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Immunogenicity trends 1 and 3 months after second BNT162B2 vaccination among healthcare workers in Israel

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ARTICLE INFO

Keywords:
BNT162b2
COVID-19
Healthcare workers
Immunogenicity
Serology

ABSTRACT

Objectives: We evaluated the antibody response to the BNT162B2 vaccine among healthcare workers (HCWs) to identify factors associated with decreased immunogenicity.

Methods: This prospective cohort study included consenting HCWs who completed a questionnaire regarding background illnesses, medications, and post-vaccination allergic reactions or rash. All HCWs were tested for anti-spike antibodies (LIAISON SARS-CoV-2 S1/S2 IgG assay) 1 and 3 months after the second vaccine dose. A multivariate mixed linear model was adjusted to participants’ data and fit to predict antibody levels after the second BNT162B2 vaccine dose, based on antibody levels at 1 month and the slope between 3 months and 1 month. Multivariate analyses identified factors associated with lower antibody levels.

Results: In total 1506 HCWs were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies. Older age was associated with lower mean antibody levels (−1.22 AU/mL, p < 0.001, 95%CI −1.43 to −1.01). In addition, male sex (−22.16 AU/mL, p < 0.001, 95%CI −27.93 to −16.39), underlying condition (−10.86 AU/mL, p = 0.007, 95%CI −18.81 to −2.91) and immunosuppressive treatment (−28.57 AU/mL, p = 0.002, 95%CI −46.85 to −10.29) were associated with significantly lower mean antibody levels. Allergic reactions after vaccine administration or peri-vaccination glucocorticosteroid treatment were not correlated with antibody levels.

Conclusions: Most HCWs had measurable antibodies at 3 months. Risk factors for lower antibody levels were older age, male sex, underlying condition, and immunosuppressive treatment. These factors may be considered when planning booster doses during vaccine shortages. Yael Shachor-Meyouhas, Clin Microbiol Infect 2022;28:450.e1–450.e4 © 2021 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
Introduction

Since the World Health Organization (WHO) declared a pandemic for coronavirus disease 2019 (COVID-19), more than 3 million lives have been claimed worldwide; by May 2021, 6363 of these were in Israel [1]. In Israel, vaccination with Pfizer/BioNTech BNT162b2 began in late December. By late April 2021, more than 5 million Israeli citizens were fully vaccinated [2]. Northern Israel’s only tertiary medical centre has been involved with the vaccination campaign from the beginning. Of its 5499 healthcare workers (HCWs), 88% were fully vaccinated.

The high effectiveness of the vaccine in Israel has been published [3–5], but data on immunogenicity are sparse, particularly among immunocompromised or haemodialysis patients, and after the first or second dose of the vaccine [6–8]. A campaign to vaccinate all HCWs at our institution was launched on 20th December 2020.

This brief report presents the antibody levels among HCWs 1 and 3 months after the second vaccine dose.

Methods

A prospective cohort study was conducted on fully vaccinated HCWs who consented to participate and were tested for blood samples at the beginning of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-spike levels 1 and 3 months after the second vaccine dose in February and April 2021, respectively. The study was conducted at Rambam Health Care Campus (RHCC), a 1000 bed tertiary university hospital.

The LIAISON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Saluggia, Italy) was used to detect anti-spike S1/S2 IgG antibodies. The cut-off value was 15 AU/mL according to Israeli Ministry of Health instructions [9]. Primary outcome measures were the difference in antibody levels at two time points (1 and 3 months) and the association between that difference and age, sex, underlying disease, per-vaccination glucocorticosteroids (GCS), immunosuppressive therapy, and allergic reactions or rash after vaccination.

All participants completed an online questionnaire which included questions about age, sex, underlying diseases (yes/no question with a dropdown list of conditions), per-vaccination GCS, immunosuppressive therapy, post-vaccination allergic reactions or rash, contact with patients with confirmed SARS-CoV-2 infection, and flu-like illness after vaccination.

