT162b2 vaccine is effective in a high-risk real-life exposure scenario, but the protection rates afforded in these settings are lower than those previously described. Household members of patients infected with SARS-CoV-2 and individuals with a confirmed significant exposure to SARS-CoV-2 are still at risk of being infected even if fully vaccinated.

Introduction

During the COVID-19 pandemic, policymakers are required to make decisions based on incomplete data in an ever-changing environment[1,2]. Any assessment of the effect of the vaccine by use of observational data is complicated by two factors. First, the probability to be infected is greatly influenced by personal behavior and transmission rates in the individual's immediate surroundings; second, the probability to be tested for SARS-CoV-2 depends on multiple factors, such as education or testing availability[3]–and often on the presence of symptoms.

Household studies are an efficient way of assessing vaccine effectiveness in a given population, allowing for analyses of infection rates when exposure is confirmed with a high degree of certainty.[4-7] The probability to be tested for SARS-CoV-2 when one's household member had already been infected is extremely high. This allows for a closer analysis of asymptomatic infection, which is often not tested and therefore underdiagnosed–potentially impacting the vaccine effectiveness analyses published thus far.

We conducted this retrospective study in order to evaluate vaccine effectiveness given verified and significant exposure to SARS-CoV-2.

Methods

We performed an observational cohort study that included household members of confirmed SARS-CoV-2 cases, and estimated the effectivness of the BNT162b2 vaccine in this high-risk setting. Participants were considered for inclusion from 20/12/2020 onwards, corresponding to the starting date of the Israeli SARS-CoV-2 vaccination rollout program. The occurrence of a first episode of infection was recorded up to 03/8/2021; by that time roughly 50% of the entire Israeli population had been vaccinated. Additional household infections were recorded for ten extra days. The follow-up period corresponds to the time when the Alpha variant was the dominant strain in Israel.[9–11]

We analyzed household contacts of confirmed SARS-CoV-2 cases, thereby including solely a population at a very high risk of contracting SARS-CoV-2. Thus, we essentially examined vaccine effectives given confirmed exposure, comparing those exposed but not infected to those exposed and infected, across vaccination statuses.

Study population

We used the comprehensive database of the Maccabi Healthcare Services, a 2.5-million-member state-mandated health fund in Israel. For the purpose of this analysis, only households with two adults were included, so the protective effect of vaccination could be assessed in a relatively homogenous adult population, given reports of both lower transmission and lower susceptibility in children[12]. Transmission dynamics could be influenced by age, and children are more likely to be asymptomatic and less likely to be tested. Additionally, including more than two members would have required a correction for the number of 'individuals at risk' as well as for 'degree of exposure'. That is, children may affect the magnitude of exposure, as they increase the number of persons per household[12], potentially adding confounding effects as their relative contribution to exposure, due to age-varying transmission dynamics and additive exposure, is unknown.

The analysis is focused on couples in order to achieve the best means to calculate the risk for any person from significant exposure. Households with no confirmed SARS-CoV-2 infections prior to the study, with a confirmed index case diagnosed during the study period and with one additional adult were included in the study. The period used for screening for lack of prior infection was from the beginning of the pandemic in Israel on 28/2/2020.

Participants were classified into one of three vaccination-status groups at the time of the index case (the confirmed exposure): Unvaccinated; Recently Vaccinated Once, i.e. those vaccinated with the first vaccine dose within 0-7 days before the index infection, and Fully Vaccinated, i.e. those who were 7 or more days post the second dose by the time of the confirmed exposure. The Recently

Vaccinated Once was used as a reference period, when the vaccination's protective effect is presumably still insignificant (as opposed to persons more than 7 days after the 1st dose, when some protection does probably exist)[13]. This enabled us to compare persons who chose to be vaccinated and were either fully protected or not protected at all, and thus control for possible inherent differences between those who chose not to be vaccinated at all. Comparison to other vaccination statuses (where the vaccine was presumably partially effective) is included in the supplementary.

