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Original article

Association between IgG antibody levels and adverse events after first and second Bnt162b2 mRNA vaccine doses

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ABSTRACT

Objectives: This study sought to correlate the SARS-CoV-2 IgG antibody response level to the BNT162b2 (Pfizer BioNTech) mRNA vaccine after the first and second doses with the reported adverse events.
Methods: This cohort study examined the adverse events profiles of people vaccinated with BNT162b2 in our institute between late 2020 and May 2021. Adverse events, age, and sex were reported using an electronic questionnaire, and their SARS-CoV-2 IgG antibody levels were retrieved from the hospital database.
Results: Between 20 December 2020 and 31 May 2021, the adverse events questionnaire was completed by 9700 individuals who received the first vaccine dose and 8321 who received the second dose. After the first and second doses, the average antibody levels were 62.34 AU/mL (mean 4–373) and 188.19 AU/mL (mean 20–392), respectively. All of the adverse events, except local pain, were more common after the second vaccine dose. Multivariate analysis showed that after the first vaccine dose, female sex and younger age (but not IgG titres) were associated with a higher probability of adverse events (OR 2.377, 95% CI, 1.607–3.515, p = 0.000; OR 0.959, 95% CI, 0.944–0.977, p £0.000; OR 1.002, 95% CI, 0.995–1.008, p £0.601; respectively); however, all three parameters were associated with the incidence of adverse events after the second dose (OR 2.332, 95% CI, 1.636–3.322, p = 0.000; OR 0.984, 95% CI, 0.970–0.999, p £0.039; OR 1.004, 95% CI, 1.001–1.007, p £0.022; respectively).
Discussion: Adverse events are significantly more common after the second BNT162b2 vaccine dose than after the first dose. We found an association between sex, age, and SARS-CoV-2 IgG antibody titre with the incidence of adverse events. **Eyal Braun, Clin Microbiol Infect 2022;28:1644**

Introduction

Since the COVID-19 outbreak in December 2019, due to SARS-CoV-2, several vaccines have been developed in an attempt to ease the burden of the pandemic. The first vaccine approved for mass use by the United States Food and Drug Administration (FDA) was the BNT162b2 (Pfizer BioNTech; New York, NY, USA) mRNA vaccine. This vaccine was found to be effective in reducing the number of people infected with SARS-CoV-2 and contributed to fewer cases of severe disease [1].

Israel was one of the first countries to start the mass vaccination of its adult population, as early as December 2020. Out of a population of 9.3 million, approximately 6 million people received the first vaccine dose and 5.5 million the second dose.

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Rambam Health Care Campus participated in this nationwide endeavour and vaccinated most of its employees and a substantial number of the general population in Haifa district, mostly family members of its personnel. All of the vaccinated people were offered two serology tests, 3 weeks after the first dose (just before the second dose was given) and 3 weeks after the second dose.

Reported adverse events after BNT162b2 vaccination are common. Early studies showed that safety over a median time of 2 months was similar to other common antiviral vaccines. Reported adverse events to vaccination were relatively mild [2,3]. However, the influential voice of anti-vaccination campaigners worldwide led many people to reject or postpone the SARS-CoV-2 vaccination in general, and therefore jeopardized the efforts to slow and halt the pandemic's progress. Older age, male sex, and immunosuppression were shown to be risk factors for lower antibody levels [4,5]. Little is known about the correlation between post-immunization serology levels with the type, number, and severity of adverse events [6]. In order to curtail COVID-19 morbidity, some countries (including Israel) have already begun offering a third [7] and even a fourth dose. There is a high probability of periodic booster doses becoming a reality. Hence, there is an urgent need to understand the "natural history" of the BNT162b2 vaccine's adverse events and the subsequent correlation with serology levels and immunity.

This study aimed to examine the correlation between SARS-CoV-2 serology levels, evaluated 3 weeks after the first and second doses of the BNT162b2 vaccine with the number and exact types of adverse events.

Methods

This single centre retrospective cohort study was performed in Rambam Health Care Campus, a 1000-bed teaching and tertiary hospital in Northern Israel.

