**Examining the association between vaccine reactogenicity and antibody titer dynamics after the third dose of BNT162b2 vaccine using a mixed-effects model**

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Running title: Fever and antibody titers after third BNT162b2 dose

Word counts: 1989

Number of Tables and Figures: 2 tables, and 1 figure

Supplementary Tables and Figures: 3 tables, and 1 figure

**Authorship statement:**

NM contributed to the study design, data collection, statistical analysis, and interpretation of data, as well as the drafting and editing of the manuscript. MN and FO contributed to data collection and edited the manuscript. MF contributed to data collection and performed the laboratory tests. TM and ST contributed to data interpretation, supervision of the analysis, and edited the manuscript. HH contributed to the study design, data collection, data interpretation, and edited the manuscript. TY contributed to the study design, data collection, data interpretation, supervision of the analysis, and edited the manuscript. All authors made critical revisions to the manuscript for important intellectual content and approved the final manuscript. All authors meet the ICMJE authorship criteria.

**Abstract**

**Background**: To mitigate the COVID-19 pandemic, many countries have recommended the use of booster vaccinations. The relationship between the degree of adverse vaccine reactions and elevated antibody titers is of interest; however, no studies have investigated the temporal changes in antibody titers based on repeated measurements after a third dose of the BNT162b2 vaccine.

**Methods**: This prospective longitudinal cohort study was conducted with 62 healthcare workers who received a third dose of the BNT162b2 at Okayama University Hospital, Japan. Venous blood draw and fingertip whole blood test sample collection were conducted at the early (3 to 13 days) and 1-month time points; only FWT sample collection was conducted at the 2-month time point. Information on adverse reactions within 1 week after vaccination was also obtained. The association between fever of 37.5°C or higher and antibody titers after the third dose of BNT162b2 was examined using a mixed-effects model and Poisson regression with robust variance.

**Results**: A trend toward higher antibody titers in the early period after vaccination was observed in the febrile individuals, but the differences were not significant at 1 and 2 months post-vaccination (the partial regression coefficient for fever was 8094.3 [-1910.2, 18,098.8] at 1 month after vaccination, and 1764.1 [-4133.9, 7662.1] at 2 months after vaccination in the adjusted models).

**Conclusion**: The findings suggest that the presence of fever after the third vaccine does not predict

a sustained elevation in serum antibody titers.

**Keywords**: SARS-CoV-2, Vaccine, Antibody, Reactogenicity, Adverse reaction, Mixed-effects model

**Abbreviations**

CI, confidence interval; FWT, fingertip whole-blood test; HCW, healthcare worker; VST, venous serologic test

## Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in 2019 and has caused a global pandemic [1]. In response, several vaccines have been developed to limit the severity of the pandemic [2],[3],[4]. Since July 2021, a third dose of vaccine has been recommended owing to the decline in antibody titers over time and the reduction in vaccine efficacy to prevent infection with the emergence of new variants [5]. Some of the developed vaccines use unconventional mechanisms, such as the mRNA vaccines; furthermore, the high rate of mild to moderate adverse reactions after vaccination, such as fever and malaise, has hindered vaccine uptake [6], [7]. There is interest in the relationship between adverse reactions and a possible increase in antibody titers, but reports on this

issue are conflicting. Some studies have reported a positive association between adverse reactions to the second dose of the BNT162b2 vaccine and antibody titers at 3 weeks post-vaccination [8], [9],[10], while others have found no significant association [11], [12].

These discrepancies are partially explained by studies focusing on antibody titers at a single point in time, such as 2–3 weeks after vaccination, and few studies have compared changes in antibody titers over time in the early post-vaccination period, when adverse reactions are most likely to occur. A mixed-effects model can be used to describe the time-dependent changes in antibody titers because it can assess these changes over time despite missing data, which is not accounted for in the conventional analysis of variance model that assumes complete data sets [13]. However, few previous studies on antibody titer dynamics have applied such a model. In addition, although a third vaccine dose has been recommended in many countries, no study has investigated the association between adverse reactions to a third dose and subsequent antibody titers. Therefore, using a mixed-effects model and multiple regression analysis, we compared whether the antibody titer trajectories early after the third vaccine dose differed depending on the presence or absence of fever as an adverse reaction in a sample of Japanese healthcare workers who received a third dose of the BNT162b2 vaccine.

