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Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel

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Abstract

The individual-level effectiveness of vaccines against COVID-19 is well-established. However, few studies have examined vaccine effectiveness against transmission. We used a chain binomial model to estimate the effectiveness of vaccination with BNT162b2 (Pfizer-BioNTech mRNA-based vaccine) against household transmission of SARS-CoV-2 in Israel before and after the

Supplementary Materials Materials and Methods Supplementary Text Figures S1 to S9 Tables S1 to S8 References 7, 11, 25–31

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Delta variant emerged. Vaccination reduced susceptibility to infection by 89.4% (95% confidence interval (CI): 88.7%, 90.0%), while the vaccine effectiveness against infectiousness given infection was 23.0% (95% CI: -11.3%, 46.7%) during days 10–90 after the second dose prior to June 1, 2021. Total vaccine effectiveness was 91.8%, 95% CI: 88.1%, 94.3%). However, vaccine effectiveness is reduced over time due to the combined effect of waning of immunity and the emergence of the Delta variant.

One-Sentence Summary:

Vaccination reduced both the rate of infection with SARS-CoV-2 and transmission to household contacts in Israel.

The COVID-19 pandemic has led to unprecedented disruptions worldwide. The rapid development and deployment of vaccines against SARS-CoV-2 has provided an opportunity to control the outbreak in populations with access to vaccination. Multiple vaccines against SARS-CoV-2 effectively prevent clinical disease and reduce disease severity in those who do become infected [1–4]. This direct protection against disease is critical. However, additional population-level benefits can be derived if vaccines also reduce transmission of the virus, thereby providing protection to those who are still vulnerable to infection [1, 5].

To date, there is little direct real-world evidence about the effects of vaccination on SARS-CoV-2 transmission. A few studies have investigated the reduction in transmission in households and among healthcare workers [4, 6, 7]. Other studies have found indirect evidence for a likely effect of the vaccine on transmission by demonstrating reduced viral load in the upper respiratory tract of infected individuals [8–12]. These studies have mostly focused on the period when the Alpha variant was the dominant strain and have not examined the effects on transmission following emergence of the Delta variant [13].

Households are an ideal setting for evaluating transmission of the virus and the effects of vaccination due to the high secondary attack rate among household members [4, 14]. Detailed data on household structure and timing of infections can be used to quantify the risk of transmission. We aimed to assess the effectiveness of vaccination with BNT162b2 (Pfizer-BioNTech mRNA-based vaccine) against susceptibility to infection and against infectiousness given infection with SARS-CoV-2, comparing the pre- and post-Delta periods. We accomplished this using a chain binomial model, which is a common approach to reconstruct transmission in household settings [15], applied to data from the second-largest healthcare organization in Israel. The rapid and early rollout of mass vaccination in Israel provides a unique opportunity to evaluate the effectiveness vaccination against transmission.

We used data from the centralized database of Maccabi Healthcare Services (MHS), which captures all information on members' demographics and healthcare-related interactions. MHS is a nationwide 2.5-million-member state-mandated, not-for-profit healthcare delivery organization in Israel, representing a quarter of the Israeli population. The full dataset, covering the period from June 1, 2020 to July 28, 2021, included information on 2,472,502 individuals from 1,327,647 households. Among these, 1,471,386 individuals received two

doses of BNT162b2 as of July 28, 2021 (prior to the widespread introduction of booster doses). There were 202,298 detected infections caused by SARS-CoV-2 (8.2% of the total population), with 6,483 infections in fully vaccinated individuals at the time of their PCR test date and 186,975 infections in unvaccinated individuals (unadjusted risk ratio=6.6%) (Table S1 and Figure S1).

Most of the households (60% of the total) had a single household member; this individual was infected in 62,295 (7.8%) of the 797,170 households. Information on the number of households and proportion of infections occurring in households of varying size can be found in Table S2. The naïve secondary attack rate (SAR), based on the vaccination status of the "index case" (defined as the first person to test positive in a household), was lower when the index case was vaccinated during the pre-Delta period (Table S3).