Our institute began offering the BNT162b2 vaccine to hospital employees and their family members on 20 December 2020. All of the individuals vaccinated at Rambam were sent an online questionnaire 1 week after receiving the first vaccine dose. The questionnaire asked them to voluntarily report any side effects experienced during the first week after vaccination.

The questionnaire was aimed at collecting data regarding the following adverse events: chills, diarrhoea, emergency room visits due to vaccination related events, general fatigue, weakness, headache, local pain and heat, swelling, muscle or joint pain, paraesthesia, rash, restriction of range of motion at the vaccination site, enlarged lymph nodes, and systemic fever (temperature >38°C).

Those who completed the questionnaire were subsequently asked to take blood tests for anti-spike SARS-CoV-2 levels immediately before the second vaccine dose (3 weeks after the first dose) and 1 month after receiving the second dose.

The study included individuals who completed the online questionnaire, agreed to be tested for serology IgG levels as detailed above, and gave informed consent. We then examined the correlation between antibody levels and each of the adverse events listed above and the cumulative number of events after both the first and the second vaccine doses. The LIAISON SARS-CoV-2 TrimericS IgG assay (Diasorin, Saluggia, Italy) was used for serology tests, a new generation of chemiluminescence immunoassay, for the quantitative determination of anti-trimeric spike protein specific IgG antibodies to SARS-CoV-2 in human serum or plasma samples, and provided an indication of the presence of neutralizing IgG antibodies against SARS-CoV-2. The samples were examined on a LIAISON XL instrument. A negative result was defined as <33.8 AU/mL.

Data analysis

Descriptive statistics in terms of mean, SD, and percentage were calculated for all study parameters. The differences between quantitative parameters (age and serologic result) and the first and second doses were examined by Student's *t*-test, which was also used to determine the difference between serologic results and the occurrence of side effects. Fisher's exact tests or Pearson's χ^2 test were used for the categorical parameters to determine the difference between the two vaccine doses. The number of adverse events per patient was calculated and Pearson correlation was used to describe the relationship between the number of adverse events and serological levels. Multivariate regression analysis was used to identify risk for adverse events. The multivariate logistic regression model was used to predict adverse events according to independent variables (age, sex, and serologic results); $p < 0.05$ was considered significant. Adverse events served as dependent variables. The continuous variables were not dichotomized, and sex was the only dummy variable used. The Hosmer test was used for the overall evaluation of the final model, and the OR and 95% CI were calculated. The Wald method was used for CI calculation. The SPSS version 27 (IBM Corp, Armonk, NY, USA) was used for all of the statistical analyses.

The study was approved by the hospital's Internal Review Board (#0172-21-RMB).

Results

Study population characteristics

Between 20 December 2020 and 31 May 2021, 15 999 and 14 924 people in our institute received the first and second BNT162b2 SARS-CoV-2 vaccine doses, respectively. The database included 9700 cases who received the first dose and 8321 cases who received the second dose and completed the questionnaire after each dose. Because completing the questionnaires was optional, some participants did not complete both. Serological tests were taken by 1155 out of 9700, and 1180 out of 8321 participants, after the first and second doses, respectively. The sex of the study population was 5369 (55%) male for the first and 4582 (55%) for the second doses. Average age was 55.1 ± 17.7 years after the first dose and 56.1 ± 17.2 after the second dose. The average antibody titre after the first and second doses was 62.34 (4–373) AU/mL and 188.19 (20–392) AU/mL, respectively.

Adverse events profile

Adverse effects were common among the vaccinated cohort, with at least one being reported after the first and second vaccine doses by 81.3% (7889 out of 9700) and 83.3% (6933 out of 8321), respectively.

All of the adverse events, except local pain, were more common after the second vaccine dose. The significant differences were most prominent between doses with respect to chills, fatigue, weakness, headache, nausea and vomiting, paraesthesia, swollen lymph nodes, and systemic fever (Table 1).

