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Research Note

Antibody responses to BNT162b2 mRNA COVID-19 vaccine and their predictors among healthcare workers in a tertiary referral hospital in Japan

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A B S T R A C T

Objectives: This study aimed to determine antibody responses in healthcare workers who receive the BNT162b2 mRNA COVID-19 vaccine and identify factors that predict the response.

Methods: We recruited healthcare workers receiving the BNT162b2 mRNA COVID-19 vaccine at the Chiba University Hospital COVID-19 Vaccine Center. Blood samples were obtained before the 1st dose and after the 2nd dose vaccination, and serum antibody titers were determined using Elecsys® Anti-SARS-CoV-2S, an electrochemiluminescence immunoassay. We established a model to identify the baseline factors predicting post-vaccine antibody titers using univariate and multivariate linear regression analyses.

Results: Two thousand fifteen individuals (median age 37-year-old, 64.3% female) were enrolled in this study, of which 10 had a history of COVID-19. Before vaccination, 21 participants (1.1%) had a detectable antibody titer (≥0.4 U/mL) with a median titer of 35.9 U/mL (interquartile range [IQR] 7.8 – 65.7). After vaccination, serum anti-SARS-CoV-2S antibodies (≥0.4 U/mL) were detected in all 1774 participants who received the 2nd dose with a median titer of 2060.0 U/mL (IQR 1250.0 – 2650.0). Immunosuppressive medication ($p < 0.001$), age ($p < 0.001$), time from 2nd dose to sample collection ($p < 0.001$), glucocorticoids ($p = 0.020$), and drinking alcohol ($p = 0.037$) were identified as factors predicting lower antibody titers after vaccination, whereas previous COVID-19 ($p < 0.001$), female ($p < 0.001$), time between 2 doses ($p < 0.001$), and medication for allergy ($p = 0.024$) were identified as factors predicting higher serum antibody titers.

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Conclusions: Our data demonstrate that healthcare workers universally have good antibody responses to the BNT162b2 mRNA COVID-19 vaccine. The predictive factors identified in our study may help optimize the vaccination strategy. **Takahiro Kageyama, Clin Microbiol Infect 2021;27:1861.e1–1861.e5**

Introduction

BNT162b2 mRNA vaccine against COVID-19 has shown promising efficacy both in a clinical trial [1] and in nationwide mass vaccination settings [2]. The vaccine has also shown short-term efficacy in a large-scale prospective cohort study targeting healthcare workers, a population that should be prioritized for vaccination [3]; however, the factors that predict the effectiveness of BNT162b2 mRNA vaccine have not been fully explored.

As the humoral responses have been shown to play essential roles in the protection against and the survival from SARS-CoV-2 infection [4–6], the antibody status after vaccination can provide important information to predict long-term effectiveness and to optimize the vaccination strategy. However, antibody responses after vaccination have been assessed only in small-scale studies [7–12]. Here, we report the antibody responses and their predictive factors in 2015 healthcare workers who received the BNT162b2 mRNA COVID-19 vaccine.

Methods

We recruited healthcare workers in Chiba University Hospital who were receiving the BNT162b2 mRNA COVID-19 vaccine (Pfizer, Inc., and BioNTech) at the Chiba University Hospital COVID-19 Vaccine Center.

Background information was collected by a web-based questionnaire. We considered that a subject had a history of COVID-19 when 1) the subject answered so in the web questionnaire and 2) the subject had been registered as a PCR-positive case in the hospital registry.

Blood samples were obtained 0-2 weeks before the 1st dose and 2-5 weeks after the 2nd dose of vaccination. Antibody responses were analyzed using Elecsys® Anti-SARS-CoV-2S on Cobas 8000 e801 module (Roche Diagnostics, Rotkreuz, Switzerland). This system allows for the quantitative detection of antibodies, predominantly IgG, aiming at the SARS-CoV-2 spike protein receptor-binding domain. The measurement threshold is $\geq$ 0.4 U/mL, and values $\geq$ 0.8 U/mL are considered positive. Samples with a titer >250 U/mL were diluted x10 at a time until the titer became $\leq$250 U/mL according to the manufacturer's protocol.

We first performed univariate linear regression analyses to identify factors associated with the serum anti-SARS-CoV-2S antibody titer after vaccination. We next performed a multivariate linear regression analysis with a stepwise method using factors that showed a p-value <0.1 in univariate analyses. Statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY). A two-sided p-value <0.05 was considered statistically significant.

