

**Short term safety of booster immunization with BNT162b2 mRNA COVID-19 vaccine
in healthcare workers**

Dr. Yael Paran^{1,2*}, Dr. Esther Saiag^{1,3} *, Dr. Avishay Spitzer^{1,4,5}, Dr. Yoel Angel^{1,6,7}, Dr. Michal Yakubovsky^{1,2}, Dr. Hagit Padova^{1,8}, Prof. Ronen Ben-Ami^{1,2}, Ilana Goldinger^{1,9}, Prof. Ronni Gamzu¹, Prof. Eli Sprecher^{1,10,11}, Prof. David Zeltser^{1,13}, Dr. Oryan Henig^{1,2}

On behalf of the CoviBoost Study Group Investigators.

1. Sackler Faculty of Medicine, Tel Aviv University, Israel.
2. Department of Infectious Diseases and Infection Control, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
3. Department of Information Systems and Operations, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
4. Department of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
5. Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel.
6. Division of Anesthesiology, Intensive Care, and Pain Management, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
7. Department of Physician Affairs, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
8. Department of Patient Safety, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
9. Laboratory Medicine Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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10. Division of Research and Development, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
11. Division of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
12. Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
13. Department of Internal Medicine "D", Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel.

* Both authors Contributed equally

Corresponding author contact information:

Yael Paran MD, DTMH, 8/6 Hasne st. Ramat Gan, 5237219, Israel.

Phone number 00972-524262723.

Email: Yaelp@tlvmc.gov.il Yaelp@tlvmc.gov.il

Alternative corresponding author:

Oryan Henig MD, Weizmann 6, Tel Aviv. Israel

Phone number 972-50-694-0113

Email: oryanh@tlvmc.gov.il

Abstract:

This study demonstrated good short-term safety profile after a third dose of BNT162b2 vaccine among HCWs.

There were more frequent local reactions and less systemic reactions compared to the second dose.

HCW's who reported reactions had higher pre-booster titer of anti-S1 antibodies compared to those reported no reactions.

Key Points:

Booster, Side effects, Antibodies, BNT162b2, covid-19

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Introduction

A 2-dose series of the BNT162b2 mRNA vaccine was shown to prevent symptomatic and asymptomatic SARS-CoV-2 infection,¹⁻⁴ with an acceptable safety profile.¹⁻⁵ Waning vaccine effectiveness, coupled with a surge of infections due to the Delta SARS-CoV-2 variant, prompted the Israeli ministry of health to recommend a third (booster) dose of the vaccine for adults aged 60 years and above as well as HCWs above the age of 30 years.⁶ However, the safety of repeat of BNT162b2 dosing in immunocompetent individuals has not been systematically assessed. Here, we report on the short-term incidence of adverse events following BNT162b2 booster vaccination among HCWs.

Methods

This study was conducted at the Tel Aviv Sourasky Medical Center, a tertiary medical center in Tel Aviv Israel. HCWs aged 30 years or older were included in this study if they had previously completed a 2-dose BNT162b2 vaccination series, had no documented previous infection with SARS-CoV-2, and were not immunocompromised. Informed consent was obtained by means of an electronic form. The BNT162b2 dose (30 mcg in 0.3 ml delivered to the deltoid muscle) was identical to primary series doses. Adverse events were monitored using a structured 13-item questionnaire administered after the second and third doses of the vaccine. The questionnaire was sent to participants 3-7 days after vaccination.

Anti-spike receptor binding domain (S1 RBD) IgG antibodies titer ("pre-booster antibody titer") was measured up to 7 days prior to immunization using indirect chemiluminescent microparticle immunoassay on the ADVIA Centaur XP system (Siemens, Tarrytown, New York). sCOVG (SARS-CoV-2 IgG) assay are reported in Index Values. A conversion factor between Index Values and the WHO binding antibody units (BAU/mL) has been established. 1.00 Index on the sCOVG Assay would have a WHO BAU/mL value of 21.8.

The study was approved by the TASMC institutional review board (approval numbers 0565-21-TLV and 0530-21-TLV).

Comparison with rate of adverse events after second dose

For comparison with reported rates of local and systemic reactions after the second dose, we relied on historical anonymous records from our institution of similar questionnaires screening for adverse events.