## Materials and Methods

## Study design and participants

A prospective longitudinal cohort study was conducted in 127 healthcare workers (HCWs) at Okayama University Hospital, Japan who received a third dose of the BNT162b2 vaccine in December 2021. All participants agreed to participate in the study and provided written informed consent. All participants had previously received two doses of the BNT162b2 vaccine, with the second dose given at least 8 months before the study. The study protocol was approved by the Okayama University Hospital Ethics Committee (K 2112-044).

## Sampling and measurement of antibody titers

For severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titer measurement, the participants provided blood samples immediately before receiving a third dose of the BNT162b2 vaccine and again at any point during the period from 3 to 13 days after vaccination. Antibody titers at approximately 1 month (28–30 days) and 2 months (53–55 days) after vaccination were also measured. The exact day of blood collection was decided by each participant. Venous blood draw and fingertip whole blood test (FWT) sample collection were both conducted at the early and 1-month time points; only FWT sample collection was conducted at the 2-month time point for convenience and minimally invasive procedures.

The venous blood samples were tested using the Elecsys anti-SARS-CoV-2 S immunoassay

(Roche Diagnostics International AG, Rotkreuz, Switzerland), which is an established venous serologic test (VST). Serum samples for VST were diluted 5- or 10-fold, as appropriate, and measured by a Cobas 8000 analyzer series e801 (Roche Diagnostics International AG). For the FWT, fingertip whole blood (30 μL) was collected and the Mokobio SARS-CoV-2 IgM & IgG Quantum Dot immunoassay (Mokobio Biotechnology R&D Center Inc., USA) was used to measure the antibody titer targeting the S protein receptor-binding domain [14]. The upper limit of the FWT was defined as 30,000 IU/mL in accordance with the manufacturer's instructions; values exceeding this limit were considered invalid.

Adverse reactions after the third dose of BNT162b2

Okayama University Hospital conducted a post-vaccination adverse reaction survey using a Google questionnaire form approximately 1 week after the HCWs had received a third dose of the BNT162b2 vaccine. The questionnaire collected information on age, sex, preexisting medical conditions, history of allergies, previous SARS-CoV-2 infection, and any adverse reaction to the third vaccine dose and use of antipyretic analgesic medications to alleviate the associated discomfort. Adverse reactions were categorized as either local reactions (e.g., pain, redness, and swelling) or systemic reactions (e.g., fever greater than 37.5°C, headache, fatigue, and myalgia). No data were missing because the Google form was set up for mandatory responses. We linked the adverse reaction

survey results with the antibody test results using the respondent's name.

Statistical analysis

A mixed-effects model was used to examine the IgG dynamics (assessed by VST) up to 30 days after receiving the third vaccine dose according to the presence or absence of fever over 37.5°C. The covariates for fixed effects included the presence or absence of fever, sex, age group (younger group aged under 40, aged 40–49, and elderly group aged 50–69), and each interaction term. Previous studies have reported that the IgG concentration peaks between 4 and 30 days after the second vaccination [15]; therefore, time was modeled using a quadratic term. This model also included interaction terms for time and each covariate. In addition to this basic model, we included the use of antipyretics during the presence of adverse reactions. By applying a random intercept model, any variability in the baseline information of individual participants was included as a random effect. On the basis of each of the fitted models, the IgG kinetics in the febrile and nonfebrile groups were compared up to 30 days post-vaccination.

We used multiple regression analysis to analyze the effect of fever on antibody titers at 1 and 2 months post-vaccination, adjusting for age and sex. For antibody titers at 1-month post-vaccination, VST data were used; at 2 months post-vaccination, FWT data were used. The correlation between FWT and VST was validated by Spearman's rank correlation coefficient test.

All analyses were performed using Stata/SE 17 (StataCorp LLC, College Station, TX, USA). P values less than 0.05 were considered significant.

## Results

### Study participants

The study was conducted from December 13, 2021, to February 8, 2022. A total of 76 of the 127 HCWs who consented to have their antibody titers measured also responded to the adverse reaction survey (response rate: 59.8%). Among these 76 HCWs, 10 never participated in any sampling, and four participated only in the pre-vaccination sampling. Excluding these 14 HCWs, 62 participants (21 with fever and 41 without fever) were included in the final analysis. Table 1 shows a comparison of these participants' characteristics according to the presence or absence of fever as an adverse reaction. The febrile group had a lower percentage of those with preexisting medical conditions or a history of allergy. No participants had a history of SARS-CoV-2 infection. Table S1 presents the frequency and timing of antibody titer testing for the 30 days after vaccination according to fever status. In total, 252 data points were collected from the 62 participants.