We used a chain binomial model for household transmission to estimate how the probability of infection per day depended on characteristics of susceptible individuals and their household contacts [15, 16]. An individual's infection probability is modeled as the risk of escaping infection from the community and any/all infectious household members on each day of exposure (see Materials and Methods in the supplementary material (SM)). We used multiple imputation to generate latent data for when a person with a positive polymerase chain reaction (PCR) test was infected and infectious. This was accomplished using random samples from three different Gamma distributions representing the delay between onset of infectiousness and the date of the PCR test, the date of infection and the onset of infectiousness (i.e., the latent period), and the onset of infectiousness to the end of infectiousness (i.e., the infectious period) (Fig. 1 and Table S4; SM Materials and Methods). We performed sensitivity analyses to confirm the robustness of our results to variability in the delay distributions and performed a simulation study to validate our approach (Figs. S2–S5; Tables S5–S7; SM Materials and Methods).

The pairwise daily probability of infection from the community and from each infected household member was modeled as a function of the time-varying number of SARS-CoV-2-positive individuals in the population, characteristics of the susceptible individual (including age and vaccination status), and their household contact's vaccination status. We considered four categories of vaccination: unvaccinated, 10 days from dose 1 to <10 days from dose 2, 10 days to <90 days from dose 2, and 90 days from dose 2 to account for partial vaccination, full vaccination, and waning of vaccine-induced immunity. Vaccine effectiveness against susceptibility to infection was estimated from the coefficient of the susceptible individual's vaccination status, while vaccine effectiveness against infectiousness given infection was estimated from the coefficient of the vaccination status household member. To determine the impact of the Delta variant, we allowed the vaccine effects to vary before and after June 1, 2021 (i.e., the pre- and post-Delta period, respectively). We estimated the effects by averaging over 100 draws from the delay distributions used in the multiple imputation process; the variance of the estimates across these 100 draws was estimated using the law of total variance (Figs. S6–S8).

For the period before June 1, 2021 (prior to the emergence of the Delta variant), receipt of two doses of the vaccine was associated with a vaccine effectiveness against susceptibility

to infection (*VE_S*) of 89.4% (95% confidence interval (CI): 88.7%, 90.0%) within 10–90 days of receiving the second dose, and 58.3% (95% CI: 45.8%, 67.9%) more than 90 days after receiving the second dose. The vaccine effectiveness against infectiousness given infection (*VE_I*) was 23.0% (95% CI: –11.3%, 46.7%) within 10–90 days and 6.9% (95% CI: –124.8%, 61.4%) more than 90 days after the second dose (Table 1). The total vaccine effectiveness (*VE_T*), which combines the reduction in the risk of infection and the risk of infectiousness given infection among vaccinated individuals, was estimated to be 91.8% (95% CI: 88.1%, 94.3%) within 10–90 days, and 61.1% (95% CI: 5.2%, 84.1%) more than 90 days after the second dose for all vaccine effects (Table 1).

Following the emergence of the Delta variant, we observed a marked reduction in the vaccine effectiveness against susceptibility to infection compared to the pre-Delta period. During this period, the VE_S was 72.0% (95% CI: 65.9%, 77.0%) within 10–90 days and 40.2% (95% CI: 37.6%, 42.6%) more than 90 days after the second dose. A similar finding was observed for the total vaccine effectiveness: VE_T = 65.6% (95% CI: 4.9%, 87.6%) within 10–90 days and 24.2% (95% CI: 9.0%, 36.9%) more than 90 days after the second dose. There was a high degree of uncertainty in the estimates of vaccine effectiveness against infectiousness given infection during the Delta period (Table 1). Allowing for differences in vaccine effectiveness for the post-Delta period improved the model fit, based on a comparison of the Akaike Information Criteria (Figs. S9 and S10).

We further analyzed the effect of vaccination on infectiousness given infection when restricting our data to the susceptible unvaccinated population (i.e., children <12 years of age). We observed a larger reduction in risk for children exposed to a vaccinated versus unvaccinated infectious household member, with VE_I = 41.0% (95% CI: -13.7%, 69.4%) between 10–90 days from receiving the second dose (Table S8). The corresponding vaccine effect during the Delta period was not significantly different from zero.