Treatment with GCS was defined as either chronic or GCS treatment 1–2 days before or after vaccine administration to relieve allergic reactions. Increased antibody levels after 3 months were defined as any antibody level increase between 1 and 3 months. Individuals with increased antibody levels at 3 months were examined with Abbott ARCHITECT SARS-CoV-2 IgG assay to detect anti-NC antibodies to rule out asymptomatic SARS-CoV-2 infection. The positivity threshold was ≥1.4, using a lower, provisional ‘grey zone threshold’ (≥0.5–1.39) to improve diagnostic yield. All HCWs with signs and symptoms suggesting SARS-CoV-2 infection were examined with molecular assay (polymerase chain reaction, PCR).

Data were analysed with SPSS software (version 27). A multivariate linear mixed model was fit to predict the adjusted difference of 3-month antibody levels by the 1-month level and by baseline participant characteristics as potential predictors (specifically age, sex, presence of underlying condition, per-vaccination GCS, immunosuppressive therapy, and allergic reactions or rash following vaccine administration). The model also included the time after the second vaccine dose (1 and 3 months).

The study was approved by the hospital’s Internal Review Board (#021-021).

Results

Overall, 1506 HCWs were evaluated at 1 month and 1209 (80.3%) at 3 months; 1194 (79.3%) were evaluated at both time points. At 1 month, six participants had negative serology (0.4%), of which only three were retested at 3 months and remained seronegative. Of the 1-month participants, four were seropositive (21–58 AU/mL) and became seronegative at the 3-month evaluation point.

At 3 months, a total of seven HCWs were seronegative, five of whom were >60 years old, including two with underlying disease. Two younger HCWs were also seronegative and had underlying disease.

Mean age was 48.39 ± 12.47 (range 19–91) years and the female-to-male ratio was 2.5:1. Underlying conditions were reported in 211 participants (14%); hypothyroidism in 134 (8.9%), autoimmune disease in 94 (6.2%), cardiac disease in 51 (3.4%), lung disease in 47 (3.1%), immunodeficiency in 29 (1.9%), chronic renal disease in nine (0.6%), and active oncological disease in seven (0.5%). Peri-vaccination GCS or long-term immunosuppressive therapy was reported by 74 (4.9%) HCWs.

Seven participants were diagnosed with SARS-CoV-2 infection, of whom six were diagnosed less than 7 days after the second vaccine dose. One participant was diagnosed 1.5 months after the second dose; this individual was mildly symptomatic and had increased antibody levels 3 months after vaccination.

At 1 month, age correlated inversely with antibody levels: for each 1-year increase in age a 1.39 AU/mL decrease in antibody levels was noted (95%CI −1.64 to −1.13, p < 0.001). Male sex was associated with a mean decrease of 23.08 AU/mL in antibody levels compared to female sex (p < 0.001, 95%CI −30.01 to −16.16). Underlying condition and immunosuppressive treatment were also associated with a reduction from baseline in mean antibody levels (13.44 AU/mL, p < 0.005, 95%CI −22.80 to −4.08 and 35.23 AU/mL, p 0.002, 95%CI −57.48 to −12.98, respectively).

At 3 months, for each 1-year increase in age, a 0.87 AU/mL decrease in antibody levels was observed (p < 0.001, 95%CI −1.12 to −0.62). Males had lower antibody levels (by 19.10 AU/mL) than females (p < 0.001, 95%CI −25.84 to −12.37), and participants receiving immunosuppressive treatment had lower antibody levels (by 35.71 AU/mL) (p < 0.001, 95%CI −57.36 to −14.06) than those not receiving it.

The mixed linear model showed that antibody levels were significantly lower at the 3-month time point than at the 1-month point (−58.63 AU/mL, p < 0.001, 95%CI −60.95 to −56.32). The older the participant, the lower the mean antibody levels; in addition, male sex, underlying condition, and immunosuppressive treatment predicted significantly lower mean antibody levels. Allergic reactions after vaccine administration or peri-vaccination GCS treatment were not correlated with antibody levels (Table 1). No interaction was found between age group and sex. The mean antibody titre distribution by age group is shown in Fig. 1. Supplementary Material Fig. S1 presents the median antibody titre distribution by age group.

