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BRIEF REPORT

Effectiveness of a Third Dose of BNT162b2 mRNA Vaccine

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A retrospective cohort study was carried out in a large Israeli health maintenance organization to determine vaccine effectiveness (VE) of a third dose of BNT162b2 vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Of nearly 1 million members receiving 2 doses of BNT162b2 in January–February 2021, infection rates (based on polymerase chain reaction results) were compared between those who received a third dose with those who did not during August–October 2021 (maximum, 70 days). Crude VE was 92.9% (95% confidence interval [CI], 92.6%–93.2%) and adjusted VE was 89.1% (95% CI, 87.5%–90.5%). We conclude that the third dose provides added protection against SARS-CoV-2 infection for those vaccinated 6 months ago.

Keywords. vaccine effectiveness; COVID-19; SARS-CoV-2; Pfizer-BioNTech vaccine; mRNA BNT162b2.

The United States (US) Food and Drug Administration announced emergency approval for the use of the BNT162b2 messenger RNA (mRNA) vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in December 2020 [1] after the vaccine developer reported 95% vaccine effectiveness (VE) [2]. In that same month, Israel rolled out a national vaccination campaign using the BNT162b2 vaccine (2-dose schedule with a 21-day interval) for the population aged ≥16 years. By April 2021, >50% of those aged ≥16 years and 88% of those aged ≥50 years had been fully vaccinated, with the number of new cases (7-day average) dropping to 140 per day by April 2021 [3]. Initial population-based studies in Israel comparing the vaccinated and unvaccinated reported VE rates of 95% [4, 5]. The Alpha variant was the predominant variant at the time of the vaccination drive. However, Israel experienced a new wave of largely Delta variant–based infection from mid-June 2021.

The Israel Ministry of Health implemented a second national vaccination campaign in August 2021, providing a third dose of the BNT162b2 vaccine, after studies [6] indicated that protection against SARS-CoV-2 was waning 6 months after the first national vaccination campaign. Both national campaigns initially targeted the population aged ≥60 years, broadening the age bracket of the target population, on a week-to-week basis. To determine VE against SARS-CoV-2 infection of the additional dose, we carried out a retrospective cohort study, based on data extracted from the database of Maccabi HealthCare Services (the second-largest health maintenance organization [HMO] in Israel). We compared infection rates during August to mid-October 2021 (70-day period) between those vaccinated (2 doses) in the first months of the first vaccine campaign with those receiving the third dose in the second national campaign.

METHODS

Study Population

The study population was drawn from all active HMO members who did not leave the HMO during the study period and had no evidence of infection (positive polymerase chain reaction test [PCR] or immunoglobulin G serology) prior to day 7 postvaccination of last dose and up to the start of the study period (7 August 2021). The study population was comprised of 2 groups: those who had received 2 doses of the vaccine and were at least 7 days post–second vaccination in January–February 2021 (herein referred to as the "2-dose group"), and those who had received the third dose of the vaccine (July to mid-October 2021) and were at least 7 days postvaccination (herein referred to as the "3-dose group"). The groups were dynamic, such that persons in the 2-dose group contributed days to the 2-dose group up until vaccination with the third dose, and contributed days to the third dose group from day 8 after third vaccination, providing that they had not been infected or died in the intervening period. Unvaccinated members and members receiving only 1 dose were excluded from the study.

Outcome and Covariate Measures

Having a positive PCR result in the 70 days of follow-up (7 August 2021–15 October 2021) was the outcome variable. Other measures were age group, gender, socioeconomic status (SES), population group (Other/Arab), and religiosity (Orthodox Jew/Other). SES, population group, and religiosity are all based on census and national survey classifications applied to home address.

Statistical Analysis

Incidence rates were calculated as number of first positive PCR results per 1000 person-days. For the 3-dose group, number of days for each participant was calculated from day 8 after receipt

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of the third dose to the earliest of the following endpoints: first PCR-positive result, death, and end of the follow-up period (15 October 2021). For the 2-dose group, number of days was calculated from the start of the follow-up period (7 August 2021) to the earliest of the following endpoints: first PCR-positive result, receipt of third vaccine dose, death, and end of the follow-up period. Crude VE rates were calculated as follows: 1 – (incidence rate in 3-dose group / incidence rate in 2-dose group). These rates were adjusted using 2 different methods. First the 3-dose group was matched by age group, gender, SES, population group, and religiosity to the 2-dose group. Second, a Generalized Liner Models (GLM) model (Poisson) was used that included calendar period (10-day consecutive periods) in addition to the factors described above. Calendar period was included to allow for the rapidly changing risk of infection over time. Crude and adjusted analyses were repeated twice: stratified by age and stratified by number of follow-up days. Analyses were carried out using R software, version 3.6.2. Confidence intervals (CIs) were calculated as 95% confidence levels. The study was carried out in August 2021 after being approved by the Maccabi HealthCare Services institutional review board and Helsinki committee (number 0178-20-MHS) and was exempted from informed consent.

