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Research note

The effect of a third-dose BNT162b2 vaccine on anti-SARS-CoV-2 antibody levels in immunosuppressed patients

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ABSTRACT

Objectives: The recent surge in coronavirus disease 2019 cases led to the consideration of a booster vaccine in previously vaccinated immunosuppressed individuals. However, the immunogenic effect of a third-dose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in immunosuppressed patients is still unknown.

Methods: This was an observational cohort study of 279 previously vaccinated immunosuppressed patients followed at a single tertiary hospital in Israel. Patients were administered a third dose of the Pfizer-BioNTech mRNA vaccine (BNT162b2) between July 14 and July 21, 2021. Levels of IgG antibodies against the spike receptor-binding domain of SARS-CoV-2 were measured 3 to 4 weeks after vaccination.

Results: Of the cohort of 279 patients, 124 (44.4%) had haematologic malignancies, 57 (20.4%) had rheumatologic diseases, and 98 (35.1%) were solid organ-transplant recipients. Anti-SARS-CoV-2 antibody levels increased in 74.9% of cases. Across the entire cohort, the median absolute antibody levels (expressed in AU/mL) increased from 7 (interquartile range (IQR), 0.1–69) to 243 (IQR, 2–4749) after the booster dose. The response significantly varied across subgroups: The transplant cohort showed the greatest increase in absolute antibody levels (from 52 (IQR, 7.25–184.5) to 1824 (IQR, 161–9686)), followed by the rheumatology (from 22 (IQR, 1–106) to 1291 (IQR, 6–6231)) and haemato-oncology (from 1 (IQR, 0.1–7) to 7.5 (IQR, 0.1–407.5)) cohorts. The χ^2 test was 8.30 for difference in fold change ($p = 0.016$). Of the 193 patients who were seronegative at baseline, 76 became seropositive after vaccination, corresponding to a 39.4% (95% CI, 32.8%–46.4%) seroconversion rate. Transplant patients had the highest seroconversion rate (58.3% (95% CI, 44.3%–71.2%)), followed by rheumatology (44.1% (95% CI, 28.9%–60.5%)) and haemato-oncology (29.7% (95% CI, 22%–38.8%); $\chi^2 = 11.87$; $p = 0.003$) patients.

Discussion: A third dose of BNT162b2 is immunogenic in most immunosuppressed individuals, although antibody response may differ based on the type of disease and immunosuppression. The antibody level that correlates with protection is still unknown; thus, future studies are needed to evaluate clinical outcomes. **Esther Saiag, Clin Microbiol Infect 2022;28:735.e5–735.e8**

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Introduction

The Pfizer-BioNTech mRNA vaccine (BNT162b2) has a 90% to 95% vaccine effectiveness according to several large real-world studies [1,2]. Despite an initial decline in new cases in most vaccinated populations, the vaccine showed decreasing effectiveness in Israel, as well as in other countries [3]. The subsequent increase in coronavirus disease 2019 (COVID-19) cases, possibly due in part to the emergence of new variants and waning immunological protection, is especially worrying for immunosuppressed populations, who are at risk for worse disease outcome [4–6]. Low levels of neutralizing antibodies are associated with an increased risk of breakthrough severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, suggesting that humoral response to vaccination could serve as a correlate of protection [7].

In early July 2021, the Israeli Ministry of Health recommended a third (booster) vaccine dose for immunosuppressed individuals at least 5 months after the second dose. Herein, we report on the effect of a third-dose BNT162b2 on anti-SARS-CoV-2 antibody levels in 279 immunosuppressed individuals followed at the Tel-Aviv Medical Center and vaccinated in late July 2021.

Methods

Participants were included if they met the following conditions: immunosuppressed patients who (a) received the third vaccine dose as recommended by the Israeli Ministry of Health, (b) had a serological measurement prior to this dose, and (c) were between the ages of 18 and 90 years. Children and pregnant women were excluded. Due to the retrospective design of this study, the data were anonymized and patients did not have to sign a consent form. The study was approved by the Tel-Aviv Medical Center institutional review board (approval #TLV-21-0568).