Of 1194 HCWs fully vaccinated and screened for antibody levels at both time points, only 66 had increased antibody levels at 3 months, of which only one was diagnosed with SARS-CoV-2 infection; the rest were anti–NC–antibody-negative at both 1 and 3 months. No risk factors were identified compared with other participants, except for a higher SARS-CoV-2 exposure rate in the group with decreasing antibody levels, but this was not statistically significant (Supplementary Material Table S1).
Discussion

Three months after full BNT162b2 vaccination, most tested HCWs still had a measurable level of SARS-CoV-2 antibodies, with 0.6% seronegative cases and only one confirmed SARS-CoV-2 case. Lower levels were associated with older age, male sex, and underlying condition, as well as immunosuppressive therapy.

When examining healthy populations similar to our HCWs, age is a key factor in measured antibody levels, with the lowest levels seen among participants >60 years old. Other studies examining serology after BNT162b2 vaccination have demonstrated similar results 1 month or less after vaccination among healthy participants, as well as patients with immunodeficiency and haemodialysis [6–8,10,11]. A study conducted in Israel observed lower antibody levels after the first BNT162b2 dose among older HCWs, especially those >60 years old [10]. Another recent study followed Israeli HCWs up to 5 weeks after the second vaccine dose, and also demonstrated lower levels among those aged >66 years, males, and HCWs with other chronic conditions or immunodeficiency [12].

An important observation from our data is the lower antibody levels found among males and those with an underlying condition both 1 and 3 months after BNT162b2 vaccination. This finding is supported by other studies and is also seen after other vaccinations (e.g. vaccines for hepatitis B and measles) [13–16].

The difference in antibody levels between 3 months and 1 month revealed a smaller absolute decrease in antibody levels with increasing age. However, the absolute antibody levels at 1 month were also lower as age increased, indicating that the relative reduction does not differ by age. This finding should be studied further and correlated with clinical efficacy.

Nevertheless, the fact that only seven people had no measurable antibodies and were not infected with SARS-CoV-2 is encouraging; these HCWs will be followed. Future studies could provide insight regarding the decrease in antibody levels and its significance.

Also interesting was the lack of association between reported post-vaccination allergic reactions or rash and antibody levels, which was also reported by Grupper et al. among transplant patients [6].

Finally, a small group of HCWs experienced increased antibody levels between 1 and 3 months. No association was found; these HCWs should be followed up, and more research is needed to understand this phenomenon and its clinical significance, which is currently unknown.

Our study has several limitations. First, no information was available regarding cellular immunity and/or neutralizing antibodies, or on the protection from asymptomatic carriage or infection. There have been reports regarding neutralizing antibodies indicating a correlation between anti-S antibody titres and neutralization antibody levels after BNT162b2 vaccine [17]. Second,
our cohort of HCWs were generally healthy and young, with no very old individuals. The rise in antibody titre in 66 HCWs was not detected early enough to perform a molecular test, which might have verified diagnosis of SARS-CoV-2; however, that group was asymptomatic and exposed to fewer infected people. This group should be further followed.

Conclusion

Our findings are encouraging since most HCWs had measurable antibodies at 3 months with a low number of subsequently confirmed SARS-CoV-2 cases. Despite lower antibody levels among HCWs who were older, male, or receiving immunosuppressive treatment, their reduction in antibody levels was lower than in the other groups, which is also encouraging.

Author contributions

YSM, KH, HDY, and MSC wrote the manuscript. YSM, KH, HDY and MH conceived and designed the study, MSC did the laboratory testing. YSM, KH, HDY, AW, MM, GH, NH, VG, IN, HC, JT and NP coordinated the patient enrolment and blood testing. HDY and RA conducted the statistical analysis. HDY, KH, MSC, RA, and YSM performed data preparation. All authors read and approved the submission.

Transparency declaration

The authors declare that they have no conflicts of interest. No special funding was received for this study.

Acknowledgements

This study was performed in collaboration with the Israeli Ministry of Health. The authors would like to thank Mira Shiloah, Nelly Zaltzman Bershadsky, Rotem Cohen, Rotem Daniel, Sara Tzafrir, Marianna Sherman, Anat Reiner-Benaim, Ronit Leiba, and Deborah Hemstreet for their contributions toward the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.11.014.

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