Associations between side effects, participant characteristics, and antibody levels

The IgG antibody titre levels were correlated to adverse events after the first and second vaccine doses. Higher levels related to the injection site, chills, and headaches were evident after the first dose, and even higher after the second dose. All of the other adverse

Table 1
Side effects profile after the first and second vaccine doses

Parameter		Vaccination		Total, *n* (%)	p
		First, *n* (%)	Second, *n* (%)		
Number of participants		9700	8321	18 021	
Sex	Female	4331 (45)	3739 (55)	8070 (45)	
	Male	5369 (55)	4582 (55)	9951 (55)	
Age (average ± SD) y		55.1 ± 17.7	56.1 ± 17.2	55.5 ± 17.5	
Chills		466 (5)	1631 (21)	2097 (12)	<0.001
Diarrhoea		198 (2)	257 (3)	455 (2.7)	<0.001
ER cause of visit		0	9	9	
ER visit due to vaccination		0	13	13	
General fatigue		1916 (21)	3326 (42)	5242 (31)	<0.001
General weakness		1343 (15)	2923 (37)	4266 (25)	<0.001
Headache		1267 (14)	2198 (28)	3465 (20)	<0.001
Local heat at vaccination site		714 (8)	868 (11)	1582 (9)	<0.001
Local pain at injection site		7403 (79.6)	6351 (79.4)	13 754 (79.5)	0.82
Local redness & swelling >5 cm		402 (4)	519 (6.5)	921 (5.3)	<0.001
Muscle/joint pain		2287 (25.1)	2613 (33.2)	4900 (28.9)	<0.001
Nausea/vomiting		336 (3.7)	672 (8.6)	1008 (5.9)	<0.001
Paraesthesia		2	454 (5.5)	456 (2.5)	<0.001
Restricted range of motion		2402 (25.9)	2707 (34.1)	5109 (29.7)	<0.001
Subcutaneous nodule at injection site		404 (4.5)	480 (6.1)	884 (5.3)	<0.001
Swollen lymph nodes		90 (1.0)	212 (2.7)	302 (1.8)	<0.001
Systemic fever >38°C		53 (0.6)	520 (6.6)	573 (3.4)	<0.001

Abbreviation: ER, emergency room.

events, except for paraesthesia, diarrhoea, and >5 cm swelling, were also associated with higher IgG titre levels (Table 2).

An examination of the relationship between the number of adverse events and antibody titre levels demonstrated a weak but significant correlation after both vaccine doses ($r = 0.12$, $p < 0.0001$ vs. $r = 0.27$ $p < 0.0001$, respectively). The antibody titres after the first and second vaccine doses were on average 53 ± 31.9 AU/mL and 169.5 ± 60.1 AU/mL, respectively, when no adverse events were observed as compared to 63.5 ± 35.5 AU/mL and 191 ± 58.4 AU/mL, respectively, when one adverse event or more were observed ($p < 0.001$). The accumulated number of adverse events was also weakly but significantly associated with higher titre levels after the first and second vaccine doses ($r = 0.12$, $p < 0.001$ and $r = 0.268$, $p < 0.0001$, respectively).

Multivariate analysis for sex and age after the first vaccine dose showed that female sex and younger age (but not IgG levels) were associated with the occurrence of adverse events (Table 3). However, all three parameters, including IgG titres, were associated with adverse events after the second dose. Notably, female sex was by far the most predictive factor (Table 3).

Discussion

Vaccination remains the most powerful therapeutic tool available in the attempt to control SARS-CoV-2 infection in terms of its burden on healthcare systems. Studies have shown that antibody levels are predictive of immunity against SARS-CoV-2 infection [5]. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. However, the potential for adverse events after vaccination deters many people from being vaccinated against COVID-19, making them more susceptible to the disease.

We demonstrated that most adverse events were more common after the second vaccine dose, with the exception of local pain, which was the most commonly reported side effect. These findings were similar to those from previous clinical trials [8,9].