Immunogenicity was assessed via a chemiluminescent micro-particle immunoassay (SARS-CoV-2 IgG II Quant assay on the Alinity i system; Abbott), which is used to quantify IgG antibody levels in patient sera [8,9]. The assay detects IgG antibodies against the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 (anti-S), with 50 arbitrary units (AU)/mL as a positive cut-off and an upper limit of quantification of 40 000 AU/mL, as defined by the manufacturer. The results of this assay were shown to correlate with SARS-CoV-2 neutralization *in vitro* [10]. To calculate fold-change between levels before and after the third dose, we replaced measurement values of 0 with 0.1.

The *t*-test or *U* test was used to compare parametric or nonparametric continuous data across two groups, respectively. The Kruskal–Wallis test was used to compare nonparametric continuous data across three groups. The χ^2 test was used to identify associations between categorical variables. Pearson's correlation was used to test associations between two continuous variables. Linear regression or logistic regression was used to detect associations between a set of covariates and a continuous or binary outcome, respectively. The proportion of patients who developed an antibody response is reported with point estimates, and CIs were calculated using Wilson's method. All tests were two-sided, setting a significance level of 0.05. All statistical analyses were performed in R, version 3.5.0.

Results

Overall, 279 immunosuppressed patients were vaccinated with a third BNT162b2 dose (Table 1). Among these patients, 124 (44.4%) had haematologic malignancies, 57 (20.4%) had rheumatologic diseases, and 98 (35.1%) were solid organ-transplant recipients. The median age was 69 years, and 36.9% were female. Demographic

characteristics differed across the three subgroups. The transplant patients were youngest (median: 63 years), and the haemato-oncology patients were oldest (median: 72 years). The rheumatologic patients were predominantly female (70.2%), whereas the haemato-oncological (25.0%) and transplant (32.7%) cohorts were not. The distribution of clinical conditions within each cohort can be found in Table S3.

All patients had their antibody levels measured at baseline, and a second sample was obtained after 3 to 4 weeks (median: 25 days; Fig. 1A). In general, antibody levels increased in 74.9% of cases. The median anti-S IgG level at baseline was 7 AU/mL (interquartile range (IQR), 0.1–69 AU/mL) for all patients and increased to a median of 243 AU/mL (IQR, 2–4749 AU/mL) after the booster dose. This corresponded to a median fold-change of 18.0 (IQR, 1.03–96.6), which differed significantly across the subgroups: The transplant cohort showed the highest increase (median: 29.2 (IQR, 9.2–88.1)), followed by the rheumatology (median: 15.5 (IQR, 4–102)) and haemato-oncology cohorts (median: 7.8 (IQR, 1.0–95.8); Kruskal–Wallis $\chi^2 = 8.30$; $p = 0.016$; Fig. 1B).

This trend was consistent with baseline absolute antibody levels, for which the haemato-oncology cohort had lower levels (median: 1 AU/mL (IQR, 0.1–7 AU/mL)) compared with the rheumatology (median: 22 AU/mL (IQR, 1–106 AU/mL)) and transplant cohorts (median: 52 AU/mL (IQR, 7.25–184.5 AU/mL); Kruskal–Wallis $\chi^2 = 63.64$; $p < 0.001$; Fig. 1C). The fold-change after the booster dose was not associated with sex but was negatively correlated with age (Fig. S1), with older patients exhibiting a lower response ($R = -0.18$; $p = 0.003$). Linear regression using the absolute difference in antibody levels as a continuous outcome revealed a similar trend, with age being the only significant predictor ($\beta = -1.54$ per 1 year of age (95% CI, -2.40 to -0.68); $p < 0.001$) when correcting for sex, days between vaccine and serology, and baseline antibody levels (Table S1).

Of the 193 patients who were seronegative at baseline (anti-S IgG <50 AU/mL), 76 were seropositive (anti-S IgG ≥ 50 AU/mL) after vaccination, representing a 39.4% (95% CI, 32.8%–46.4%) seroconversion rate (Table 1). The rate significantly differed across subgroups, with the haemato-oncology cohort having the lowest seroconversion rate (29.7% (95% CI, 22%–38.8%)), followed by the rheumatology (44.1% (95% CI, 28.9%–60.5%)) and transplant cohorts (58.3% (95% CI, 44.3%–71.2%); $\chi^2 = 11.87$; $p = 0.003$). Logistic regression using seroconversion as a binary outcome revealed that decreasing age (OR: 0.97 per 1 year of age (95% CI, 0.94–0.99); $p = 0.019$) and higher antibody levels at baseline (OR: 1.33 per 1 log-unit (95% CI, 1.20–1.49); $p < 0.001$) were associated with greater odds of seroconverting (Table S2).