The probability of transmission per day from an infected household member to a susceptible adult during the pre-Delta period was 0.021 (95% CI: 0.020, 0.021), leading to a secondary attack rate of 0.10 (95% CI: 0.09, 0.10) (Table S9 and SM Materials and Methods). The risk of transmission from an infectious household member was approximately 100 times higher than the average risk of infection from the community. During the period when the Delta variant was dominant, there was no meaningful increase in the household transmission probability, while there was an increase in the risk of infection from the community (*RR*=1.13, 95% CI: 1.09, 1.16) (Table S9). Children <12 years old had a lower risk of infection from both the community and an infectious household member, whereas adults 40–64 years and 65 years of age had a lower risk of infection from the community but a higher risk of infection within the household compared to individuals aged 12–39 years (Table S9). In a sensitivity analysis, we found children were slightly less infectious than adults (see SM).

To date, there is limited evidence with which to compare our estimates of vaccine effectiveness against infectiousness and transmission. A study of over 550,000 households in England showed vaccination with both the ChAdOx1 nCoV-19 and BNT162b2 vaccines

reduced the odds of transmission from a vaccinated and infected household member by 40-50% compared to unvaccinated index cases [1, 4]. A similar study in Denmark estimated the reduction in transmission to be 42% during the Delta period [17]. In previous studies, the index case in each household was defined as the earliest case of laboratory-confirmed COVID-19, by diagnosis date, and all secondary infections in the household were attributed to the index case [4]. In contrast, by inferring the date of infection, we do not assume that the index case in the household was necessarily the first individual to be diagnosed, and we account for the risk of transmission from other infected household members and from the community. With our approach, we show a lower and uncertain reduction in infectiousness given infection, compared to simpler methods [17-19]. A comparable statistical approach was used in another study in Israel, where they actively followed and tested household members of confirmed cases and observed a notably higher reduction in infectivity, though with large uncertainty; however, the study was limited to healthcare workers, who normally represent a younger and healthier population, thereby potentially leading to a stronger vaccine effect [7]. Other studies investigating the reduction in infection risk among household members of vaccinated versus unvaccinated healthcare workers were conducted in Scotland and Finland, and provide indirect evidence of a lower risk of infection among household contacts of vaccinated individuals [1, 6, 20].

Our analyses suggest that prior to the emergence of the Delta variant, breakthrough cases among vaccinated individuals had slightly reduced infectiousness compared to unvaccinated cases. However, both waning of vaccine-induced immunity and the emergence of the Delta variant were associated with a reduction in the VE_I . These results are in agreement with recent findings in a UK study, where the secondary attack rate was similar for vaccinated and unvaccinated index cases infected with the Delta variant [13]. However, vaccination still reduces the risk of transmission by providing protection against susceptibility to infection, even if this effect is reduced over time because of both waning immunity and the Delta variant, as highlighted in real-world settings [13, 21, 22].

This study has several important limitations. We did not have information on the true infection times (and duration of infectiousness) of infected household members. To overcome this limitation, we sampled from three delay distributions parameterized from the literature to determine the potential infection status of each individual through time. Our approach is suboptimal, however, since it was not computationally feasible to estimate the parameters of the delay distributions conditional on the observed data, e.g. using an expectation-maximization or Markov chain Monte Carlo approach. As a result, parameter estimates do not reflect uncertainty in the delay distribution parameters. This could lead to artificially narrow confidence intervals for some parameters. In addition, the VE_I estimates were dependent upon the specification of the time from onset of infectiousness to testing (Figure S5). Also, individuals who were infected but did not receive a SARS-CoV-2 test would be misclassified in our dataset. This is likely to have only a minor impact on our estimates, though the VE_I could be underestimated if the probability of detection per day is low (see SM, Tables S6 and S7). We estimated a negative VE_I in partially vaccinated cases, suggesting possible sources of bias in our analysis (e.g. partially vaccinated individuals may be less likely to isolate at the first sign of symptoms). This effect is mitigated during the post-Delta period (Table 1). Controlling for the age of infectious individuals did not

resolve the potential bias (Table S10). Finally, our results do not include the period when the Omicron variant has become dominant, although recent findings suggest that secondary attack rates among unvaccinated household members are comparable to the Delta variant [23].