The study procedures for sample collection and those for analyses were approved by Chiba University Ethics Committee on February 24th, 2021 (No. HS202101-03) and April 21st, 2021 (No. HS202104-01), respectively. All study subjects gave written informed consent before undergoing any study procedures.

Results

Out of 2838 employees in Chiba University Hospital, 2549 (89.8%) received at least one dose of BNT162b2 mRNA COVID-19 vaccine (30 μg) from March 3rd to April 9th, 2021, and 2015 individuals (71.0%) were enrolled in this study. Demographics and background information are summarized in Table 1.

Before vaccination, serum anti-SARS-CoV-2S antibody ($\geq$0.4 U/mL) was detected only in 21 subjects (1.1%) with a median titer of 35.9 U/mL (IQR 7.8 – 65.7). Eighteen subjects (0.9%) had a positive titer ($\geq$0.8 U/mL) and 8 out of these 18 subjects (44.4%) had a history of COVID-19.

After vaccination, serum anti-SARS-CoV-2S antibody ($\geq$0.4 U/mL) was detected in all 1774 participants who received the 2nd dose with a median titer of 2060.0 U/mL (IQR 1250.0 – 2650.0) (Supplementary Fig. 1A). Only one subject, who had received aggressive immunosuppressive treatment for a severe autoimmune condition, had a negative titer (0.7 U/mL). The distribution of post-vaccination antibody titers according to age and sex is shown in Supplementary Fig. 1B. In those who were seropositive before vaccination, the antibody titers substantially increased with a median fold change of 412.4 (IQR 309.2 – 760.5) following the 2nd dose.

The results of univariate and multivariate linear regression analyses are summarized in Table 1. The factors retained in the final multivariate model (adjusted R^2 0.188) were immunosuppressive medication, age, time from 2nd dose to sample collection, previous COVID-19, sex, time between 2 doses, glucocorticoids, medication for allergy, and drinking alcohol (Fig. 1).

Discussion

All subjects who received 2 doses of BNT162b2 mRNA COVID-19 vaccine had a detectable level of serum anti-SARS-CoV-2S antibody, and all but one subject who were seronegative before vaccination became seropositive (99.9%). In addition, all of 18 subjects who were already seropositive before vaccination showed substantial antibody responses after the 2nd dose. These results are consistent with previous smaller-scale studies [7,8,11,12] and indicate that the vast majority of young-adult healthcare workers have good antibody responses following 2 doses of the BNT162b2 vaccine.

The large sample size of our study allowed for establishing a stable multivariate model to determine background factors that predict antibody responses. The strongest and the most significant factor was receiving immunosuppressive drugs. Receiving glucocorticoids was also identified as an independent predictor even though our study population was mostly healthy workers and only 14 (0.9%) and 9 (0.6%) were taking glucocorticoids and immunosuppressant, respectively. Our data confirm the results of previous studies which demonstrated reduced antibody responses among patients on immunosuppressive regimens [13].

Unexpectedly, medication for allergy was also identified as a factor significantly associated with higher antibody titers. Although we have no information on the drug and diagnosis for the medication, we speculate that the majority were taking anti-histamine drugs for cedar pollen allergy, which is very common in Japan in spring. Interestingly, some studies have suggested potential therapeutic effects of histamine H1 receptor antagonists on COVID-19 [14]. Together with alcohol consumption as a negative predictor, these novel associations deserve further investigation.

Table 1
Background information and results of univariate/multivariate linear regression analysis for post-vaccine antibody titer