Study outcomes

The study's primary outcome was SARS-CoV-2 infection (regardless of symptoms) within ten days of SARS-CoV-2 diagnosis in an additional adult member of the same household (where an index infection occurred). Both index and additional cases were defined by at least one positive SARS-CoV-2 polymerase chain reaction (PCR) test recorded in the MHS computerized database, considering that all such testing in MHS members is recorded centrally. Household members of confirmed cases were considered not infected if all PCR tests were negative or if no SARS-CoV-2 testing was performed. In Israel, RT-PCR tests are readily available and offered for free, and the tests are obtained from nasopharyngeal swabs, using nationally approved SARS-CoV-2 polymerase-chain-reaction (PCR) testing kits[8,14]. Governmental recommendations in Israel state that unvaccinated individuals in close contact with an infected SARS-CoV-2 individual should self-quarantine and be tested. Testing is not mandatory but advised and is necessary in order to shorten the individual's self-quarantine period.

Data

The MHS databases were used for this study. As annual disengagement rates are lower than 1%, longitudinal data are available for nearly all persons insured in the MHS.

Statistical analysis

Model 1:

We assessed the probability of a SARS-CoV-2 infection occurring from one day and up to 10 days after a previously diagnosed SARS-CoV-2 infection in a given household; a window that was based on the clinical course of the infection alongside preliminary investigations of data which demonstrated that most household non-index infections occured in the first days after the index case's positive test (Table S10).

The probability of being infected was calculated separately for the three vaccination status groups, namely the Unvaccinated, those Vaccinated within 0-7 days of the first dose of the vaccine, and the Fully Vaccinated. For the primary endpoints, vaccine effectiveness was defined for Unvaccinated versus Fully Vaccinated and for Recently Vaccinated Once versus Fully Vaccinated as one minus the risk ratio. Adjustment for age, sex, socioeconomic status (SES) and the following comorbidities, each calculated separately as binary variable: diabetes, cancer, cardiovascular diseases, obesity, asthma, hypertension and immunosuppression was applied. SES index of members' enumeration area is based on several parameters including household income, educational qualifications, household crowding, material conditions and car ownership, and is ranked from 1 (lowest) to 10. The adjusted risk ratio (RR) was calculated using log binomial model.

Corrected vaccine-effectiveness rates

Individuals differ when it comes to their decision to be tested for SARS-CoV-2. Their vaccination status, perceived risk of infection, and symptomatology could all affect this decision[15]. Furthermore, the Israeli Ministry of Health's regulations indicating that fully vaccinated persons were not obliged to exercise self-quarantine when exposed to a confirmed SARS-CoV-2 individual may have affected the likelihood of vaccinated persons to be tested after exposure. We hence carried out a secondary analysis attempting to account for differing testing behavior possibly resulting in missed SARS-CoV-2

diagnoses. We calculated corrected vaccine effectiveness rates, assuming that untested individuals were *as likely* to be infected as tested ones. Therefore, we calculated a corrected effectiveness rate, simulating a scenario in which 100% of adult household members are tested, under the assumption that the probability of test positivity remains constant (rather than decreases in untested individuals). This analysis intends to demonstrate the least-favorable (or strictest) scenario for vaccine effectiveness, enabling us to estimate *lower-bound effectiveness*.

A further sensitivity analysis was conducted to examine whether results would change if a different time interval were to define 'index' and 'additional' cases (instead of 1-10 days, 2-, 3- or 4-to-10-day intervals). Results did not materially change (Figure S3).

Model 2

In this model, our analyses addressed the problem of defining an "index" infection as opposed to an "additional" infection, in light of a known time lag between the infection event and its detection (positivity lag and symptom lag)[16]. That is, it could be argued that the temporal sequence of household infections reflects the time of *testing* (or *detection*), but not necessarily the time of *infection*, especially when these are close (i.e., the index infection and the additional infection are actually reversed).