Vaccination can prevent transmission by both providing protection against infection (including asymptomatic infections) and reducing the infectiousness of vaccinated individuals who do become infected. Neither of these are typically directly measured in vaccine trials. By analyzing data on confirmed SARS-CoV-2 infections among household members in Israel, we provide measures of effectiveness of BNT162b2 against susceptibility to infection and against infectiousness given infection. Our results show evidence of a slight reduction in the infectiousness of vaccinated individuals who become infected in addition to protection against susceptibility to infection, leading to an overall reduction in the risk of transmission. However, the ability of vaccination to prevent transmission is reduced over time due to waning of vaccine-induced immunity and lower effectiveness against the Delta variant. It is highly unlikely that population-level transmission of SARS-CoV-2 can be eliminated through vaccination alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DMW has received consulting fees from Pfizer, Merck, GSK, and Affinivax for topics unrelated to this manuscript and is Principal Investigator on research grants from Pfizer ad Merck on unrelated topics. JLW and FWC have received consulting fees from Revelar Biotherapeutics Inc. FWC has received consulting fees from Whitespace Ltd. VEP is a member of the WHO Immunization and Vaccine-related Research Advisory Committee (IVIR-AC) and has received reimbursement from Merck and Pfizer for travel expenses to Scientific Input Engagements unrelated to the topic of this manuscript. All other authors declare that they have no competing interests.

Data and materials availability:

According to the Israeli Ministry of Health (IMOH) regulations, individual level data cannot be shared openly. Specific requests for remote access to deidentified data should be referred

to Dr. Sivan Gazit (gazit_s@mac.org.il) from Maccabi Institute for Research & Innovation. IRB Approved –MHS-033–21.

Reproduction code is open source and provided by the authors[24].

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Table 1.

Vaccine effectiveness against susceptibility to infection (VE_S); vaccine effectiveness against infectiousness given infection (VE_I); total vaccine effectiveness (VE_T) at different time ranges since vaccination, both before and after the emergence of the Delta variant (June 1, 2021).

Vaccine effectiveness measure	Time since vaccination	Estimate pre-Delta [95% confidence interval]	Estimate post-Delta [95% confidence interval]
Vaccine effectiveness against susceptibility to infection			
VE _{S1}	10d dose 1 and <10d dose 2	62.7% [61.5%, 63.8%]	72.1% [66.7%, 75.6%]
VE _{S2}	10d dose 2 and <90d dose 2	89.4% [88.7%, 90.0%]	72.0% [65.9%, 77.0%]
VE _{S3}	90d dose 2	58.3% [45.8%, 67.9%]	40.2% [37.6%, 42.6%]
Vaccine effectiveness against infectiousness given infection			
VE 11	10d dose 1 and <10d dose 2	-15.9% [-27.9%, -5.0%]	38.3% [-24.2%, 69.3%]
VE 12	10d dose 2 and <90d dose 2	23.0% [-11.3%, 46.7%]	-27.9% [-248.9%, 53.1%]
VE ₁₃	90d dose 2	6.9% [-124.8%, 61.4%]	-27.9% [-53.7%, -6.5%]
Total vaccine effectiveness			
VE T1	10d dose 1 and <10d dose 2	56.8% [52.2%, 60.9%]	82.8% [64.8%, 91.6%]
VE _{T3}	10d dose 2 and <90d dose 2	91.8% [88.1%, 94.3%]	65.6% [4.9%, 87.6%]
VE _{T3}	90d dose 2	61.1% [5.2%, 84.1%]	24.2% [9.0%, 36.9%]

d – days.

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