Discussion

This analysis shows that a third dose of BNT162b2 is immunogenic in several immunocompromised populations, including patients with haematologic malignancies, rheumatologic diseases, or solid-organ transplants. The vaccine led to a median 18-fold increase in antibody levels, measured 3 weeks after administration. To the best of our knowledge, this is the first work to compare response to a booster dose across different subgroups of immunosuppressed patients, whose heterogeneity was reflected by a significantly different seroconversion rate (58.3% (95% CI, 44.3%–71.2%) in the transplant cohort, 44.1% (95% CI, 28.9%–60.5%) in the rheumatology cohort, and 29.7% (95% CI, 22%–38.8%) in the haemato-oncology cohort ($\chi^2 = 11.87$; $p = 0.003$)).

Recent studies showed that a third dose is immunogenic in solid-organ transplant recipients [11,12]. Benotmane et al. reported a 49% seroconversion rate in 159 kidney transplant recipients who received a third dose of the mRNA-1273 (Moderna) vaccine [13].

Table 1

Patient characteristics and anti-severe acute respiratory syndrome coronavirus 2 IgG antibody response to booster vaccine in 279 immunosuppressed individuals

	All patients	Haemato-oncology cohort	Rheumatology cohort	Transplant cohort	p-value
N (%)	279 (100)	124 (44.4)	57 (20.4)	98 (35.1)	
Patient characteristics					
Age (y), median (IQR)	69 (59.5–74)	72 (65.8–76)	69 (61–76)	63 (52–70.8)	<0.001
Sex, n (%)					
Female	103 (36.9)	31 (25.0)	40 (70.2)	32 (32.7)	<0.001
Male	176 (63.1)	93 (75.0)	17 (29.8)	66 (67.3)	
Days from booster to serology, median (IQR)	25 (23–27)	23 (23–27)	29 (25–30)	23 (23–27)	<0.001
Antibody levels					
Anti-S IgG before booster, AU/mL, median (IQR)	7 (0.1–69)	1 (0.1–7)	22 (1–106)	52 (7.25–184.5)	<0.001
Anti-S IgG after booster (AU/mL), median (IQR)	243 (2–4749)	7.5 (0.1–407.5)	1291 (6–6231)	1824 (161–9686)	<0.001
Antibody response					
Fold-change, median (IQR)	18.0 (1.03–96.6)	7.8 (1.00–95.8)	15.5 (4.0–102)	29.2 (9.2–88.1)	0.016
Seroconversion rate ^a (%), (95% CI), n/N	39.4 (32.8–46.4), 76/193	29.7 (22–38.8), 33/111	44.1 (28.9–60.5), 15/34	58.3 (44.3–71.2), 28/48	0.003

IQR, interquartile range.

^a The seroconversion rate is the proportion of seronegative patients at baseline who displayed anti-S IgG levels greater than the 50 AU/mL cutoff after the booster vaccine. Absolute numbers from which the rates are derived are reported as well.