Therefore, this final analysis examined household members who shared the *same* vaccination status. That is, both members had the same vaccination status on the day of first positive PCR test in that given household. These couples are referred to hereinafter as *homogeneously vaccinated couples*. This method eliminates the need to determine the order of infections within a given household, as the vaccination status of the additional infection is identical to that of the index infection at the time of the first household infection. Therefore, the scenario analyzed in model 2 is one where exposure

certainly occurred (whether from the infected household member or from another significant mutual exposure outside the household), and vaccine protectiveness is examined in either the 'index' or 'additional' household member, who share the same vaccination status. As the status is identical, the analysis is symmetrical, and the order of infection does not affect the probability of an infection across different vaccination statuses. As couples were included in this analysis even if positive results were obtained on the same day, there is a difference in the population of couples between the two models.

Thus, for each vaccination status group, we calculated the proportion of couples in which both members tested positive within 0-10 days out of the total number of homogenous couples in which at least one member tested positive. We then implemented this model again, this time calculating the proportion of couples in which both members tested positive within 1-10 days out of the total number of homogenous couples in which at least one member tested positive – as was done in *model 1*.

Confidence intervals for binomial probability were calculated, based on Wilson's score interval, for additional infection probability and for additional patient being tested probability. All statistics were performed using Python version 3.1 with the stats models package.

Ethics declaration

The study protocol was approved by the MHS Institutional Review Board (033-21-MHS). Informed consent was waived by the IRB, as all identifying details of the participants were removed before computational analyses.

Results

From 20/12/2020to 17/03/21 data were available for 1,312,372 households that included 2,455,924 individuals. We excluded 784,404 households of only one member and 345,365 households with varying numbers of children. Next, we excluded 8,034 households in which an infection was recorded before December 20, 2020.

Out of the remaining 173,569 households, 6,351 households had at least one recorded infection by March 8, 2021. In the first model, the cohort included 4,024 households stratified into 'index' infection and 'additional' infection occurring within 10 days across defined vaccination status groups; in the second model, there were 3,672 homogenously vaccinated couples of the three vaccination groups (Figure 1).

The mean age of all adult household members was 58.9 years (SD, 13.5). Females constituted roughly 50% (Tables 1, S5-S6). The age and gender of participants by vaccination groups appear in Supplementary Tables S1-S1a, S3-S3a and Figure S2.

The interval between obtaining samples and their delivery to patients was 0-1 days, with 28% of the cases receiving their results on the day of the test and 71% a day later.

There were no missing data apart from Body Mass Index for 5% of the participants, which were treated as not obese in the adjustment calculation.

Model 1 - Rates of additional household infections occurring 1-10 days after the index infection according to vaccination-status groups

Rates of additional COVID-19 infections occurring within ten days of the index infection were 37.5% (95% CI, 35.7 to 39.3) and 41.7% (95% CI, 38 to 45.5) of the Unvaccinated and Recently Vaccinated Once household members of SARS-CoV-2-infected patients, respectively. The proportion of vaccinated household members who tested positive for SARS-CoV-2 in the same time period was significantly lower at 7.5% (95% CI, 5.6 to 10) (Tables 2, S7-8).

Adjusted vaccine effectiveness for Fully Vaccinated compared to Unvaccinated participants was 80.4% (%95 CI, 73.6 to 85.5), and for Fully Vaccinated individuals compared to those who were Recently Vaccinated Once it was 82.0% (%95 CI, 75.6 to 86.8).

The probability of being tested after being exposed and its effect on estimated vaccine effectiveness

We recorded the likelihood of persons living in households with confirmed SARS-CoV-2 cases to be tested for possible infection within ten days of the index diagnosis. The rates of PCR testing were 79.4% (95% CI, 77.9-80.9), 85.3% (95% CI, 82.3-87.8) and 57.2% (95% CI, 53.1-61.3) for the Unvaccinated, Recently Vaccinated Once, and Fully Vaccinated participants (Figure 2, Tables S2).