### Antibody titer kinetics throughout the 1-month post-vaccination period

The IgG kinetics were modeled using the quadratic term for time in a mixed-effects model

with and without fever (Table S2). As shown in Figure 1, the IgG concentration tended to rise faster and peak higher in the febrile group. The model that included antipyretic use during the adverse reaction period yielded the same results (Table S3).

Antibody titers at 1 and 2 months post-vaccination according to the presence of fever

The correlation between the FWT and VST data was calculated using 374 paired samples collected during the first month after vaccination, and a significantly high correlation was observed (Spearman's rank correlation coefficient, 0.939; p-value <0.001) (Fig. S1).

The VST values were available for 30 participants 1 month after vaccination and the FWT values were obtained from 24 participants (excluding one participant with the FST value exceeding 30000 IU/ml) 2 months after vaccination (Table 2). At 1 month after vaccination, the partial regression coefficient for fever was 8094.3 [-1910.2, 18,098.8] in the adjusted model, which was higher, but not significantly higher. At 2 months after vaccination, the partial regression coefficient for fever remained slightly higher at 1764.1 [-4133.9, 7662.1] in the adjusted model.

Discussion

In this prospective cohort study, a mixed-effects model and multiple regression analysis

were used to examine the relationship between fever as an adverse reaction and the antibody titer dynamics after vaccination with a third dose of BNT162b2. The results showed a trend toward higher antibody titers in the febrile group during the first 30 days after vaccination; however, the partial regression coefficients at 1 and 2 months after vaccination were not significant.

To our knowledge, no studies have investigated the association between the appearance of adverse reactions and elevated antibody titers after a third dose of BNT162b2. Moreover, previous studies have reported mixed results regarding this association after a second dose of BNT162b2. For example, a study of 564 HCWs in Greece reported an association between adverse reactions and antibody titers 3–4 weeks after the second vaccine dose [16]. A Croatian study found no significant association between adverse reactions and antibody titers 8–13 days after the second dose of BNT162b2 [11]. A German study using penalized linear regression to examine the association between adverse reactions and antibody titers 2–4 weeks after the second dose of BNT162b2 found only a weak correlation for some adverse reactions and reported that antibody levels could not be predicted from the presence or severity of adverse reactions [17].

These conflicting findings may be related to the scarcity of studies on the dynamics of antibody titers in the early post-vaccination period, which is typically when adverse reactions occur. Additionally, most of the studies measured antibody titers after vaccination at a single time point only, and this time point varies among studies. A Japanese study with longitudinal sample collection found

no significant association between adverse reactions and elevated antibody titers [10].

Missing data can complicate the investigation of antibody titer dynamics. The number of participants who complete all sample collections is inevitably smaller than the initial sample size. Although a mixed-effects model is effective in studies with limited sample sizes or missing values [13], few studies have examined the association between adverse reactions and antibody titer dynamics over time after vaccination using a mixed-effects model.

We found a trend for higher antibody titers during the first 30 days after vaccination in the febrile group. Compared with the nonfebrile group, the partial regression coefficients of the febrile group were higher at 1 and 2 months after vaccination (with the 2-month regression coefficient being lower than the 1-month coefficient), but the differences were not significant. Although the participants who had a fever after vaccination may have temporarily had higher antibody titers, its clinical significance appears to be small. However, our sample size was small. Furthermore, caution is needed when generalizing findings from HCWs who treat COVID-19 patients. There may also have been some misclassification regarding previous SARS-CoV-2 infection. Since FWT values were used in the analysis after 2 months of vaccination for convenience and minimally invasive methods, compatibility with VST values up to 1 month after vaccination should be considered. However, this study was conducted to compare post-vaccination fever and non-fever groups, and the high correlation coefficient between VST and FWT indicates that FWT values are sufficient indicators for comparing

the two groups [18]. Finally, although some reports have suggested an association between symptoms other than fever or the severity of fever and increased antibody titers [19],[20], we only used fever as exposure in this study, which can be expressed as a more objective value. Future studies should take these factors other than fever into account.

Despite these limitations, the mixed-effects model allowed us to examine differences in antibody titer dynamics after a third vaccine dose according to the presence or absence of fever. The mixed-effects model was also able to overcome the variation in the timing and frequency of measurements, which were based on the participants' decisions. Future studies should include a larger sample size and use a mixed-effects model to examine the longitudinal associations between the presence of adverse vaccine reactions and elevated antibody titers.