Variable	All (n = 2015)		Post-vaccine antibody titer available (n = 1774)		Linear regression analysis for post-vaccine antibody titer			
					Univariate		Multivariate	
	Data available, n	Value	Data available, n	Value	Regression coefficients (B)	95% confidence interval	Regression coefficients (B)	95% confidence interval
Age (year-old), median (IQR)	2015	37 (29-47)	1774	39.3	−0.016	−0.020 − −0.011	−0.016	−0.021 − −0.012
Sex female, n (%)	2015	1296 (64.3)	1774	1168 (65.8)	0.306	0.200 − 0.412	0.264	0.156 − 0.372
Nationality Japanese, n (%)	2015	2004 (99.5)	1774	1765 (99.5)	0.303	−0.412 − 1.018		
Job category	2015		1774		0.211*	0.102 − 0.320		
Nurse		672 (33.3)		559 (31.5)				
Doctor		589 (29.2)		494 (27.8)				
Pharmacist		58 (2.9)		57 (3.2)				
Dentist		19 (0.9)		11 (0.6)				
Others		677 (33.6)		653 (36.8)				
Body mass index category	1515		1512		0.014	−0.097 − 0.124		
<18.5		150 (9.9)		150 (9.9)				
18.5-25		1120 (73.9)		1118 (73.9)				
≥25		245 (16.2)		244 (16.1)				
Smoking	1515		1512		−0.200	−0.308 − −0.093		
Never, n (%)		1141 (75.3)		1139 (75.3)				
Ex-smoker, n (%)		323 (21.3)		323 (21.4)				
Current smoker, n (%)		51 (3.4)		50 (3.3)				
Alcohol	1515		1512		−0.111	−0.197 − −0.024	−0.084	−0.163 − −0.005
No, n (%)		417 (27.5)		417 (27.6)				
Sometimes, n (%)		863 (57.0)		860 (56.9)				
Every day, n (%)		235 (15.5)		235 (15.5)				
Comorbidities	1515		1512					
Asthma, n (%)		158 (10.4)		158 (10.4)	−0.041	−0.224 − 0.141		
Atopic dermatitis, n (%)		134 (8.8)		134 (8.9)	−0.007	−0.204 − 0.189		
Hypertension, n (%)		114 (7.5)		114 (7.5)	−0.343	−0.553 − −0.132		
Dyslipidemia, n (%)		97 (6.4)		97 (6.4)	−0.213	−0.441 − −0.014		
Thyroid disease, n (%)		55 (3.6)		55 (3.6)	0.092	−0.206 − 0.390		
Malignancy, n (%)		36 (2.4)		36 (2.4)	−0.022	−0.388 − 0.344		
Diabetes mellitus, n (%)		25 (1.7)		25 (1.7)	−0.388	−0.826 − 0.049		
Autoimmune disease, n (%)		13 (0.9)		13 (0.9)	−2.609	−3.200 − −2.019		
Ischemic heart disease, n (%)		5 (0.3)		5 (0.3)	−0.485	−1.458 − 0.487		
Cerebral infarction, n (%)		4 (0.3)		4 (0.3)	0.179	−0.909 − 1.266		
Interstitial lung disease, n (%)		2 (0.1)		2 (0.1)	−5.383	−6.895 − −3.870		
Chronic obstructive pulmonary disease, n (%)		0 (0.0)		0 (0.0)	NA	NA		
Current medication	1515		1512					
Allergy, n (%)		188 (12.4)		188 (12.4)	0.150	−0.019 − 0.319	0.177	0.023 − 0.331
Hypertension, n (%)		102 (6.7)		102 (6.7)	−0.397	−0.619 − −0.176		
Dyslipidemia, n (%)		77 (5.1)		77 (5.1)	−0.117	−0.371 − 0.137		
Inhaled corticosteroid, n (%)		32 (2.1)		32 (2.1)	−0.300	−0.687 − 0.088		
Thyroid disease, n (%)		27 (1.8)		27 (1.8)	−0.027	−0.449 − 0.395		
Diabetes mellitus, n (%)		20 (1.3)		20 (1.3)	−0.179	−0.668 − 0.309		
Glucocorticoids, n (%)		14 (0.9)		14 (0.9)	−2.386	−2.956 − −1.815	−0.747	−1.377 − −0.117
Immunosuppressant, n (%)		9 (0.6)		9 (0.6)	−4.294	−4.987 − −3.601	−4.105	−4.889 − −3.322

(*continued on next page*)

Table 1 (*continued*)

Variable	All (n = 2015)		Post-vaccine antibody titer available (n = 1774)		Linear regression analysis for post-vaccine antibody titer			
					Univariate		Multivariate	
	Data available, n	Value	Data available, n	Value	Regression coefficients (B)	95% confidence interval	Regression coefficients (B)	95% confidence interval
Insulin, n (%)		3 (0.2)		3 (0.2)	−0.943	−2.197 − 0.311		
Antimicrobial, n (%)		3 (0.2)		3 (0.2)	−1.065	−2.319 − 0.189		
Previous COVID-19, n (%)	2015	10 (0.5)	1774	9 (0.5)	1.761	1.051 − 2.472	2.059	1.358 − 2.760
Flu symptoms within a year, n (%)	1515	539 (35.6)	1512	539 (35.6)	0.027	−0.090 − 0.144		
Exposure to COVID-19 patient	1515		1512		0.159	0.056 − 0.262		
Hardly, n (%)		1333 (88.0)		1331 (88.0)				
<15 minutes, n (%)		76 (5.0)		76 (5.0)				
≥15 minutes, n (%)		106 (7.0)		105 (6.9)				
Time between 1st and 2nd doses (day), mean (SD)	1987	21.2 (0.7)	1774	21.1 (0.6)	0.185	0.104 − 0.266	0.164	0.082 − 0.254
Time between 2nd dose and sample collection (day), median (IQR)	1774	15 (14-21)	1774	15 (14-21)	−0.045	−0.058 − −0.032	−0.041	−0.054 − −0.028