The corrected lower-bound effectiveness of Fully Vaccinated compared to Unvaccinated individuals was 72.0% (95% CI, 65.2-77.5) and 73.0% (95% CI, 66.0-78.5) when Fully Vaccinated were compared to Recently Vaccinated Once participants.

Model 2 - Vaccine effectiveness among household members with the same vaccination status

(homogeneous couples)

Additional infections occurred in 49.8% (95% CI, 48-51.6) of homogenously unvaccinated couples

and in 12.5% (95% CI, 9.1-17.0) of homogenously vaccinated couples within the ten-day window

(Table 3). Demographic data is presented in Table S3.

Using this approach, adjusted vaccine effectiveness in fully vaccinated individuals was 76.4% (95% CI,

67.5 to 82.8) when compared to unvaccinated ones and 78.4% (95% CI, 69.9 to 84.4) when

compared to participants recently vaccinated once. For homogenously vaccinated household

members, the corrected effectiveness (lower-bound effectiveness) compared to unvaccinated ones

was 70.1% (95% CI, 61.3 to 76.9) and 70.5% (95% CI, 61.2 to 77.4) compared to the control group of

individuals recetly vaccinated once (Figure S1 and Table S4).

Implementing *model 2* analysis on days 1-10 (as opposed to 0-10) yielded similar results to *model 1*

(Table S9).

Discussion:

While the mRNA BNT162b2 vaccine effectivness has been well demonstrated in a randomized

controlled trial and in retrospective general-population studies, the real-life vaccine effectiveness in

protecting individuals with high-risks of exposure to SARS-CoV-2- infected patients has not been

previously demonstrated. Moreover, the question of vaccine effectiveness given confirmed exposure

has not yet been established.

In this large cohort, we examined household contacts of confirmed SARS-CoV-2 individuals to best

ensure exposure, after which we analyzed vaccine effectiveness. 7.5% of fully vaccinated individuals

who are household members of confirmed SARS-CoV-2 patients were infected within ten days.

Infection rates among unvaccinated or those who received only one vaccine dose within seven days

were much higher at 37.5% and 41.7%, respectively. These figures translate into vaccine

effectiveness rates of 80.3% and 82.0% when fully vaccinated persons were compared to

participants who were either unvaccinated, or vaccinated only once within seven days of the index

infection.

While these rates are somewhat lower than vaccine effectivness rates in the original BNT162b2

randomized controlled trial, as well as effectiveness rates observed in a large sample of the Israeli

population[4], the degree of protection afforded by the vaccine is still very high, even in this very high-

risk exposure scenario. These relatively high effectiveness rates following high-risk exposure are

encouraging both for individuals who choose to be vaccinated and for policy makers attempting to

decrease viral circulation, especially in light of difficulties in maintaining social distancing and other

protective measures over time.

When we analyzed additional infection rates among households with homogenous vaccination

status (i.e. adult household members either both vaccinated or both unvaccinated), we found that in

households with two adults who were both fully vaccinated, 12.5% of household members still

tested positive for SARS-CoV-2 after exposure. While these rates were much higher for households

in which both adults were unvaccinated, the risk of infection for fully vaccinated persons is not

negligible.

The present study was designed to fill gaps in existing data. First, we included persons who were all likely exposed to SARS-CoV- and had an extremely high risk of being infected. Second, we performed secondary analyses correcting for a possible selection bias that stems from the different likelihood of persons to be tested for SARS-CoV-2, depending on their vaccination status. In these non-RCT, real-world, scenarios, those not tested are often asymptomatic, or only mildly symptomatic[17–19]. The probability of testing contacts in Israel during the study period was generally very high. Therefore, although structured screening was not performed, the high testing rates, coupled with the correction performed for the differing testing rates in the three study groups, enabled us to estimate with a high degree of confidence vaccine effectiveness for SARS-CoV-2 that is not necessarily severe and often asymptomatic – thus allowing for a real-world vaccine-effectiveness analysis not previously performed.