RESULTS

Of the 947 131 members meeting the study criteria, 8.6% received only 2 doses of the vaccine in January–February 2021 and 91.4% received a third dose of the vaccine between July and mid-October 2021. Of the 865 887 persons receiving the third dose, 83.6% received the third dose during the study follow-up period and thus contributed days to both the 2-dose and 3-dose groups in VE analyses. Demographic characteristics of the study population (Table 1) have therefore been split into 3 groups: "only 2-dose" (only contributed days to the 2-dose group); "became 3-dose" (those who contributed days to both the 2-dose and 3-dose groups); and "only 3-dose" (those who only contributed days to the 3-dose group). Individuals in the study group receiving only 2 doses of the vaccine were more likely to be younger and from a lower socioeconomic bracket and more likely to be from minority groups (Arab and Orthodox Jew).

Incidence rate and crude and adjusted VE rates are presented in Table 2. Crude VE rates were slightly higher (92.9% [95% CI, 92.6%–93.2%]) than adjusted VE rates (89.1% [95% CI, 87.5%–90.5%]). When stratified by age group, crude VE rates were 1.9% higher for the under-60 age group compared to the ≥60 age group (Table 2). Adjusted VE rates were lower than crude rates for both age groups, with difference in adjusted VE attenuated between the 2 age groups (<60 years: 88.4% [95% CI, 87.7%–89.1%]; ≥60 years: 87.7% [95% CI, 86.4%–88.8%]). When stratified by number of follow-up days, crude VE for study participants with the later follow-up period was 2.8% higher than for those with the earlier follow-up period (Table 2). Adjusted rates were again lower than crude rates for both groups and evidenced a smaller difference between groups

Table 1. Demographic Characteristics of the Study Population by Dose Group, October 2021, Maccabi HealthCare Services, Israel

Characteristic	Only 2-Dose Group[a] (n = 81 244)	Became 3-Dose Group[b] (n = 724 540)	Only 3-Dose Group[c] (n = 141 347)
Gender			
Male	39 266 (48.3)	346 837 (47.9)	72 251 (51.1)
Female	41 978 (51.7)	377 703 (52.1)	69 096 (48.9)
Age group, y			
0–17	3983 (4.9)	22 179 (3.1)	0 (0)
18–29	17 355 (21.4)	86 474 (11.9)	23 (0.0)
30–44	23 504 (28.9)	173 861 (24.0)	86 (0.1)
45–59	23 555 (29.0)	286 546 (39.5)	444 (0.3)
60–74	9299 (11.4)	116 545 (16.1)	99 825 (70.6)
≥75	3548 (4.4)	38 935 (5.4)	40 969 (29.0)
Socioeconomic status			
Low	18 120 (22.3)	84 517 (11.7)	15 353 (10.9)
Middle	40 399 (49.7)	352 140 (48.7)	68 715 (48.6)
High	22 725 (28.0)	287 883 (39.7)	57 279 (40.5)
Population group			
Other	74 720 (92.0)	701 055 (96.8)	138 646 (98.1)
Arab	6524 (8.0)	23 485 (3.2)	2701 (1.9)
Religiosity			
Other	74 020 (91.1)	696 195 (96.1)	137 053 (97.0)
Orthodox Jew	7224 (8.9)	28 345 (3.9)	4294 (3.0)

Data are presented as No. (%).

Abbreviation: SES, socioeconomic status.

[a]Only contributed days to the 2-dose group.

[b]Contributed days to both the 2-dose and 3-dose groups.

[c]Only contributed days to the 3-dose group.