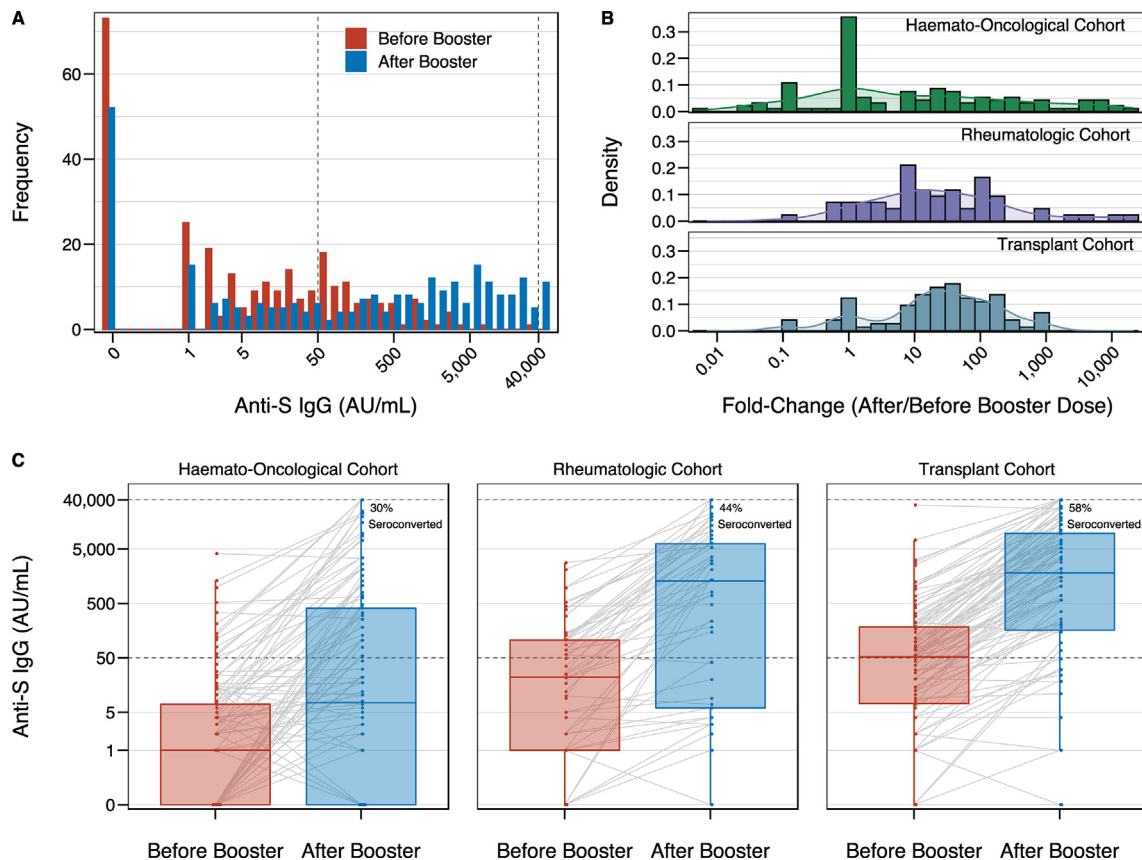


Fig. 1. Anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG antibody levels before and after a SARS-CoV-2 Bbooster vaccine in 279 immunosuppressed individuals. (A) Frequency of patients according to antibody levels before and after the booster dose. (B) Relative frequency of the fold-change in antibody levels after the booster dose. The highest fold-change is seen in the transplant cohort, and the lowest fold-change is seen in the haemato-oncology cohort. (C) Antibody levels before and after the booster dose. Each dot represents a single patient, and the median level is represented by the line in the box. Listed inside each panel is the percentage of seronegative patients at baseline who developed a positive antibody response (≥ 50 AU/mL) after the booster (i.e. seroconverted), which was highest in the transplant cohort and lowest in the haemato-oncology cohort.

Their study showed that antibody response to the third dose was affected by the response to the second dose, supporting our findings that higher baseline antibody levels are associated with greater odds of seroconversion. The relatively low seroconversion rate in haemato-oncology patients is consistent with the impaired antibody production seen in patients with haematologic malignancies who received SARS-CoV-2 vaccines [14,15].

This study has several limitations. First, data on response to the first and second vaccine doses were not available; thus, longitudinal assessments for individual patients are missing. Second, each subgroup was heterogeneous, consisting of patients with different diseases and varying immunosuppressive regimens. A granular analysis of these subpopulations is the subject of several ongoing studies. Third, our study did not include a healthy control group as a

comparison. Last, many immunological variables are still unknown or were not assessed, such as the exact antibody levels that correlate with disease protection, the presence of neutralizing antibodies against wild-type or mutant strains, and the role of T-cell response.

In conclusion, a BNT162b2 booster elevates antibody levels in immunosuppressed patients, although immunogenicity varies based on the type of immunosuppression. Further studies are needed to evaluate the effect of a booster dose on clinical outcomes, such as severe disease, hospitalization, and death.

Transparency declaration

The authors do not have any conflicts of interest to disclose. Assay reagents were provided by Siemens. This study did not receive any other funding.

Author contributions

ESa and ES_p designed and conceived the study. ESa and AG extracted the data. DB devised the methodology, performed the statistical analysis, and prepared the figures. ESa supervised the study. ESa, RBA, ES_p, and DB wrote the manuscript. All authors contributed to the final version and approved the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2022.02.002>.

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