Our study has several limitations. Data are observational, and therefore testing was not performed with the use of a strict clinical protocol. Therefore, testing was less likely to be performed for vaccinated household members, and asymptomatic cases may have been missed. We did not include data on viral strains. We assumed that all exposure within a given household posed a high risk of transmission, but we are unable to quantify the actual level of exposure within a given household. The large sample size, high vaccination rates, high testing rates, and correction performed for missing testing all partly overcome these limitations. The study results cannot be extrapolated to larger households that would involve many more exposure possibilities. Given the period in which the study was conducted, the results reflect vaccinee effectiveness given high-risk exposure against pre-Delta variants. As waning of vaccine-induced immunity against the Delta variant has been demonstrated,[20] we believe that currently the infection rates in households are probably even higher.

Household studies are an efficient way of assessing vaccine effectiveness in a given population[21–25], allowing for analyses of infection rates when exposure is confirmed with a high degree of certainty– thus avoiding the potential skewing effect of intrinsic differences among communities.

In conclusion, the BNT162b2 vaccine is highly effective in very high-risk, real-life scenarios, but the protection rates afforded in these high-risk settings are somewhat lower than those previously described in RCT or a population-based studies. Household members of SARS-CoV-2-infected patients and any other individuals with confirmed exposure to a SARS-CoV-2-infected patient are still at risk of being infected[22], even if fully vaccinated.

Notes

The authors declare they have no conflict of interest.

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Tables and Figures

Table 1. Baseline characteristics of households with a recorded SARS-CoV-2 infection.

Characteristic, mean (SD*) or %	Households with 2 members and at least one recorded infection by March 8, 2020 (N = 6,351)	Model 1 Households stratified into index case and an additional case (N=4,024)	Model 2 Households of homogenously vaccinated couples (N=3,627)
Females (%)	50%	50%	50%
Mean adult age, years (SD)	58.9 (13.5)	57.6 (13.9)	57.8 (14.5)
Households with a second recorded COVID-19 infection	2,729 (43%)	1,373 (34%)	1730 (48%)
Cancer	589 (9.3%)	362 (9.0%)	307 (8.5%)
Cardio-vascular disease	927 (14.6%)	570 (14.2%)	533 (14.7%)
Immune-suppression	184 (2.9%)	115 (2.9%)	89 (2.5%)
Diabetes mellitus	1,190 (18.7%)	746 (18.5%)	669 (18.4%)
Hypertension	2,279 (35.9%)	1441 (35.8%)	1310 (36.1%)
Asthma	895 (14.1%)	553 (13.7%)	512 (14.1%)
Obesity	1836 (28.9%)	1165 (29.0%)	1059 (29.2%)
Mean Socio- economic index (SD)	5.2 (2.1)	5.4 (1.8)	5.3 (1.8)

*SD-standard deviation

Table 2. Additional household infections occurring 1-10 days after an index SARS-CoV-2 infection, by vaccination status, Model 1.

Index case vaccination status	Additional case vaccination status	Number of households with an index infection	Number of households with an additional infection	% households with an additional infection	95% CI
Any	Unvaccinated	2,827	1,060	37.5%	35.7%-39.3%
Any	Recently Vaccinated Once	652	272	41.7%	38.0%-45.5%
Any	Fully vaccinated	545	41	7.5%	5.6%-10.0%

Table 3. Additional infection occurring 0-10 days after an index SARS-CoV-2 infection in homogeneously vaccinated couples, Model 2.

Index case vaccination status	Additional case vaccination status	Number of households with an index infection	Number of households with an additional infection	% households with an additional infection	95% CI
Unvaccinated	Unvaccinated	2975	1482	49.8%	48.0%-51.6%
Recently Vaccinated Once	Recently Vaccinated Once	381	214	56.2%	51.1%-61.1%
Fully Vaccinated	Fully Vaccinated	271	34	12.5%	9.1%-17.0%

FIGURE LEGENDS:

Figure 1. Cohort selection.

