Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Examining the association between vaccine reactogenicity and antibody titer dynamics after the third dose of BNT162b2 vaccine using a mixed-effects model

Naomi Matsumoto a,*, Hideharu Hagiya b, Masanori Nakayama c,d, Masanori Furukawa e, Toshiharu Mitsuhashi f, Soshi Takao a, Fumio Otsuka b,e, Takashi Yorifuji a

a Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 700-8558, Japan
b Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 700-8558, Japan
c Office of Innovative Medicine, Organization for Research Strategy and Development, Okayama University, Okayama, 700-8558, Japan
d Max Planck Institute for Heart and Lung Research, Laboratory for Cell Polarity and Organogenesis, Bad Nauheim, 61231, Germany
e Clinical Laboratory, Okayama University Hospital, Okayama, 700-8558, Japan
f Center for Innovative Clinical Medicine, Okayama University Hospital, 700-8558, Japan

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 (3–13 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 ºC 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.

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.

1. Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019. The rapid spread of the disease has resulted in a global pandemic, with more than 200 million cases and over 4 million deaths reported worldwide as of September 2022. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19. The disease is characterized by a range of symptoms, including fever, cough, fatigue, and shortness of breath, and can lead to severe complications such as pneumonia, sepsis, and multisystem organ failure.

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

* Corresponding author. Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Kita-ku, Okayama-shi, Okayama, 700-8558, Japan.
E-mail address: naomim@okayama-u.ac.jp (N. Matsumoto).

https://doi.org/10.1016/j.jiac.2022.09.012
Received 11 July 2022; Received in revised form 14 August 2022; Accepted 12 September 2022
Available online 19 September 2022
1341-321X/© 2022 Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
N. Matsumoto et al.  Journal of Infection and Chemotherapy 29 (2023) 39–42

China in 2019 and has caused a global pandemic [1]. In response, several vaccines have been developed to limit the severity of the pandemic [2–4]. 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 [8–10], 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.

2. Materials and methods

2.1. 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).

2.2. 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 immunosass (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.

2.3. 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.

2.4. 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.

3. Results

3.1. 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.

3.2. 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 Fig. 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 30,000 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.

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. 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.

4. 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
Finally, although some reports have suggested an association between FWT values are sufficient indicators for comparing the two groups [18]. The high correlation coefficient between VST and FWT indicates that month after vaccination should be considered. However, this study was used in the analysis after 2 months of vaccination for convenience. We also able to overcome the variation in the timing and frequency of 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 built 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.

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.

Acknowledgments

We thank Yasuhiro Nakano, Naruhito Sunada, Toru Hasegawa, Yasue Sakurada, Kou Hasegawa, Takafumi Obara, Koubes Ageta, Mika Uno, Yuta Mori, Yoko Oka, Saori Irie, Rumi Matsuo, Tomoko Kadowaki, Akibito 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).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.09.012.

