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Research note

The effect of a third BNT162b2 vaccine on breakthrough infections in health care workers: a cohort analysis

Yonatan Oster^{1,2,*}, Shmuel Benenson^{1,2,†,‡}, Ran Nir-Paz^{1,2}, Inon Buda³, Matan J. Cohen⁴¹ The Faculty of Medicine, Hebrew University of Jerusalem, Israel² Department of Clinical Microbiology and Infectious Diseases, Hadassah Hebrew University Medical Center, Jerusalem, Israel³ General Management, Hadassah Hebrew University Medical Centre, Jerusalem, Israel⁴ Clalit Health Services, Jerusalem District, Affiliated with the Hebrew University, Jerusalem, Israel

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ABSTRACT

Objectives: In August 2021, 6 months after mass vaccination of the Israeli population with the two-dose BNT162b2 mRNA vaccine, a surge of coronavirus disease 2019 infections, mostly from the delta variant, appeared also among the vaccinated. In response, the Israeli Ministry of Health initiated a booster (third dose) vaccination program. We assessed the protective effect of the third dose among health care workers (HCWs).

Methods: Infections with severe acute respiratory syndrome coronavirus 2 are monitored systematically among HCWs at the Hadassah tertiary care medical centre in Jerusalem, Israel. In this cohort, we included breakthrough infections, defined as those occurring >180 days since the second vaccine dose. The follow-up period lasted 120 days. We compared infection rates between HCWs who received the booster dose and those who received only the two-dose regimen.

Results: The rate of breakthrough infections among HCWs who received only the two-dose regimen was 21.4% (85 of 398). The rate in the boosted group was 0.7% (35/4973; relative risk 30, 95% CI 20–50). Those results were seen in all age groups.

Discussion: The significantly lower rate of breakthrough infections in boosted HCWs indicates substantial protection by a third vaccine dose. **Yonatan Oster, Clin Microbiol Infect 2022;28:735.e1–735.e3**

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Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), both in the general population and health care workers (HCWs), proved to be a major leap in coping with the coronavirus disease 2019 (COVID-19) pandemic [1,2]. Israel implemented its two-dose vaccination program with the BNT162b2 vaccine at the end of 2020. After several months of extremely low

infection rates, a fourth COVID-19 wave appeared, consisting mainly of the delta variant, which also affected those who had received two-dose vaccination.

Presuming that waning immunity was the chief cause, the Israeli Ministry of Health initiated a novel booster (third dose) vaccination program at the end of July 2021. Implementation was initiated with scarce supporting data, and debate on both necessity and age limits ensued [3,4]. Initially, people aged >60 years, those who are immunocompromised, and HCWs were vaccinated, followed gradually by the general adult population [5]. We collected data on breakthrough infections, both in booster recipients and those who chose not to receive the third dose, to assess the real-life effectiveness of this vaccine on HCW breakthrough infections.

* Corresponding author. Yonatan Oster, Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, Ein Kerem, POB 12000, Jerusalem, 91120, Israel.

E-mail address: yonatano@hadassah.org.il (Y. Oster).

† Yonatan Oster and Shmuel Benenson contributed equally to this work.

‡ Current affiliation: The Faculty of Medicine, Hebrew University of Jerusalem, Israel, Unit for Infection Prevention and Control, Shaare-Zedek Medical Centre, Jerusalem, Israel.

Methods

Hadassah-Hebrew University Medical Center is a tertiary, two-campus hospital in Jerusalem, Israel. Vaccinated workers are not routinely screened for SARS-CoV-2; they are tested by PCR after significant exposures or symptoms. We compared breakthrough infection rates between HCWs who had received a two-dose BNT162b2 regimen at least 6 months earlier and those who received a third (booster) dose.

The study population included all HCWs who had received two vaccine doses. Of these, we excluded HCWs who tested positive for SARS-CoV-2 during the 6 months after the second vaccine dose. The index date of inclusion was 180 days after the second vaccination for two-dose recipients, and the date of the third vaccination for booster recipients. The follow-up period lasted 120 days. Receiving the booster vaccine was encouraged but not obligatory, and workers decided at their own discretion whether to do so.

Data were collected according to a protocol approved by the institutional ethics committee (HMO-460-12).

Comparisons according to age, sex, and profession were performed with the log-rank test. Statistical significance was determined with a 0.05 cut-off. Analyses and charts were generated with SPSS (IBM SPSS Statistics for Windows, Version 26.0; Armonk, NY).

Results

Data were available for 5371 HCWs who had received two vaccine doses in early 2021 and were not infected until August 2021. Of these HCWs, 4973 (92.6%) received a third BNT162b2 dose beginning in August 2021. Booster recipients were generally older; among HCWs older than 60 years, 673 of 695 (97%) were vaccinated (Table 1). Booster vaccination rates among male and female HCWs were 1744 of 1835 (95%) and 3229 of 3536 (91%), respectively ($p < 0.001$). Vaccination rates according to profession were 96% among physicians, 91% among nurses, and 92% in other sectors. No major side effects or safety issues were described after administration of the booster dose, although these data were not collected systematically.