Table 2
Associations between adverse events, participant characteristics, and antibody titre levels following the first and second BNT162b2 vaccine doses

Serology (AU/mL)	First vaccine dose			Second vaccine dose		
	Average ± SD		p	Average ± SD		p
	Yes	No		Yes	No	
Chills	71.7 ± 43.4	61.5 ± 34.8	0.029	208.3 ± 57.5	179.81 ± 57.8	<0.001
Diarrhoea	61.9 ± 35.6	62.1 ± 35.5	0.97	190.9 ± 49.1	187.9 ± 59.6	0.72
Fatigue	64.9 ± 38.0	61.2 ± 34.5	0.12	199.7 ± 59.3	173.8 ± 55.8	<0.001
Weakness	64.9 ± 36.2	61.3 ± 35.2	0.17	203.4 ± 59.9	174.3 ± 55.2	<0.001
Headache	67.2 ± 44.8	60.6 ± 31.5	0.012	204.6 ± 58.3	179.3 ± 57.9	<0.001
Local heat at vaccination site	67.9 ± 35.8	61.2 ± 34.9	0.052	206.9 ± 59.6	184.9 ± 58.1	<0.001
Local pain at injection site	64.0 ± 35.5	48.1 ± 31.4	<0.001	192.1 ± 58.0	167.3 ± 60.2	<0.001
Local redness and swelling >5 cm	74.8 ± 30.9	61.3 ± 35.1	0.004	195.1 ± 60.3	187.7 ± 58.9	0.29
Muscle/joint pain	64.1 ± 34.9	61.4 ± 35.6	0.26	199.6 ± 57.9	180.8 ± 58.8	<0.001
Nausea/vomiting	64.7 ± 40.9	61.9 ± 35.1	0.57	204.8 ± 59.2	185.9 ± 58.9	<0.001
Paraesthesia				199.2 ± 57.7	187.2 ± 58.6	0.26
Restricted range of motion	67.3 ± 31.2	59.9 ± 34.3	0.001	197.6 ± 58.9	181.1 ± 58.2	<0.001
Subcutaneous nodule at injection area	72.4 ± 57.2	61.2 ± 31.9	0.006	205.9 ± 57.7	186.9 ± 59.0	0.005
Swollen lymph nodes	63.3 ± 20.7	61.9 ± 35.6	0.89	208.8 ± 61.0	187.4 ± 58.5	0.021
Systemic fever >38°C	69.2 ± 20.3	62.0 ± 35.4	0.68	218.9 ± ± 55.6	184.8 ± 57.8	<0.001

Table 3
Multivariate analysis of risk factors for the prediction of adverse events after the first and second BNT162b2 vaccine doses

Parameter	After first vaccine dose		After second vaccine dose	
	OR (95% CI)	p	OR (95% CI)	p
Sex: female vs. male (reference: male)	2.377 (1.607–3.515)	0.000	2.332 (1.636–3.322)	0.000
Age at documentation (for each 1 year increment)	0.959 (0.944–0.977)	0.000	0.984 (0.970–0.999)	0.039
First serologic test (AU/mL) (for each 1 AU/L increment)	1.002 (0.995–1.008)	0.601	1.004 (1.001–1.007)	0.022

Abbreviation: OR, odds ratio.

Our study showed that most adverse events, particularly after the second dose, were significantly associated with higher IgG antibody levels, as was an increasing number of side effects. However, multivariate analysis revealed a much stronger association between female sex and adverse events, and a significant inverse correlation between age and side effects. Antibody levels were significantly (but weakly) associated with the number of adverse events after the second vaccine dose. There is little evidence to associate adverse events with antibody titre levels. A recent small study found no clear correlation [6]. The current study evaluated local and systemic adverse events after the BNT162b2 SARS-CoV-2 vaccination and its relationship with antibody levels in a large cohort of healthcare workers and their relatives. The effect of age and sex was consistent with the findings of several recently published clinical trials [10,11]. The low IgG antibody titres recently demonstrated in the older population may also account for the paucity of adverse events [10]. In general, females have higher antibody responses and report more adverse events after vaccination than males [12–14]. Older age was also adversely associated with immune response [15].

A recent smaller study of 204 healthcare workers reported similar trends regarding sex and age [5]. Instead of evaluating titre levels and the number of adverse events, a vaccine-related symptom severity index was examined; hence, unlike our study, no correlation was found with vaccine-induced antibody titre levels. The different methodology might explain the different results, as well as our much larger cohort size.

Our study cohort was much larger than cohorts in previous studies. The key strength of this study rested in its ability to precisely profile individuals who were most susceptible to adverse events. This was particularly important in light of the high probability of the need for future “booster” doses. Moreover, such a profile could give a positive meaning to such adverse events and positively impact public response to COVID-19 vaccination.