References

[1] WHO Coronavirus (COVID-19) Dashboard. WHO coronavirus (COVID-19) dashboard with vaccination data. a.d. https://covid19.who.int/. February 14, 2022
[2] Lamb YN. BNT162b2 mRNA COVID-19 vaccine: first approval. Drugs 2021;81: 495-501. https://doi.org/10.1007/s40265-021-01480-7.
[3] Polack FP, Thomas SJ, Kitchin N, Abelson 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. https://doi.org/10.1056/NEJMAO2034577/SUPPL_FILE/NEJMAO2034577_PROTOCOL.PDF.
[4] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384: 1412–23. https://doi.org/10.1056/NEJMAO2101765.
[5] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against covid-19 in Israel. N Engl J Med 2021;385:1:193–400. https://doi.org/10.1056/NEJMAO2114255/SUPPL_FILE/NEJMAO2114255_DISCLOSURES.PDF.
[6] Cai C, Peng Y, Shen E, Huang Q, Chen Y, Liu P, et al. A comprehensive analysis of the efficacy and safety of COVID-19 vaccines. Mol Ther 2021;29:2794–805. https://doi.org/10.1016/j.xmte.2021.08.001.
[7] Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. JAMA 2021;325:2201–2. https://doi.org/10.1001/ JAMA.2021.5574.
[8] Uwamino Y, Kurahiju T, Sato Y, Tomiya Y, Shibata A, Tanabe A, et al. Young age, female sex, and presence of systemic adverse reactions are associated with high post-vaccination antibody titer after two doses of BNT162b2 mRNA SARS-CoV-2 vaccine: an observational study of 646 Japanese healthcare workers and university staff. Vaccine 2022;40:1019–25. https://doi.org/10.1016/j.vaccine.2022.01.002.
[9] Lo Sasso B, Giglio RV, Vidali M, Scaczone C, Bivona G, Gambino CM, et al. Evaluation of anti-SARS-cov-2 S-RBD IgG Antibodies after COVID-19 mRNA BNT162b2 vaccine. Diagnostics 2021;11. https://doi.org/10.3390/ DIAGNOSTICS11071125.
[10] Bauernfeind S, Salzberger B, Hitzenbichler F, Scigala K, Einhäuser S, Wagner R, et al. Association between reactogenicity and immunogenicity after vaccination with BNT162b2. Vaccines 2021;9. https://doi.org/10.3390/VACCINES9101089.
[11] Maeda K, Amano M, Uemura Y, Tsujiya 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. https://doi.org/10.1038/s41598-021-01930-y.
[12] Lapit I, Rogić D, Segulić D, Zaninović L. Antibody response and self-reported adverse reactions following vaccination with Comirnaty: a pilot study from a Croatian university hospital. J Clin Pathol. 2021. https://doi.org/10.1136/JCLINPATH-2021-207572. jclinpath-2021-207572.
[13] Detry MA, Ma Y. Analyzing repeated measurements using mixed models. JAMA – J Am Med Assoc 2016;315:407–8. https://doi.org/10.1001/jama.2015.19394.
[14] Izumo T, Ruse N, Awano N, Tone M, Sakamoto K, Takada K, et al. Side effects and antibody titer transition of the BNT162b2 messenger ribonucleic acid coronavirus disease 2019 vaccine in Japan. Respi Inv 2021;59:635. https://doi.org/10.1016/J.RESINV.2021.06.003.
[15] Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months. N Engl J Med 2021;385;e564. https://doi.org/10.1056/NEJMOA2114583.
[16] Kontou E, Ranello K, Zoulas D, Bletsa A, Rompola E, Piperaki ET, et al. Antibody response following a two-dose mRNA vaccination regimen, in health care workers of a tertiary hospital in Athens, Greece. J Pers Med 2021;11. https://doi.org/10.3390/JPM11060576.
[17] Held J, Esse J, Tascilar K, Steininger P, Schober K, Irgang P, et al. Reactogenicity correlates only weakly with humoral immunogenicity after COVID-19 vaccination with BNT162b2 mRNA (Comirnaty®). Vaccines 2021;9. https://doi.org/10.3390/VACCINES9101089.
[18] Hagiya H, Hikita T, Habu T, Atada M, Yorifuji T, Toyooka S, et al. Poor vaccine responsiveness towards third-dose mRNA vaccine of COVID-19 in Japanese older people. J Infect 2022. https://doi.org/10.1001/JINF.2022.07.007. 0.
[19] Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, et al. Reactogenicity following receipt of mRNA-based COVID-19 vaccines: first approval. Drugs 2021;81: 495-501. https://doi.org/10.1007/s40265-021-01480-7.
[20] Nielsen J, Espe J, Endresen C, Krog A, Fevang B, Johnsen S, et al. Dynamics of immune responsiveness towards third-dose mRNA vaccine of COVID-19 in Norwegian people. J Infect 2022. https://doi.org/10.1016/J.JINF.2022.07.007. 0.