Statistical analysis

All statistical analyses were performed using R software version 4.0.3.

Statistical significance for continuous variables was determined using Wilcoxon's rank sum test (one-tailed) and for categorical variables using a Hypergeometric test (one-tailed). P values were corrected for multiple testing where applicable using Holm's method.

Results

Between August 1, 2021, and August 21, 2021, 2979 HCWs received a third BNT162b2 dose as part of the hospital's vaccination campaign. Median participant age was 52 years (IQR 42–62). Overall, 890 HCWs (30%) responded to the adverse event questionnaire and contributed to the safety cohort. The median age in the safety cohort was 47 years (IQR 39–55), 204 (22.9%) were older than 55 years, and 588 (66%) were female. In 97.2% of participants the time interval between second and third vaccine dose was at least 5 months. Pre-booster anti S1 IgG titers were available for 536 HCWs (60%).

The historical safety cohort included 2256 HCWs who responded to the adverse event questionnaire following the second vaccine dose. (Supplemental Table 1).

Reactions Reported After the Third (booster) Vaccine Dose

Local injection site reactions were reported by 778 HCWs (87.4%) (Supplemental Table 2). The most common local reaction was pain at the injection site reported by 461 HCWs (52%). Local reactions were significantly more frequent among persons aged 55 years or younger than among persons older than 55 years: 92.7% versus 81.9%, $P < 0.001$ (Figure 1a).

Systemic symptoms were reported by 505 HCWs (56.7%). The most frequent symptoms were fatigue (37.8%), myalgia (25.5%) and headache (21.1%) (Figure 1a).

Systemic symptoms were significantly more frequent among persons aged 55 years or younger than among persons older than 55 years: 61.3% versus 42.2% ($P < 0.001$) (Figure 1a).

No participant required emergency treatment for local or systemic reactions and no immediate type allergic reactions were reported. Seven (0.8%) reported a systemic rash.

Comparing their own overall experience after the third vaccine dose with the experience they recalled after the second dose, 206 participants (23.1%) reported more severe reactions after the third dose, 245 (27.5%) reported milder reactions after the third dose, and 421 (47.3%) reported similar degree of reactions. Eighteen participants (2%) responded that they did not recall and could not compare their experience. (Figure 1b).

Comparison between reactions reported after the third dose (current cohort) and after second dose (historical cohort) vaccine.

Compared with local reactions reported after the second vaccine dose, reactions were more frequent after the third dose: 92.7% versus 89.6% for persons aged 55 years or younger ($P = 0.039$) and 81.9% versus 75.3% for persons older than 55 years ($P = 0.058$) (Figure 2).

Systemic symptoms were less frequent after the third vaccine dose compared to the second dose: 61.3% versus 71.8% for persons aged 55 years and younger ($P < 0.001$) and 42.2% versus 48.6% for persons older than 55 years ($P = 0.06$) (Fig. 2).

Pre-Booster titer of anti-S1 IgG antibodies and association to reported reactions to third dose (booster) vaccine.

The median pre-booster titer of anti-S1 IgG antibodies was significantly higher for participants who reported local and systemic reactions compared with those who reported no reactions after the booster dose (4.61 [IQR 2.89-8.24] vs 3.35 [IQR 1.79-5.12], $p < 0.0001$) (supplemental figure S1 and Supplemental table S3). There was no significant difference in the anti-S1 IgG antibody titers between the age groups with a median titer of 4.24 (IQR 2.72-7.63) in persons 55 years or younger and 4.42 (IQR 1.89-8.33) in persons older than 55 years.

Discussion

In this observational study of immunocompetent HCWs who received a third (booster) vaccine dose BNT162b2, the local and systemic reactions within a week after vaccination were mild and were similar to those observed in previous studies that evaluated the safety of the BNT162b2 primary series.^{1, 7} There were no severe adverse events. As noted for the primary BNT162b2 series, local reactions and systemic symptoms were more frequent in persons 55 years or younger than in older individuals.^{1, 7}

Significantly, more local but fewer systemic reactions were reported following the third versus the second vaccine dose. The median pre-booster anti-S1 IgG titers were higher in persons who reported local and systemic reactions than for those who reported no symptoms, as was also reported recently by Rechavi et al.⁸ This finding suggests that humoral immune priming is associated with local and systemic symptoms after booster vaccination. Previous studies have shown that the humoral response to an mRNA vaccine persisted longer in the regional lymph nodes than in peripheral blood. Turner et al.⁹ found that while circulating IgG and IgA-secreting plasmablasts in peripheral blood that target the S protein declined and became undetectable three weeks after the second immunization, S-binding B cells and plasmablasts persisted in the germinal centers of draining lymph nodes on the side of immunization for at least 12 weeks after immunization.