Table 2. Crude and Adjusted Vaccine Effectiveness Rates, Comparing 3-Dose With 2-Dose Receipt of BNT162b2 Vaccine, August to Mid-October 2021, Maccabi HealthCare Services, Israel

Measure	Population	Group	Total No. of Person-Days	Total No. of PCR-Positive Persons	Incidence/1000 Person-Days	VE, % (95% CI)
Crude rates	Total population	2-dose	19 845 270	17 830	0.90	92.9 (92.6–93.2)
		3-dose	39 537 837	2512	0.06	
	Age <60 y	2-dose	17 542 277	16 451	0.94	92.6 (92.2–93.0)
		3-dose	22 627 091	1566	0.07	
	Age ≥60 y	2-dose	2 302 993	1379	0.60	90.7 (89.9–91.4)
		3-dose	16 910 746	946	0.06	
	1–35 d period	2-dose	16 329 153	15 698	0.96	92.0 (91.6–92.4)
		3-dose	27 912 508	2142	0.08	
	36–70 d period	2-dose	3 516 117	2132	0.61	94.8 (94.1–95.3)
		3-dose	11 625 329	370	0.03	
Adjusted (matched)[a]	Total population	2-dose	17 790 141	15 705	0.88	92.6 (92.2–92.9)
		3-dose	32 002 228	2092	0.07	
Adjusted (GLM model)	Total population					89.1 (87.5–90.5)

Abbreviations: CI, confidence interval; GLM, Generalized Linear Model; PCR, polymerase chain reaction; VE, vaccine effectiveness.

[a]Matched for gender, age group, socioeconomic status, population group, and religiosity, with each group comprising 320 467 persons.

(1–35 days: 88.9% [95% CI, 88.2%–89.6%]; 36–70 days: 89.1% [95% CI, 87.5%–90.5%]).

From the GLM model of the total study population, other measures associated with infection outcome, independent of number of doses received, were calendar period, age group, SES, population group, and religiosity. The risk of infection increased 1.5-fold (95% CI, 1.45- to 1.57-fold) in the first 30 days (third 10-day period compared to first 10-day period), decreasing 0.28-fold in the seventh 10-day period (95% CI, .25- to .31-fold). Risk of infection increased with decreasing age. Orthodox Jews had a 1.93-fold higher risk of infection (95% CI, 1.82- to 2.03-fold), whereas the Arab population had an 0.65-fold lower risk (95% CI, .60- to .70-fold). Risk of infection increased with decreasing SES; compared to those with high SES, the risk was 1.25-fold higher (95% CI, 1.21–1.29) for middle SES and 1.48-fold higher (95% CI, 1.40–1.55) for low SES.

DISCUSSION

The findings presented here indicate that providing an additional dose of BNT162b2 vaccine 6 months after initial 2-dose vaccination bolsters protection against infection, with a VE of 89%. The decision to revaccinate with a third dose appears, at this early stage, to have been a good decision.

Evidence from Israel (Kertes et al, preprint data [7]) and the US [6] has shown that vaccination with 2 doses of BNT162b2 drops over a 6-month period. Given that the majority of Israel's population was vaccinated within months of the first campaign, comparison of 3 doses with an unvaccinated population was not carried out, given the large bias potential of those choosing not to be vaccinated. While VE drops over time, the 2-dose regimen would still confer protection for at least some of the population, and therefore we consider an 89% VE to be an excellent outcome.

Our findings are comparable with other studies carried out in Israel. In a national study, focusing on the 60-and-over population, with a maximum follow-up period of 31 days, the adjusted VE rate was 89.7% [8]. Another Israeli HMO study that followed up members aged ≥40 years for a maximum 20-day period also found a reduction in infection rates of between 70% and 84% [9]. The longer follow-up period in the present study indicates that while the risk of infection increased in the first month of follow-up, rates of infection dropped by the second month. We suggest that the initial rise reflects the surge in infections at the beginning of the infection wave, and that the drop reflects the impact of the vaccine on overall infection rates.

Given that the majority of infection in the current wave in Israel is due to the Delta variant, we suggest that the high VE found here indicates that the majority of the fourth wave of infection was secondary to the declining effectiveness of the initial 2 doses and not because of introduction of the Delta virus. In a large US study, Tartof et al [6] did not find significant differences in VE decline between those infected with the Delta virus and those infected with other variants.

Although encouraging, these results are based on a relatively short follow-up period. Although the findings were age-adjusted, the age group ≥60 years was overrepresented among persons who received the third vaccine dose, and a longer follow-up period may provide a more balanced result. Both the decision to vaccinate and to carry out a PCR test are voluntary, and bias cannot be ruled out. Despite these limitations, the findings here indicate that introduction of the third dose was effective in reducing SARS-CoV-2 infection rates in Israel.

Notes

Disclaimer. The sponsor had no role in the study design, collection, analysis and interpretation of the data, writing of the article, or decision to submit the report for publication.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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