This study was limited in that most of the cohort consisted of healthy adults, and the participants could not be checked for significant medical background conditions or a significant history of allergies. There was also potential selection bias, as we could not influence who completed the adverse events questionnaire, who completed which questionnaire, or who performed serology tests.

Notably, all SARS-CoV-2 vaccines prevent infection by inducing specific antibodies. However, the association between the antibody levels and the level of protection is very complicated.

Currently there is scarce evidence for relating the antibody levels to the strength of immune response, and cellular response is sometimes better correlated with protection than with antibody titre levels [16]. There is also no general recommendation for vaccinated people to perform routine serological screening. We believe that the comprehensive profiling of adverse events could serve as a useful surrogate for immunity and help with evaluations of predicted protective response. To that end, further research that examines the possibility of developing a comprehensive adverse events profile to predict the clinical outcomes is necessary.

In conclusion, high levels of vaccine-mediated IgG antibodies were associated with a more frequent and higher number of adverse events. Female sex and younger age were stronger predictors of the occurrence of adverse events.

Author's contributions

EB, ZSA and GB wrote the manuscript. EB, NAH, GB conceived and designed the study. EB, NAH, AV, MM, YSM, MH, coordinated the patient enrolment and blood testing. RL conducted the statistical analysis. EB, NAH, YSM, KH, ZSA and GB performed the 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.07.002.

References

[1] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603–15.
[2] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
[3] Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-Based Covid-19 vaccine candidates. N Engl J Med 2020;383:2439–50.
[4] Shachor-Meyouhas Y, Hussein K, Dabaja-Younis H, Szwarcwort-Cohen M, Almog R, Weissman A, et al. Immunogenicity trends 1 and 3 months after second BNT162B2 vaccination among healthcare workers in Israel. Clin Microbiol Infect 2022;28:450–e1–4.
[5] Coggins SAA, Laing ED, Olsen CH, Goguet E, Moser M, Jackson-Thompson BM et al. Adverse effects and antibody titres in response to the BNT162b2 mRNA COVID-19 vaccine in a prospective study of healthcare workers. 2021 [cited…]. medRxiv Prepr Serv Heal Sci. https://doi.org/10.1101/2021.06.25.21259544.
[6] Lapić I, Rogić D, Šegulja D, Zaninović L. Antibody response and self-reported adverse reactions following vaccination with Comirnaty: a pilot study from a Croatian university hospital. 2021 [cited…]. J Clin Pathol. https://doi.org/10.1136/jclinpath-2021-207572.
[7] 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.
[8] Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis 2021;21:939–49.
[9] Takeuchi M, Higa Y, Esaki A, Nabeshima Y, Nakazono A. Does reactogenicity after a second injection of the BNT162b2 vaccine predict spike IgG antibody levels in healthy Japanese subjects? PLoS One 2021;16:e0257668.

[10] Müller L, Andrée M, Moskorz W, Drexler I, Walotka L, Grothmann R, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 coronavirus disease 2019 vaccination. Clin Infect Dis 2021;73:2065–72.
[11] Oyebanji OA, Wilson B, Keresztesy D, Carias L, Wilk D, Payne M, et al. Does a lack of vaccine side effects correlate with reduced BNT162b2 mRNA vaccine response among healthcare workers and nursing home residents? Aging Clin Exp Res 2021;33:3151–60.
[12] Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and gender differences in the outcomes of vaccination over the life course. Annu Rev Cell Dev Biol 2017;33:577–99.
[13] Cook IF. Sex differences in injection site reactions with human vaccines. Hum Vaccin 2009;5:441–9.
[14] Maeda K, Amano M, Uemura Y, Tsuchiya K, Matsushima T, Noda K, et al. Correlates of neutralizing/SARS-CoV-2-S1-binding antibody response with adverse effects and immune kinetics in BNT162b2-vaccinated individuals. Sci Rep 2021;11:22848.
[15] Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. J Allergy Clin Immunol 2020;145:1309–21.
[16] Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol 2010;17:1055–65.