There are several limitations to our study. First, the study was questionnaire based with relatively low response rate, and therefore subjected to recall and report bias. However, the questionnaire was sent to participants up to one week after receiving the booster dose to minimize this effect. Second, only short-term reactions occurring up to 7 days after vaccination were assessed. Third, the cohort size was small with predominance of young participants, as expected from a cohort of HCWs, and was not powered to detect rare adverse events such as myocarditis and anaphylaxis.

In conclusion, a third dose of BNT162b2 was associated with generally mild short-term local and systemic reactions, which were more frequent among younger vaccine recipients. Compared to the second vaccine dose, the third dose was associated with more local reactions and fewer systemic symptoms. No severe adverse events were encountered. Monitoring of late-onset adverse events is ongoing.

Acknowledgements

Potential conflicts of interest:

None of the authors have any conflicts of interest to declare. The study was not funded.

Patient consent statement:

The study was approved by the Tel Aviv Sourasky Medical Center institutional review board (approval numbers 0565-21-TLV and 0530-21-TLV).

The Helsinki committee has exempted us from obtaining written informed consent of the patients involved in our manuscript.

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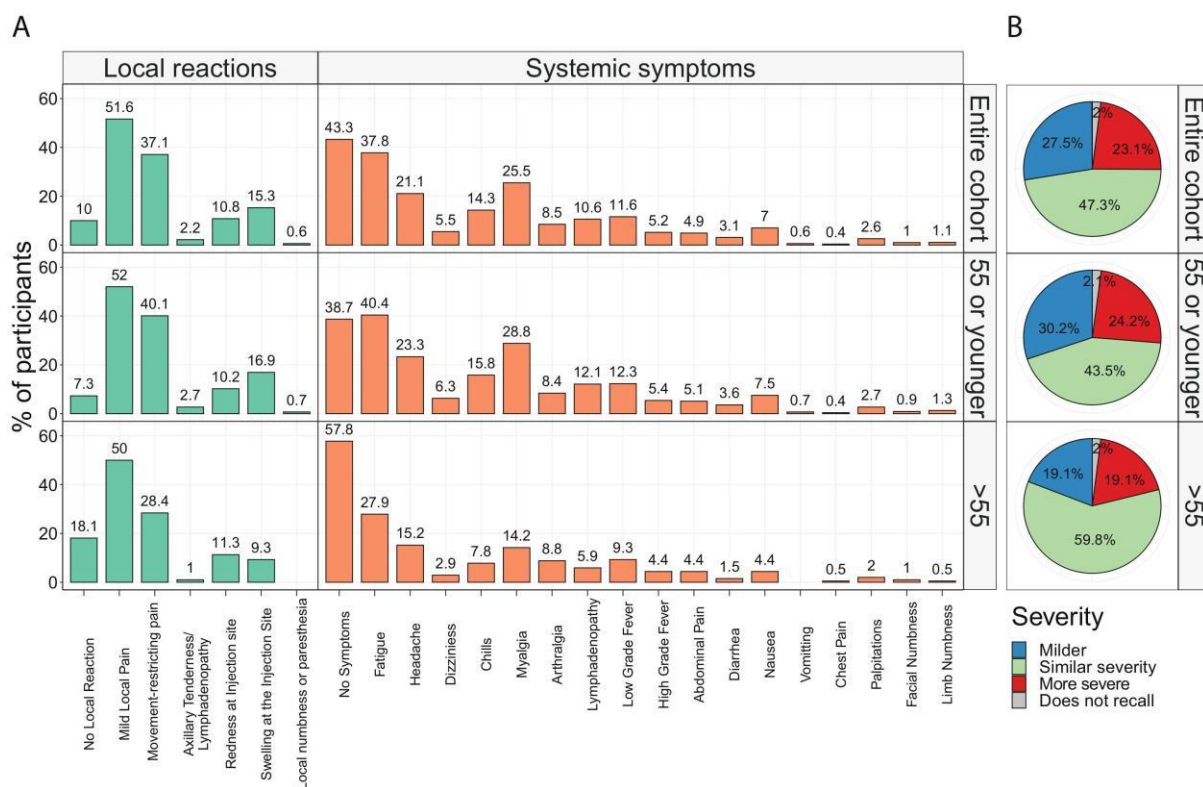
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Figures Legends:

1. **Figure 1:** A. Third vaccine dose reactions B. Reaction to third dose vaccine in comparison to second vaccine dose (for the same vaccine participants).
2. **Figure 2:** Local and systemic reactions in the study cohort in comparison to reactions reported after the second dose.

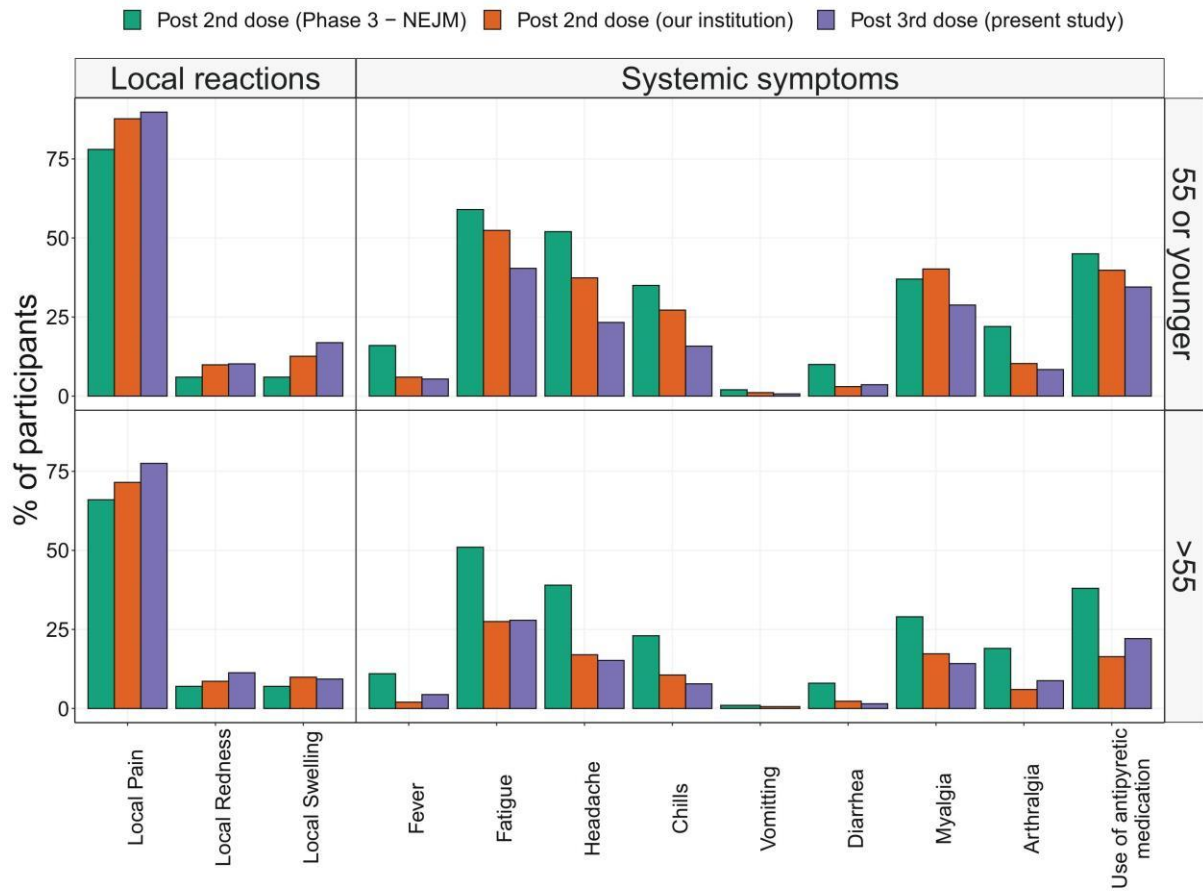
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Figure 1



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Figure 2



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