Figure 2. Probability of the second adult in the household to be tested within 10 days of the index infection – cumulative rates of PCR tests among household members of confirmed COVID-19 infections.
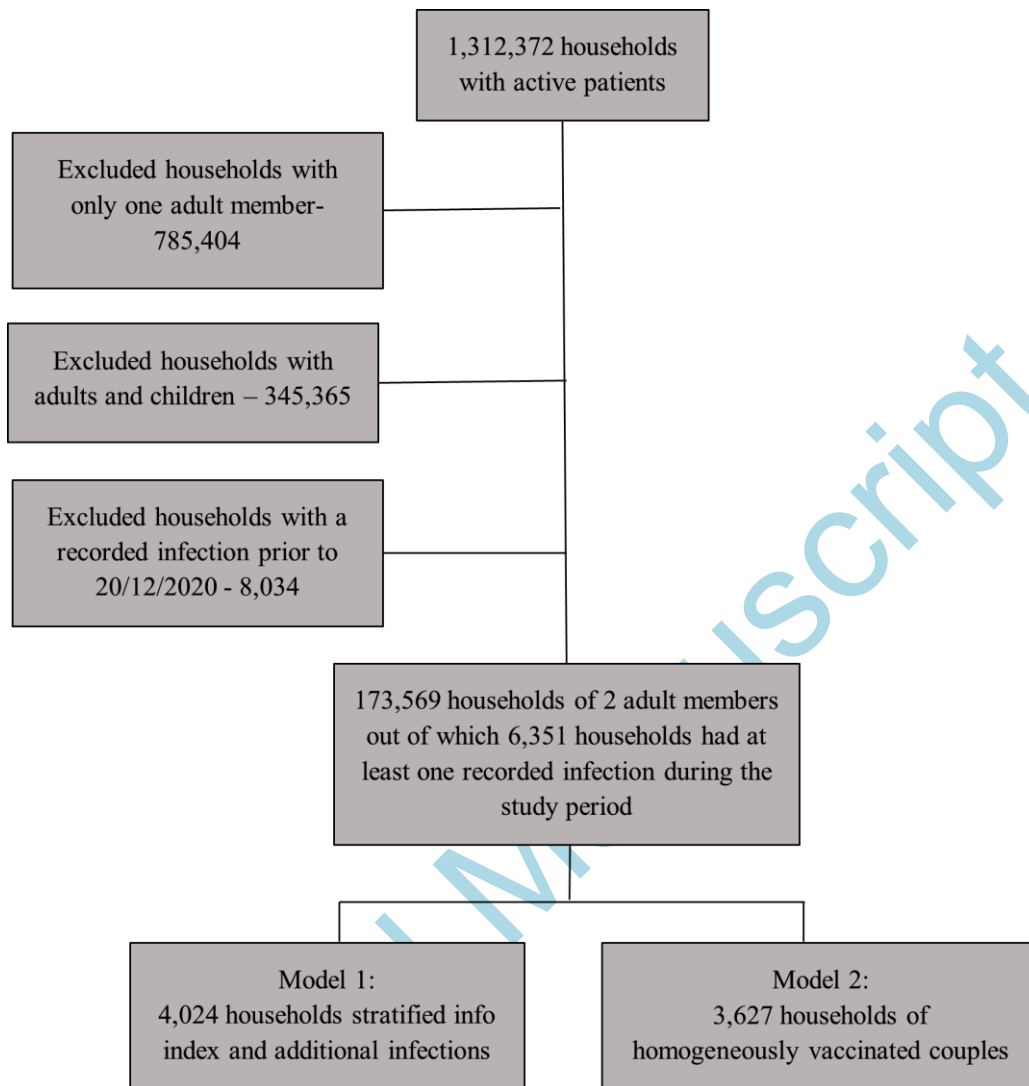
Figure 1

Figure 2