*Nurse vs. non-nurse (other combinations did not yield p-value<0.1). IQR, interquartile range; SD, standard deviation.
Increment units were 1 year for "Age" and 1 day for both "Time between 1st and 2nd doses" and "Time between 2nd dose and sample collection".
Sex was recoded into 0: male and 1: female. The other dichotomous variables were recoded into 0: no/absent and 1: yes/present. The categorical variables were recoded into 0, 1, and 2 in the order listed.

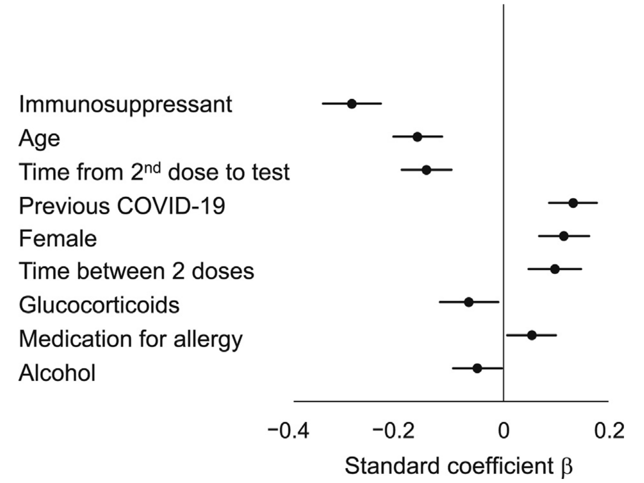

Fig. 1. Multivariate linear regression model to predict anti-SARS-CoV-2S antibody titers after vaccination. Shown are the variables retained in the final multivariate linear regression model to explain anti-SARS-CoV-2S antibody titers after vaccination. A dot and bar represent standardized coefficient β and 95% confidence interval for the variable.

While only 10 participants (0.5%) in our study had a history of COVID-19, it was the fourth most significant factor in our multivariate model. Its influence might have been underestimated since 2 participants who had the highest titers did not have a history of previous COVID-19 but both were seropositive before vaccination, and one had had close contact with an infected individual. Again, this result is consistent with previous reports [11,12,15,16] and consolidates the evidence that the BNT162b2 vaccine induces more robust antibody responses in individuals previously infected with SARS-CoV-2.

Among demographic factors, older age has been repeatedly reported to associate with reduced antibody responses after COVID-19 vaccination [7,8,11,12]. Our study population is younger than those in previous studies and supplement the evidence. Sex difference has also been reported to associate with antibody responses to various degrees [8,11,12]. Our large-scale data confirm the notion that women tend to have a greater antibody response to the BNT162b2 vaccine than men.

Our study has some limitations. First, this is a single-center study in Japan with mostly Japanese subjects. Second, neutralizing activity was not measured. However, the assay we employed has been shown closely correlated with the titer of neutralizing antibody [17], and 99.5% of our study subjects achieved a serum antibody level above the cut-off of 133 U/mL to predict a neutralizing activity. Third, we only assessed the antibody responses and did not assess the cellular ones. Fourth, most clinical information was collected with a questionnaire and cannot be verified.

Nevertheless, we provide large-scale data on antibody responses to the BNT162b2 mRNA COVID-19 vaccine. Universally good responses demonstrated in our study further support the use of this vaccine in a wide range of populations, and the predictive factors identified may help optimize the vaccination strategy and generate hypotheses for future studies.

Transparency declaration

We have no conflict of interest to declare. This study was supported by a donation to Chiba University Hospital and the Future Medicine Founds at Chiba University.

Author's contributions

Conception of the work: TK, KI, ST, HI, TN, KY, HN. Data collection: TK, KI, ST, TT, HI, YO, AK, KM, HH, TAN, SO, IY, HM. Data analysis and interpretation: TK, KI, ST, HI, KY, HN. Drafting of the article: TK, KI, ST, HN. Critical revision of the article: TK, KI, ST, HN.

Final approval of the version to be published: TK, KI, ST, TT, HI, YO, AK, KM, HH, TAN, SO, IY, HM, TN, KY, HN.

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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.2021.07.042.

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