Overall, booster recipients had a remarkably reduced infection risk in the 120 days after vaccination. The breakthrough infection rate was 85 of 398 (21%) in the two-dose group and 35 of 4973

(0.7%) in the booster group (relative risk: 30; 95% CI, 20–50). Similar effectiveness was observed in all age groups (Table 1). The most distinctive protection was noted in those older than 45 years of age, with a 30% absolute risk reduction ($p < 0.001$). Almost all breakthrough infections were mild or asymptomatic; only one HCW required a short hospitalization in each group.

Discussion

These results clearly show that a booster vaccine dose with BNT162b2 significantly improved protection against SARS-CoV-2 during the delta variant surge. This effect was seen in all age groups, most conspicuously in those older than 45 years of age. The rate of booster receipt was higher in male HCWs and physicians versus other HCWs. The sex difference might be explained by pregnancy or fertility-related concerns. In all subgroups, however, vaccination rates were >90%. This is an impressive compliance rate considering the paucity of information supporting this strategy.

The sudden appearance of breakthrough infections among those who received two-dose vaccination could be explained either by waning immunity or by weaker vaccine protection against new variants (i.e. the delta variant at that time). The Israeli Ministry of Health's decision to recommend a third dose was made in times of uncertainty. These results ultimately support that decision, as do studies showing decreases in antibody titres 6 months after the second vaccine dose [6]. The protective effect of the booster dose against infection has also been seen in the community setting and in persons older than 60 years [5,7]. In addition, the booster vaccine has been shown to prevent severe outcomes [8]. A similar dilemma currently exists regarding a surge of breakthrough infections among boosted individuals, caused primarily by the omicron variant.

A limitation of this study is the lack of routine testing for SARS-CoV-2 of HCWs at our hospital; thus, some infections were probably missed. However, at our hospital, PCR tests for SARS-CoV-2 are easily available for all HCWs, as previously described [9]; thus, we assume that the rate of missed cases was not significant and was similar in both groups. Another limitation is the lack of systematic monitoring of adverse events after the booster. However, no vaccine-related serious adverse events were reported, and no HCWs were hospitalized due to a vaccine-related event.

Table 1
Breakthrough infection rate among two- and three-dose-vaccinated health care workers >180 days after the second vaccine dose

Characteristic	Two-dose group (N = 398)		Three-dose (booster) group (N = 4973)		p-value ^a
	n (%) ^b	Breakthrough infections n (%) ^c	n (%) ^b	Breakthrough infections n (%) ^c	
Sex					
Female	307 (8.7)	65 (21.2)	3229 (91.3)	26 (0.8)	<0.001
Male	91 (5)	20 (22)	1744 (95)	9 (0.5)	<0.001
Profession					
Nursing	153 (9.3)	30 (19.6)	1485 (90.7)	16 (1.1)	<0.001
Physicians	51 (4.2)	12 (23.5)	1137 (95.8)	5 (0.4)	<0.001
Other	194 (7.6)	43 (22.2)	2351 (92.4)	14 (0.6)	<0.001
Age group (y)					
<30	124 (12.2)	20 (16.1)	889 (87.8)	5 (0.6)	<0.001
30–45	183 (8.9)	36 (19.7)	1869 (91.1)	14 (0.7)	<0.001
45–60	69 (4.2)	22 (31.9)	1542 (95.8)	13 (0.8)	<0.001
>60	22 (3.1)	7 (31.8)	673 (96.9)	3 (0.4)	<0.001
Total	398 (7.4)	85 (21.4)	4973 (92.6)	35 (0.7)	<0.001

^a Log-rank p-value comparing two-versus three-dose groups.

^b Percent of total participants in the subgroup.

^c Percent of breakthrough infections per study group and subgroup (sex, profession, age group).

In conclusion, our study demonstrates strong protection against SARS-CoV-2 infection from a booster dose, which in turn reduces unnecessary isolation and quarantine, thus enabling optimal hospital functioning.

Transparency declaration

Conflict of interest

None

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None

Author contributions

YO: conceptualization, data curation, original draft; SB: supervision, validation, review and editing; RNP: supervision, validation, review and editing; IB: project administration, resources, review and editing; MJC: conceptualization, methodology, analysis, original draft.

References

- [1] Benenson S, Oster Y, Cohen MJ, Nir-Paz R. BNT162b2 mRNA Covid-19 vaccine effectiveness among health care workers. *N Engl J Med* 2021; 384:1775–7.
- [2] Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* 2021;397:1819–29.
- [3] Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, et al. Considerations in boosting COVID-19 vaccine immune responses. *Lancet* 2021;S0140–6736:2046–8.
- [4] Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med* 2021;385:1244–6.
- [5] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *N Engl J Med* 2021;385:1393–400.
- [6] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 2021;385:e85.
- [7] Saciuk Y, Kertes J, Shamir Stein N, Ekka Zohar A. Effectiveness of a third dose of BNT162b2 mRNA vaccine. *J Infect Dis* 2022;225:30–3.
- [8] Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;398:2093–100.
- [9] Oster Y, Wolf DG, Olshain-Pops K, Rotstein Z, Schwartz C, Benenson S. Proactive screening approach for SARS-CoV-2 among healthcare workers. *Clin Microbiol Infect* 2021;27:155–6.