**Declaration of Competing Interest:**

None declared.

**Acknowledgments:**

We thank Yasuhiro Nakano, Naruhiro Sunada, Toru Hasegawa, Yasue Sakurada, Kou Hasegawa, Takafumi Obara, Kouhei Ageta, Yuta Mori, Yoko Oka, Saori Irie, Rumi Matsuo, Tomoka Kadowaki,

Akihito Higashikage, Takao Hikita, Shinichi Toyooka, Yoshinobu Maeda, and Yoshinori Yokokura for their valuable support in data collection. We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript. This study was supported by a grant from Okayama Prefecture for investigating the COVID-19 outbreak (7402000035).

**Funding:**

This work was supported by Okayama Prefecture for investigating the COVID-19 outbreak [grant no. 7402000035]. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or in the decision to submit the manuscript for publication.

**Data availability statement:**

Data cannot be shared for privacy or ethical reasons.

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Figure legends

**Fig. 1. IgG dynamics during 1 month post-vaccination**

The red line shows the IgG concentration means predicted by the mixed-effects model in the febrile group, and the blue line shows the predicted means in the nonfebrile group. The area of each color indicates the 95% confidence interval (CI) of the regression curve. Day 0 is a negative value owing to the effect of the modeling prediction.

**Fig. S1. Correlation between fingertip whole-blood test (FWT) and venous serologic test (VST)**

Samples for FWT and VST were obtained simultaneously from 127 healthcare workers who worked at Okayama University Hospital. Of the 462 paired specimens, 374 paired samples were compared with Spearman's rank correlation coefficient test; 75 paired samples with invalid FWT results and 13 paired samples with FWT values over 30,000 were excluded.

Table 1. Participant characteristics

| Characteristic | | With fever | | Without fever | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| Sex | male | 6 | 28.6 | 12 | 29.3 |
| Age (years) | < 40 | 9 | 42.9 | 20 | 48.8 |
| | 40–49 | 7 | 33.3 | 12 | 29.3 |
| | 50–69 | 5 | 23.8 | 9 | 22.0 |
| Underlying diseases | Yes | 2 | 9.5 | 5 | 12.2 |
| Allergy history | Yes | 9 | 42.9 | 20 | 48.8 |
| Previous SARS-CoV-2 infection | Yes | 0 | 0.0 | 0 | 0.0 |
| Total | | 21 | 100 | 41 | 100 |

## Table 2. Regression model of antibody titers at 1 and 2 months post-vaccination

IgG (VST) at 1 month

| | n/N | % | Crude model | | Adjusted model | |
|---|---|---|---|---|---|---|
| Fever | 9/30 | 30.0 | 8577.2 | [-699.6, 17,853.9] | 8094.3 | [-1910.2, 18,098.8] |
| Age: 40–49 | 10/30 | 33.3 | | | 2634.4 | [-8851.6, 14,120.5] |
| Age: 50–69 | 11/30 | 36.7 | | | -940.7 | [-12,320.8, 10,439.5] |
| Female sex | 24/30 | 80.0 | | | 157.2 | [-11,514.7, 11,829.1] |
| Intercept | | | 15,577.7 | [10,496.6, 20,658.8] | 15,063.6 | [3770.5, 26,356.7] |

IgG (FWT) at 2 months

| | n/N | % | Crude model | | Adjusted model | |
|---|---|---|---|---|---|---|
| Fever | 6/24 | 25.0 | 1254.8 | [-4530.3, 7040.0] | 1764.1 | [-4133.9, 7662.1] |
| Age: 40–49 | 8/24 | 33.3 | | | 3936.4 | [-1992.2, 9865.0] |
| Age: 50–69 | 7/24 | 29.2 | | | 989.9 | [-5473.9, 7453.6] |
| Female sex | 17/24 | 70.8 | | | -4705.7 | [-10,288.6, 877.3] |
| Intercept | | 30.0 | 7067.5 | [4175.0, 9960.1] | 8672.5 | [3628.6, 13,716.5] |

The references for the categorical variables were as follows: age < 40 was used as the reference group for ages 40–49 and ages 50–69.

Male sex was the reference group for female sex.

FWT: Fingertip whole-blood test; VST: venous serologic test